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Leading-edge, translational research in psychiatry and related neurosciences in Spain: the CIBERSAM multidisciplinary consortium

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Presentation

Leading-edge, translational research in psychiatry and related neurosciences in Spain: the CIBERSAM multidisciplinary consortium

It is a pleasure to present this special issue of the *European Journal of Psychiatry* in which the groups that constitute the *Centre for Biomedical Research Network on Mental Health* (CIBERSAM) describe their major lines of research. CIBERSAM is one of the CIBER Networks created by the *Instituto de Salud Carlos III* (ISCIII, Ministry of Health and now Ministry of Science and Innovation). The ISCIII promotes leading edge biomedical research, and has been considered to be the equivalent of institutes such as the *Medical Research Council* (MRC) in the UK.

Research in this field is important in itself because of the high prevalence of mental illness, a leading cause of disability in the developed world, with a large impact on spending and social development. However, the relevance of mental disorders has not been translated into funding for psychiatry and related areas. While mental illness is responsible for 31.8% of the disability caused by all disorders it only receives from the Government a 16.9% of the budget assigned to medical research. Only through research can we open the doors to significant new scientific knowledge useful in understanding mental illness.

To palliate in part these discrepancies, the *Network of Mental Disorders: Psychotic and Affective Disorders* (REM-TAP) was created in January 2007. The commitment to a large network of groups conducting basic, clinical and translational research at top level in mental health was a complex challenge and a milestone in the history of research in this field of medicine. Only one year after, in 2008, the ISCIII decided that mental disorders are sufficiently relevant and prevalent, and the critical mass of researchers was strong enough to constitute a CIBER in mental health. During the last decade there has been a huge increment in the number and quality of international publications published in this field by Spanish groups.

CIBERSAM is composed of professionals belonging to 26 research groups from eight Autonomous regions in Spain, grouped in four important research Areas. They mainly investigate disorders such as depression, schizophrenia, bipolar disorder and anxiety disorders; comorbidity and inter-relationships of physical and mental conditions; disorders of children, adolescents, and the elderly; and generally any neuroscientific aspect related to health and mental illness. CIBERSAM is now a team of about 400 people, with a staff of 107 professionals contracted, as well as other attached members. During its first and a half year of activity, a number of multi-center research projects have been designed and public funding has been

granted in competitive calls; more than 50 original papers have been published in high impact, international journals placed in the first quartile of the ranking in the speciality. CIBERSAM has tried to achieve a leading position in research excellence, both nationally and internationally, with the clear purpose of responding to needs in research into mental illness. The data presented in this special issue attest to the tremendous effort and the potential of the Network.

The fact that different groups belonging to CIBERSAM develop their activities in different institutions, in hospitals, research institutes or universities should be emphasized. This allows the study of these diseases from a translational direction, looking for synergies between the groups. As Prof. M. Ron, member of the Scientific Council writes in her invited editorial, the work of CIBERSAM is just beginning and only time will tell whether it fulfils its initial promise of becoming more than the sum of its parts. She clearly identifies reasons for optimism, but also matters of concern. Funding for biomedical research, reform of university hospitals and a clear career structure are most important goals still unfulfilled in Spain. The funding of this Network is generous for previous standards in Spain, but modest in relation to international institutes we have to compete with. It is hoped that obstacles in the way ahead will be overcome. CIBERSAM is certainly prepared to pursue its ambitious goals.

Celso Arango
Scientific Director, CIBERSAM

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Editor-in-Chief, *The European Journal of Psychiatry*
Coordinator of Area IV, CIBERSAM

Editorial

Caught in the network: there is hope for biomedical research in Spain

Biomedical research in Spain has undergone varied fortunes. The awards of Nobel Prizes to Ramon y Cajal in 1906 and to Severo Ochoa in 1959 were only fleeting moments of light in a dark period that lasted for many decades. The combined lack of a coherent research strategy and the necessary financial resources stifled productivity and encouraged the exodus of young researchers. In 1986 two simultaneous events introduced an element of hope in this barren landscape. First, the Spanish government passed the Science and Health Law that resulted in the creation of the Carlos III Health Institute, the equivalent of the Medical Research Council (MRC) in the UK or the French Institut de la Santé et de la Recherche Médicale (INSERM) and then Spain joined the European community at the time when the European Framework Programme for Research and Development (R&D) was coming into effect. The more coherent research strategy and, more recently, the slow but steady increase of funding for R&D are creating the conditions where biomedical research in Spain could blossom. Thus while in 2006 only 1.12% of Spain's GDP went into R&D (significantly below the 1.8% average funding in other EU countries), the INGENIO 2010 programme aims to increase R&D funding to 2% of the GDP by 2010. In parallel, the number of publications in peer-reviewed journals, particularly in biomedicine, has steadily increased in the last few years and Spain now ranks 7th in Europe and 11th in the world, although the citation index has lagged behind. The interest of young investigators in biomedical subjects is also encouraging and over 30% of all PhDs awarded in 2005/2006 were in medicine, biology, chemistry and pharmacology and this burgeoning group of young researchers may soon provide the necessary critical mass that until recently has also been missing.

In 2008 the Instituto de Salud Carlos III (ISCIII) created CIBERSAM, a research network to integrate 26 clinical and basic science research groups working in the field of mental health with an emphasis on translational research to increase synergy between them, to encourage joint approaches to the same research questions and to avoid wasteful duplication. CIBERSAM provides common databases, a library of research instruments and methodologies and has plans to set up DNA and brain banks. It also has a training programme for young researchers who are encouraged to visit other groups. Four important research areas (bipolar disorder, schizophrenia, depression and other mental disorders) have been identified to provide a focus in the next few years and a scientific advisory body has been set up to provide scientific advice and to review and report on progress.

As a member of this scientific council, it has been my privilege to get to know many of the investigators involved in CIBERSAM. For a clinical scientist like myself who was part of the

exodus of an earlier generation, to witness this new departure has indeed, been a pleasure and a source of pride. Many of these investigators, now in their prime, would grace research institutions anywhere in the world and their enthusiasm and wish to succeed in their collective endeavour set an example and augur well for the future. This issue of *The European Journal of Psychiatry* samples some of the achievements and future plans of the various research groups that work under the CIBERSAM umbrella and one cannot help but to be impressed by the scope and ambition of the research programme and by the ability and hard work of the participants.

The work of CIBERSAM is just beginning and only time will tell whether it fulfils its initial promise of becoming more than the sum of its parts. There are grounds for optimism, but also reasons for concern, as important obstacles still remain in the path of biomedical research in Spain. These obstacles have been clearly identified in a recent document entitled "Health and Medical research In Spain" (www.rand.org). First, R&D funding needs to be increased still further, in particular that coming from private initiative (non-pharmaceutical), that in other countries makes a substantial contribution to R&D (nearly three times that of government funds in the UK). The reform of the university hospitals to make it possible for an increasing number of medical graduates to divide their time between clinical work and research, and a clear career structure for other biomedical researchers are also needed. One can only hope that the newly formed Ministry of Science and Innovation will tackle these challenging issues.

Maria Ron
Professor of Neuropsychiatry
University College London, Institute of Neurology

Further reading

• Universia 2007.Investigación en Medicina Clínica en España: Panorama de luces y sombras. (http//investigacion.universia.es)

• Health and Medical Research in Spain. Health research observatory. Document briefing series funded by the UK Department of Health (www.rand.org).

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UADO: A CENTRE FOR THE STUDY OF NEURO-DEVELOPMENT WITHIN THE CIBERSAM

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UADO: A centre for the study of neuro-development within the CIBERSAM

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ABSTRACT – The Adolescent Psychiatric Unit of Hospital General Universitario Gregorio Marañón (UADO), one of the 26 CIBERSAM research groups, conducts research in children and adolescent psychiatry and, since its inauguration in 2000, has grown into a reference standard in the field. The Adolescent Unit has conducted collaborative studies over the past 8 years, working with most of the main groups in the country, first as part of the *Child and Adolescent First Episode Study (CAFEPS),* and later in the context of the *Network Centre for Biomedical Research in Mental health (CIBERSAM)*. In addition to the aforesaid institutions, the Adolescent Unit has also worked in collaboration with various basic and clinical research departments as well as with foreign centres. Currently, its three main lines of research are essentially first-episode psychosis, developmental neuropsychopharmacology, and autism spectrum disorders.

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Introduction and background

The Adolescent Psychiatric Unit (UADO) of Hospital General Universitario Gregorio Marañón (HGUGM) was founded in November of 2000 and currently covers a population of approximately 3,786,572 inhabitants in the Autonomous Community of Madrid. Its primary objective is to assess and stabilise acute psychiatric cases of adolescents that require full-time hospitalisation for approximately one to three weeks. It also provides outpatient consultation services, and performs basic and clinical research (www.hggm.es/ua).

In terms of quality management, the UADO counts on the European Foundation for Quality Management (EFQM) as a functional model[1], which constitutes one more step in its constant striving for excellence and quality that has resulted in some special mentions in public quality programs, including the Community of Madrid Award for Excellence in 2008.

As part of a university hospital affiliated with the Complutense University of Madrid, the UADO provides with a variety of teaching activities to different disciplines, such as medicine, nursing, social work, occupational therapy, and psychology. Every year the UADO organizes a doctoral course within the Neuroscience Program of the Complutense University of Madrid and hosts an international meeting with eminent lecturers from all around the world, which are well known among mental health practitioners and researchers with special interest in child and adolescent psychiatry.

Furthermore, the UADO carries out clinical and basic research in co-operation with national and international centres. In recent years, the UADO has become a reference among the research groups at HGUGM because, in addition to working with foreign centres, much of the work described below is conducted with the various domestic departments at the HGUGM. Thus, at this time, the UADO shares research projects with the Departments of Internal Medicine[2], Radiology[3], Genetics[4], Nutrition[5], Cardiology[6], Neurophysiology[5], Biochemistry[7], and the Medical Imaging Laboratory[3,8-11].

The primary lines of research conducted by the UADO are summarised below and essentially comprise three broad areas: first-episode psychosis, developmental neuropsychopharmacology, and autism spectrum disorders.

1. First-episode psychoses

This has traditionally constituted the main area of interest in the UADO research program[12]. Since its inception, our research group has been deeply involved in the study of variables related to FEP from different perspectives. In 2002, the UADO took part in the *Child and Adolescent First Episode Study (CAFEPS)*[13], a co-ordinated program funded by the National Institute of Health Carlos III, through the Health Research Fund. The initial project involved 11 centres and more than 60 investigators, and lasted 3 years, from 2003 to 2006. This collaborative study was coordinated by our group. The program studied children and adolescents with FEP of less than 6 months' duration, and consisted of a 2-year clinical follow-up, including 2 neuropsychological assessments, 2 structural neuroimaging studies, 2 spectroscopies, and 4 genetic, immunologic, and biochemical tests. Since then, several publications have come out of the group, as well as 5 doctoral dissertations by members of the group, awards, courses, papers at

meetings, etc.[10,13-17]. Major findings from this study are that patients with an early onset psychosis have both diminished frontal gray matter volume at baseline and a further reduction larger than expected when compared to healthy controls[9]. Patients also show more obstetric complications[15], and a variety of developmental problems before the onset of the symptoms[13]. The results so far point towards a neurodevelopmental disease with superimposed degenerative changes in at least a subsample of the patients.

As a continuation of such a fruitful project, a new grant will allow the follow-up study to be extended to 5 years. The main objective of this project (*Neurodegenerative and Prognostic Markers in First Psychotic Episodes in Children and Adolescents: 5 year follow-up*) is to extend the follow-up period for 149 patients with FEP and 80 matched healthy controls, from 2 to 5 years. At baseline and the two-year follow-up, we already have collected genetic, clinical, cognitive, and neuroimaging data from this sample. We have also been able to detect progressive loss of cerebral grey matter, mainly in the frontal lobes, in a subgroup of psychosis patients[9]. With regards to cognition, our data shows that cognitive functioning both in the baseline and in two year follow-up remain below the healthy control data in our patient group as a whole and when it is divided into diagnostic subgroups (schizophrenia, bipolar disorder and other psychoses)[18-21]. In the extended follow-up period, our main hypothesis is that, those patients with a more progressive course of cerebral neurodevelopmental impairment (increased loss of grey matter), will also have other markers of affected brain development (such as cognitive impairment and diminished N-acetyl aspartate , a measurement of neuronal integrity quantified using proton magnetic resonance spectroscopy).

Other studies, currently being conducted in this line of research, cover a broad spectrum of topics, including basic and clinical research. Thus, the one entitled *Involvement of gene catechol-O-methyltransferase (COMT) in psychosis: Association with prefrontal cognitive performance and neurological soft signs in patients with early-onset psychosis and their first-degree relatives*, hypothesises that cognitive impairments associated with prefrontal lobe functioning, as well as the presence of neurological soft signs (NSS), could be considered risk markers and/or endophenotypes for the development of psychosis[18-21]. Furthermore, the catechol-O-methyltransferase (COMT) gene has been associated with functional deficits in the prefrontal lobe, and suggested as a susceptible gene marker for psychosis. From these assumptions, we are pursuing a comparison of the prevalence of NSS and cognitive deficits associated with prefrontal lobe functioning in individuals with FEP, their first-degree relatives, and healthy controls with no family history of psychosis, as well as the identification of possible differences in the COMT genotype for the functional Val158Met polymorphism in these three population samples.

Our group has stepped forward and started a co-ordinated study with the Department of Psychiatry of Hospital Clínic of Barcelona, in which the main goal is to investigate populations at risk, targeting the offspring of patients with schizophrenia and bipolar disorder. In our project entitled *Psychopathological, neuropsychological, and neuroimaging study of children and adolescent offspring of patients with schizophrenia and bipolar disorder,* we start from the assumption that the study of these children and adolescents may lead to identifying clinical characteristics as well as neurocognitive[18,19] and neuroimaging abnormalities

shared by both disorders[3,9,22,23], under the hypothesis that psychotic and affective symptoms may be present in both diagnoses as a continuum. We will compare their characteristics with those of control subjects. In addition, we will try to find shared characteristics and differences between offspring of individuals with these disorders. Endophenotypical markers will be studied, as the characteristics of offspring of patients with schizophrenia and bipolar disorder are delimited.

Since January 2009, the UADO is taking part, together with other 16 CIBERSAM groups, in an important collaborative project, co-ordinated by the group of Hospital Clínic of Barcelona, to study from a broad perspective, the interaction between genotype and environment in order to get a predictive model for FEP (*Gene and environment interaction: Predictive model application*).

Finally, within this line of research, our group has incorporated a study to assess the efficacy of a *Psychoeducational Treatment for Families and Patients with FEP*. This study has developed a manual as well as pilot-test interventions directed towards parents of patients with FEP, and the patients themselves. The interventions consist of family-focused psychoeducational (PE) sessions and seminars, and begin with three PE sessions offered to the patients on the one hand and to their families on the other, followed by 12 theoretical and practical (problem solving) seminars in a group format, separated for patients and relatives. The PE component educates parents about the diagnosis, course, aetiology, and therapeutics of FEP, including written material, and is compared with a non-structured intervention, both added to the "standard treatment". The outcomes of these interventions are assessed by measuring family climate and changes in the course of the disorder.

2. Developmental neuropsychopharmacology

Development is the differential factor in the comparison between adult and child / adolescent psychiatry. Since adolescence is the most active period in the development of neural structures, the UADO constitutes an optimal environment to implement studies about the potential impact of medication in such crucial stages of growth and maturation. Thus, the UADO has taken part in several studies about cardiovascular risk and metabolic side effects of medication in adults, adolescents and children in order to compare those effects in different stages of development[12,14,24]. In this context, one of our studies has shown that single doses of antipsychotics, like haloperidol and risperidone, produce negative symptoms in normal individuals and that drowsiness might be an important confounding factor in the assessment of these negative symptoms in antipsychotic trials[25]. Other studies of our group have shown that metabolic syndrome is present in almost 25% of the antipsychotic-treated patients and that this factor is associated with increased cardiovascular risk and psychopathology[24]. Furthermore, coronary heart disease risk and metabolic syndrome prevalences among patients with schizophrenia treated with antipsychotics are in the same range as the 10 to 15 years older Spanish general population.

Regarding children and adolescents with FEP, we already know that second-generation antipsychotics, especially risperidone, quetiapine and olanzapine, are the most used drugs in our context. These three drugs obtain similar clinical improvement but differ in their side effects profile.

According to our previous reviews, adolescents are not only more susceptible to the

side effects of antipsychotic medications than adults, but they are also more likely to be sensitive to the negative impact of side effects on appearance, body imaging and self-esteem[12]. In, to our knowledge, the first randomized clinical trial comparing two second generation antipsychotics in early onset psychoses, we have not found any improvement with olanzapine or quetiapine in cognition in a six months follow-up, although adolescents on both, olanzapine and quetiapine, reduced their psychotic symptoms. In this study, patients on olanzapine gained significantly more weight and side effects with both drugs seemed to be more prevalent than those reported in adult studies[6].

In the same context, our current study about the *Identification of candidate genes for the prediction of weight gain in patients treated with second generation antipsychotics,* focuses on the particular issue of the effect of medication on rapidly developing tissues and systems. In that context, weight gain, higher cardiovascular morbidity/mortality and diabetes have been mentioned as some of the potential side effects of antipsychotics[5,6], and there seems to be genetic factors involved in the production of various degrees of vulnerability to different antipsychotics. Thus, the objective of this study is to determine the possible relationship between the genotype profiles of genes related to the metabolism of obesity and their phenotypes, with those of genes related to the mechanism of action of the antipsychotics and weight gain.

3. Autism spectrum disorders

The third main line has strongly impacted the activity of the unit, both at a clinical and a research level. The continuously growing interest of the scientific community in the study of autism spectrum disorders (ASD), together with the scarcity of adequate facilities for the care of these patients, has generated great expectations in the community. This fact has motivated our team in its search for clinical data that allow child and adolescent mental health professionals to respond to the demands of parents whose children have traditionally, in many cases, been set aside or referred to unprepared professionals. In this context, the UADO has developed an integral plan of medical care globalisation for patients with ASD. Thus, early this year, for the first time, our hospital will host a program in which a group of specialised psychiatrists will co-ordinate all of the specialised medical care of patients with ASD, referring them to the appropriate specialist within the HGUGM, in case they need specialised attention. This program will facilitate the access of these patients to the universal and public health care, available in Spain for the general population, by helping them overcome administrative and procedural barriers.

In addition, an important development in research studies in this area is emerging in the unit. The study of the *Structural brain volumes and white matter structure in adolescent patients with* Asperger's *syndrome* is looking for differences between Asperger's syndrome (AS) and both, FEP patients and healthy controls, through the use of magnetic resonance imaging (MRI). The main goal of this longitudinal 1-year follow-up study is essentially to compare total and partial structural brain volumes between adolescent patients with AS, FEP, and normal controls. Secondarily, we are pursu0ing the comparison of levels of fractional anisotropy as well as structural and anisotropy level changes over 2 years in those three populations.

Another work comprises the study of oxidative metabolism in psychoses and ASD. Oxidative status and its potential damaging effects when imbalanced, in the form of abnormal polyunsaturated fatty acid composition in the cell membrane, is longitudinally assessed both, in high functioning ASD and psychosis patients. The latter group is assessed in two different treatment situations: quasi antipsychotic-naïve and after 8 weeks of exposure.

A third study within this line of research is the *Detection of urinary beta-7-casomorfine in patients with ASD*. The main purpose of this study is to evaluate the presence of beta-7-casomorfine in patients with ASD and digestive symptoms (such as chronic diarrhea). Since ASD comprise a broad variety of pathologies, our group proposes that this metabolite might be a group biological marker, present in those patients that frequently present with associated digestive symptoms.

Finally, from a therapeutic perspective, our group is conducting a study on the *Effect of 8-week omega-3 fatty acid treatment on oxidative metabolism in patients with autism spectrum disorder*. In this randomised, double-blind, crossover, placebo-controlled trial, we focus on the relationship between clinical variables and changes in oxidative metabolism, which may affect the polyunsaturated fatty acid (PUFA) composition of the neuronal membranes in patients with ASD. The objective of this study is to evaluate the effect of an 8-week omega-3 treatment on oxidative metabolism and secondarily on symptoms in patients with ASD. This controlled trial could be crucial to affording clinicians a new treatment approach, based on consistent knowledge of the pathophysiology of the disorder, in a field that lacks therapeutic tools.

Future directions

In the intensification process of UADO research that has been stated as one of our main objectives, collaborative work with other CIBERSAM groups has become a priority. The CIBERSAM currently provides Spanish researchers with an appropriate infrastructure for conducting high quality studies in different fields. Our group is currently looking forward to developing research projects with other clinical and basic research groups in order to enhance our translational research.

Another important priority for the UADO is our potential collaboration with other European groups, mainly in the context of the VII Framework Programme. More specifically, our group would like to focus its activity on the neurobiological aspects of brain development, intensifying our involvement in lines of research related to developmental neurobiology. Neuropsychopharmacology as well as neurogenetics continue to be preferential areas, especially with regard to early psychoses and ASD.

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ROLE OF PREFRONTAL CORTEX IN PHARMACOLOGICAL MODELS OF SCHIZOPHRENIA AND ANTIPSYCHOTIC ACTION

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Role of prefrontal cortex in pharmacological models of schizophrenia and antipsychotic action

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SPAIN

ABSTRACT – NMDA receptor (NMDA-R) antagonists are extensively used as schizophrenia models due to their ability to evoke positive and negative symptoms as well as cognitive deficits similar to those of the illness. Likewise, 5-HT_{2A} receptor agonists display hallucinogen actions resembling psychotic symptoms. Overall, these drugs are useful models of schizophrenia for the screening of new antipsychotic drugs. However, the cellular and network elements involved in these actions are poorly known. Data obtained by several groups in recent years indicate that the prefrontal cortex (PFC) and anatomically related areas play a major role in these actions. This paper summarizes data obtained by the authors supporting that a) NMDA-R antagonists (phencyclidine –PCP–, dizocilpine –MK–801–) and 5-HT_{2A} agonists (DOI) alter the function of PFC in a similar fashion, and b) antipsychotic drugs exert their therapeutic action, at least in part, by normalizing hyperactivity states in PFC. While the actions of NMDA-R antagonists may involve blockade of these receptors in PFC and subcortical areas, that of antipsychotic drugs, in particular atypical drugs like clozapine, appear to be mediated essentially by a local action in PFC. These results help to better understand the neurobiological basis of the action of pharmacological models of schizophrenia and the mode of action of antipsychotic drugs.

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Introduction

The present report summarizes data obtained in recent years in one of the main research lines (antidepressants, antipsychotics, brain circuits) carried out by the "Systems Neuropharmacology" group of CIBERSAM.

Schizophrenia is associated with alterations in the anatomy and function of several cortical and subcortical areas. Among these, the prefrontal cortex (PFC) seems to play a key role in the pathophysiology of the illness[1,2]. Despite the obvious difficulty in modeling these alterations in experimental models of the illness, non-competitive *N*-methyl-D-aspartate (NMDA) receptor (antagonists such as the dissociative anaesthetics ketamine and phencyclidine (PCP) and MK-801 (dizocilpine), have been extensively used as pharmacological models of schizophrenia due to their ability to evoke positive and negative symptoms of schizophrenia as well as the cognitive deficits of the illness in humans. These agents elicit a potent behavioural syndrome as well as cognitive and sensory deficits in experimental animals that resemble human schizophrenia symptoms (see Geyer *et al*.[3]; Krystal *et al*.[4] for review). NMDA receptor antagonists also induce schizophrenia symptoms in healthy subjects and aggravate them in schizophrenic patients. Furthermore, the behavioural effects of NMDA receptor antagonists are sensitive to the treatment with antipsychotic drugs that alleviate psychotic symptoms in schizophrenic patients[4]. Also, serotonergic agents such as lysergic acid diathylamine and related compounds, which are agonists of 5-HT_{2A} receptors, can produce perceptual and psychic alterations[5]. DOI (1-[2,5-dimethoxy-4-iodophenyl-2-aminopropane]) is a partial 5-$HT_{2A/2C}$ agonist that evokes long-lasting alterations in consciousness and perception. DOI acts by over stimulating 5-HT_{2A} receptors, since its behavioral, neurochemical and electrophysiological effects are blocked by the selective 5-HT_{2A} receptor antagonist M100907.

To provide a deeper insight of the brain areas and neuronal types affected by NMDA-R antagonists and DOI, we have conducted a series of electrophysiological, histological and neurochemical studies to examine the cellular and population responses of PFC, paying also a special attention to the potential reversal of these actions by conventional and second generation (atypical) antipsychotic drugs.

Methods

Animals. Adult male Wistar rats (250-300 g) (Iffa Credo; Lyon, France) were been used in most experiments. We also used 10-15 weeks old male homozygous 5-HT_{1A} receptor *knockouts* (5-HT_{1A} -/-, referred onwards as KO) and wild-type (5-HT_{1A} +/+, referred onwards as WT) mice of the same genetic background (C57BL/6). Animal procedures were performed according to the European Union regulations (O.J. of E.C. L358/1 18/12/1986) for the use of laboratory animals and were approved by the Institutional Animal Care and Use Committee.

Electrophysiological experiments. We examined the effect of psychotomimetic drugs such as the NMDA receptor antagonist phencyclicine (PCP), the preferential 5-HT_{2A} receptor agonist DOI (both with hallucinogen properties) and the antipsychotic drugs clozapine and haloperidol on the activity of PFC, assessed by a) single unit ex-

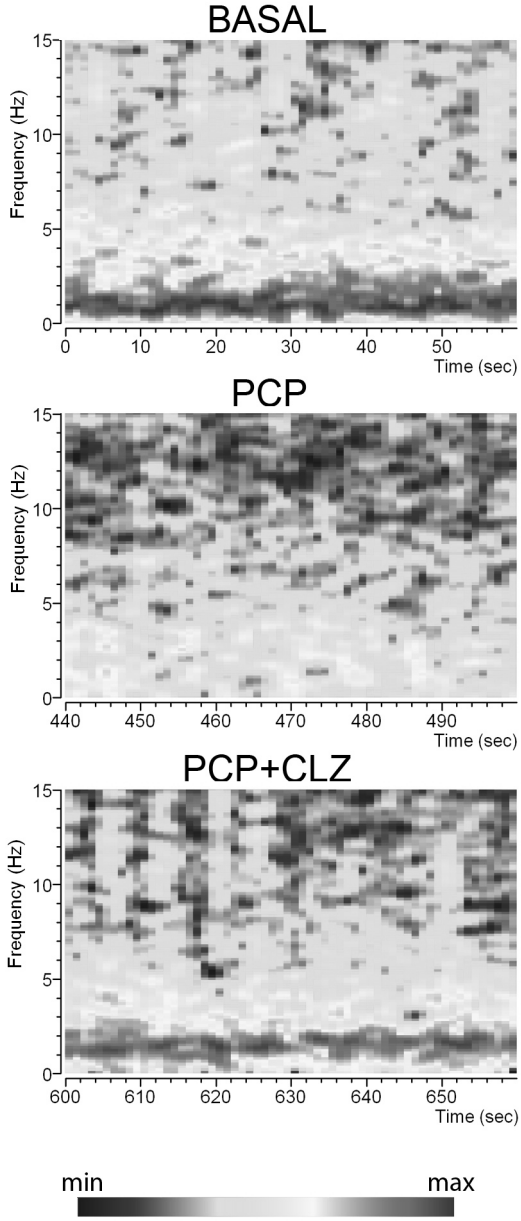

Figure 1. Representative spectrograms showing the effects of the administration of phencyclidine (PCP, 0.25 mg/kg i.v.) and clozapine (CLZ, 1 mg/kg i.v.) on low frequency oscillations recorded in mPFC. Note the marked reduction in the power spectrum induced by CPP (middle panel) and the reversal produced by CLZ. Abscissa is in s, ordinate is in Hz. The intensity of the power spectrum is color-coded (red = high intensity; blue = low intensitiy). Redrawn from data in Kargieman *et al.*[7]

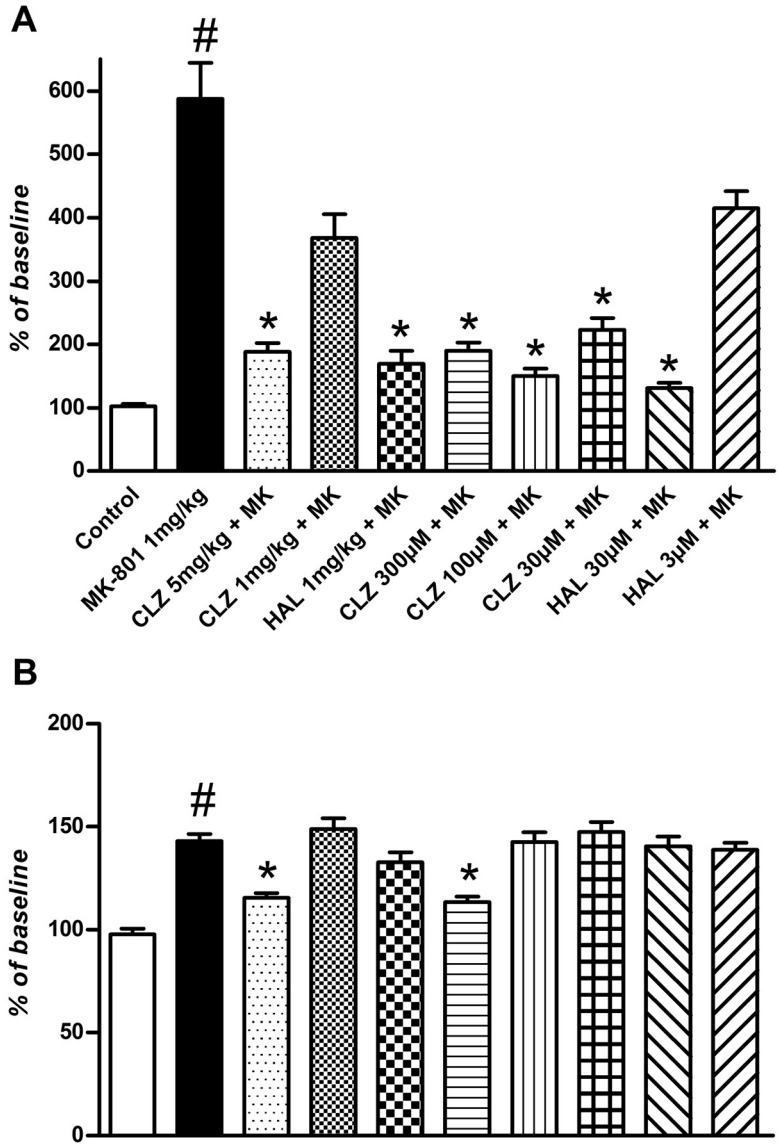

Figure 2. Bargraph showing the effect of MK-801 (MK) alone or in combination with the antipsychotic drugs clozapine (CLZ) or haloperidol (HAL) on the glutamate and serotonin output in rat PFC. Antipsychotic drugs were given systemically (CLZ, 1 and 5 mg(kg; HAL 1 mg/kg) or locally, by reverse dialysis at the stated concentrations. Redrawn from data in López-Gil *et al*.[10]

tracellular responses and/or b) local filed potentials in the chloral hydrate anesthetized rats. These variables permit to examine cellular and population responses, respectively, to drug administration. A full account of the procedures used can be found in Kargieman *et al*.[6,7] and Celada *et al*.[8]

Histological experiments. The effects of PCP and clozapina on PFC function were also examined by using the expression of the immediate early gene *c-fos* as a marker of neuronal activity. This was conducted using double *in situ* hybridization, labeling *c-fos* mRNA with radioactive oligonucleotides and the cellular phenotype (glutmatergic or GABAergic neurons) with non-radioactive oligonucleotides directed respectively towards the vesicular glutamate transporter 1 (vGLuT1) pr the GABA-synthesizing enzyme $GAD_{65/67}$ (glutamate acid decarboxylase). See Kargieman *et al*.[6,7] for details.

Microdialsyis experiments. These experiments were aimed at examining the effect of NMDA receptor antagonists and/or antipsychotic drugs on the *in vivo* release of neurotransmitters in PFC: serotonin (5-HT), dopamine (DA) and glutamate, as an index of the activity of these neuronal groups in response to drug administration. A full description of microdialysis procedures can be found in Amargós-Bosch *et al*.[9], López-Gil *et al*.[10,11]

Data analysis. The effects of drugs on the different variables used in the different studies (neurotransmitter concentrations, neuronal discharge rate, power of cortical oscillations, neuronal numbers, etc) have been assessed by one- or two-way ANOVA for independent or repeated measures, as appropriate. Student's *t*-tests have also been used. Data are expressed as means ± SEM. Statistical significance has been set at the 95% level (two-tailed).

Results

Effects of PCP on neuronal activity in PFC. Reversal by antipsychotic drugs

PCP induces a marked disruption of the activity of the PFC in the rat, increasing and decreasing the activity of 45% and 33% of the pyramidal neurons recorded, respectively (22% of the neurons were unaffected)[6,12]. Concurrently, PCP markedly reduced cortical synchrony in the delta frequency range (0.3-4 Hz) as assessed by recording local field potentials. The subsequent administration of the antipsychotic drugs haloperidol and clozapine reversed PCP effects on pyramidal cell firing and cortical synchronization[6]

Histological studies showed that PCP increased *c-fos* expression in PFC pyramidal neurons, an effect prevented by the administration of clozapine. PCP also enhanced *c-fos* expression in the centromedial and mediodorsal (but not reticular) nuclei of the thalamus, suggesting the participation of enhanced thalamocortical excitatory inputs[6,7].

Effects of DOI on neuronal activity in PFC. Reversal by antipsychotic drugs

Similarly to PCP, DOI markedly disrupts cellular and network activity in the rat PFC. DOI altered pyramidal discharge in mPFC (39% excited, 27% inhibited, 34% unaffected; n = 51)[12]. In all instances, DOI concurrently reduced low frequency oscillations (0.3-4 Hz; power spectrum: 0.25 ± 0.02 and 0.14 ± 0.01 μV^2 in basal conditions and after 50-300 μg/kg i.v. DOI, respectively; n = 51). Moreover, DOI disrupted the tempo-

ral association between active phase of local field potentials (LFP) and pyramidal discharge[8]. Both effects were reversed by M100907 (5-HT_{2A} receptor antagonist) and were not attenuated by thalamic lesions, supporting an intracortical origin of the effects of DOI.

As also observed for PCP, the alteration of low frequency oscillations induced by DOI was significantly reversed by the antipsychotic drugs haloperidol (0.1-0.2 mg/kg i.v.) and clozapine (1 mg/kg i.v.)[8].

Effects of NMDA-R antagonists on neurotransmitter release in PFC. Reversal by antipsychotic drugs

The systemic, but not local (in PFC), administration of the NMDA-R antagonists PCP, ketamine and MK-801 increased the *in vivo* 5-HT release in PFC[9,10]. Further investigations with MK-801 indicated that it also produced a large increase in the efflux of glutamate[10], possibly as a neurochemical correlate of the increase in pyramidal cell activity seen with NMDA-R[6,13].

Interestingly, whereas the local application of MK-801 could not increase glutamate efflux, both the local (in PFC) and systemic administration of clozapine were able to reverse the increased glutamate efflux induced by systemic MK-801 administration[10], suggesting an intracortical action of clozapine. Further studies examining the likely receptors affected by clozapine suggest interactions with 5-HT_{2A}, 5-HT_{1A} and $_{-1}$-adrenoceptors present in PFC pyramidal cells[11]. However, despite 5-HT_{1A}eceptors in PFC appear necessary for the atypical antipsychotic-induced increase in cortical (PFC) dopamine release[14], they play a minor role in the actions of MK-801 to modulate dopamine release[15].

Discussion

Despite the widespread use of NMDA receptor antagonists as pharmacological models of schizophrenia, their neurobiological basis of action is still poorly known. Neuroimaging studies indicate that a sub-anesthetic dose of ketamine increases the activity of the prefrontal cortex (PFC) in human volunteers[16]. In experimental animals, NMDA receptor antagonists such as MK-801 or PCP increase neuronal activity[6, 13,17]. Recent observations also indicate that NMDA receptor antagonists and 5-HT_{2A} receptor agonists produce a marked loss of slow oscillations in PFC[6,8] reflecting a disruption of the function of cortical networks, which possibly reflects the psychotomimetic properties of these compounds. This effect is accompanied by a marked expression of the immediate early gene *c-fos* in pyramidal (but not GABAergic) neurons. The differential effect of PCP in pyramidal and GABAergic neurons is consistent with a preferential blockade of NMDA receptors in GABAergic neurons[18], subsequently leading to pyramidal cell disinhibition. However, since thalamic neurons also expressed *c-fos,* it cannot be discarded that PCP can also act in subcortical areas, this leading to an activation of thalamocortical inputs.

The increased PFC activity observed in electrophysiological experiments is also paralleled by an increased neurotransmitter release in PFC[9-11,15,19,20]. This likely reflects the activation of local and extended neuronal networks, including the activation of PFC descending afferents to the monoaminergic midbrain nuclei (raphe nuclei and ventral tegmental area) which contain the cell bodies of serotonergic and dopamienrgic neurons, respectively.

Interestingly, the above effects produced by NMDA receptor antagonists (and –when

examined– by 5-HT_{2A} receptor agonists), such as increased pyramidal neuron activity, loss of cortical synchrony, increased *c-fos* expression and increased neurotransmitter release, are antagonized or reversed by classical (haloperidol) and atypical (clozapine) antipsychotic drugs. This suggests that the above alterations in PFC function are intimately related to schizophrenia. One interesting observation is that both the local and systemic administration of antipsychotic drugs were able to antagonize the drug-induced PFC abnormalities, supporting that antipsychotric drugs normalize cortical function by a local action in PFC, yet some differences exist between haloperidol and clozapine when antagonizing MK-801 effects on serotonin and glutamate release. This may reflect a distinct interaction of classical and atypical drugs with monoamine receptors in PFC which is possibly related to the distinct activity of both drugs on negatrive/cognitive symptoms. Overall, the above observations suggest that the normalization of PFC function by antipsychotic drugs is related to their therapeutic activity in schizophrenia.

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THE AFFECTIVE DISORDERS MULTIDISCIPLINARY RESEARCH TEAM: RESEARCH PROJECTS AND COLLABORATIONS

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The Affective Disorders Multidisciplinary Research Team: Research projects and collaborations

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SPAIN

ABSTRACT – Affective disorders constitute a serious public health problem due to their high prevalence and their impact on disability and quality of life (QoL). The Affective Disorders Multidisciplinary Research Team is devoted to investigating different aspects of affective disorders, articulated in the following research lines: analysis of functioning and disability patterns in patients with major depression and bipolar disorder; development of the ICF Core Sets for bipolar disorder; studies on the effectiveness and efficacy of therapeutic interventions for bipolar and depressed patients through clinical trials; analysis of suicidal behaviour in order to develop prevention programmes; evaluation of the differential impact on health and functioning of subsyndromal symptoms of depression in the general population; evaluation of the impact on mental health of ageing trends in Europe through a community epidemiological study; and analysis of specific psychosocial problems of people living with brain disorders. All of these projects will contribute to the

body of knowledge on epidemiology and the impact of affective and other mental disorders through the development and validation of new evaluation strategies, and aim to find ways to improve healthcare delivery.

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Introduction

Affective disorders constitute a serious public health problem due to their high prevalence and their impact in disability and quality of life (QoL). Prevalence of depressive disorders in Europe is around 8.6%[1], with major depression being one of the most frequent mental disorders in the general population[2]. The Global Burden of Disease Study estimated that in 1990, major depression was the fourth leading cause of disability-adjusted life years (DALYs) worldwide, and predicted that it will be the second by 2020[3]. Bipolar disorder is a severe, chronic and recurrent illness. The prevalence of all bipolar disorders has been estimated as at least 5%[4], and they are the ninth most common cause of years lived with disability (YLD)[5].

The Affective Disorders Multidisciplinary Research Team (http://www.trastornosafectivos.com) at La Princesa University Hospital and Autónoma University of Madrid includes clinicians and researchers from varied backgrounds (psychiatry, primary care, statistics, psychology and sociology). Their activities were centred initially on different aspects of research on affective disorders but have extended to the application of methods developed within these conditions to other areas of medicine. In 2008, the team joined CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), created to improve clinical care and mental health through the knowledge generated by research in psychiatry and neuroscience.

The Affective Disorders Multidisciplinary Research Team is mainly devoted to coordinating and participating in European projects, although it is also involved in several national multi-centre projects. The main research lines being developed by the team at present are: epidemiology and nosology of mental disorders; analysis of the effectiveness and efficacy of therapeutic interventions through clinical trials; evaluation of functioning and disability in patients with mental disorders; and development and validation of new objective and subjective measures. The projects that articulate these research areas are described below.

Functioning and Disability in Affective Disorders

Disability is a multidimensional phenomenon resulting from the interaction between the individual's health status and the physical and social environment. The International Classification of Functioning, Disability and Health (ICF)[6,7], developed by the World Health Organization (WHO) provides an adequate, universally accepted framework for documenting the interaction

between health status and environmental features[8], as well as the differential distribution of disability among different groups in different contexts. However, until recently, few clinical interventions and research models have been based on this classification.

"Functioning and Disability in Affective Disorders" is a project run by the Affective Disorders Multidisciplinary Research Team along with Barcelona's Clinic Hospital, also a member of CIBERSAM, which obtained funding from the Spanish Health Sciences Research Fund (FIS). The project is connected with the MHADIE ("Measuring Health and Disability in Europe") Consortium, funded by the European Union Sixth Framework Programme (www.mhadie.it), which aims to demonstrate the feasibility and utility of applying the ICF model in the measurement of different impairments in 10 European countries. The Spanish branch is focusing on analysing functioning and disability patterns in patients with major depression and bipolar disorder, studying the predictive and mediator variables related to disability in affective disorders[9], and comparing traditional clinical measures such as severity and comorbidity with functioning measures based on the ICF.

During data collection, two cohorts of patients were collected: one of patients with major depression from La Princesa University Hospital and Heath Area 2 (Madrid), and another of patients with bipolar disorder from La Princesa University Hospital (Madrid) and Clinic Hospital (Barcelona). A review of the literature found that a high percentage of bipolar patients show significant disability in different areas of functioning, including work, family, and social life[10]. A study by Martinez-Arán *et al*.[11] showed that low-functioning bipolar patients were cognitively more impaired than highly-functioning patients, and the variable that best predicted psychosocial functioning in all bipolar patients was verbal memory. A new instrument to assess functional impairment in subjects with bipolar disorder has also been developed and validated: The Functioning Assessment Short (FAST) scale[12]. Using a multilevel modeling approach we have been able to prove that social, environmental and personal factors seem to play a significant role in explaining depressed and bipolar disorder patients' functioning after controlling for health condition/medical factors[13,14].

Core Sets for Bipolar Disorders

Another application of the ICF to bipolar disorder is the "Development of the ICF Core Sets for Bipolar Disorder", funded by the European Union Sixth Framework Programme through the "Multidisciplinary Research Network on Health and Disability in Europe" (MURINET www.murinet.eu). ICF Core Sets are subgroups of ICF items selected to capture those aspects of functioning that are most likely to be affected by specific disorders. The final definition of the ICF Core Sets for bipolar disorder will be determined at an ICF Core Sets Consensus Conference, which will integrate evidence from preliminary studies, namely, a systematic literature review where parameters included in recent papers are analysed; semi-structured interviews with people having bipolar disorder; an international expert survey; and a cross-sectional study. The aim of these ICF Core Sets for bipolar disorder is to stimulate research leading to improved understanding of functioning, disability and health in bipolar disorder[15].

Independent Clinical Trials

Our group is currently taking part in two clinical trials promoted by CIBERSAM. The first one is based on the observation of current findings suggesting that some intervention is needed in order to improve both affective symptoms and cognitive dysfunction, which are highly relevant and persistent in bipolar patients. The trial entitled "Comparative Efficacy of Two Psychosocial Strategies of Intervention (Neurocognitive vs. Psychoeducative) as Add-on Therapy versus Treatment as Usual in Bipolar Disorder", funded by FIS, is the first study on the efficacy of cognitive remediation programmes for bipolar disorder. The method consists of a randomized controlled clinical trial with three phases: 1) cognitive rehabilitation plus pharmacological treatment; 2) psychoeducation plus pharmacological treatment; and 3) pharmacological treatment alone (control group). Psychopathological, neuropsychological and functional assessments will be administered pre- and post-intervention, and during a 12-month follow-up to assess the long-term effects of the interventions.

Depressed patients are also being recruited at our unit for a different clinical trial, "Therapeutic Strategies for Major Depression Resistant to SSRI Treatment: Pragmatic, Parallel, Randomised Clinical Trial, with Masked Evaluations" (DEPRES). The project, also with funding from FIS, aims to determine which is the best treatment option for patients with a diagnosis of SSRI-resistant major depressive disorder. Patients are being randomly assigned to one of the five treatment arms: 1) therapeutic optimisation (control group); 2) optimisation plus augmentation with lithium; 3) optimisation plus combination with nortryptiline; 4) optimisation plus problem-solving psychotherapy; and 5) substitution for venlafaxine. Demographic, clinical and pharmacological factors involved in therapeutic response to the main strategies for the treatment of SSRI-resistant major depression will be also assessed.

Study of Suicidal Behaviour in Madrid

Our team coordinated the "Study of Suicidal Behaviour in the Community of Madrid", funded by the Instituto Madrileño de Salud Pública, to analyse the characteristics of suicide attempts in the Madrid region, and the response of the health system. Although suicidal behaviour can be considered a separate diagnostic category[16], it is also very closely related to affective disorders, since it is commonly a complication of these and other psychiatric conditions[17]. Due to the variability of suicidal behaviour across countries[18], suicide prevention policies to be applied in a specific place should be based on site-specific. Owing to the lack of general data about suicidal behaviour in Madrid, the first step for prevention was to identify the characteristics of people who attempt suicide there. The study analysed the clinical records of all persons presenting at four general public hospitals in Madrid after a suicide attempt between November 9, 2007 and March 8, 2008. The hospitals, all members of CIBERSAM, were Gregorio Marañón University General Hospital, Ramón y Cajal University Hospital, San Carlos University Clinical Hospital, and Doce de Octubre University Hospital. There were 1009 identified suicide attempts[19]. Some of the findings about the quality of the clinical records of suicide attempters are being published at present[19]. Furthermore, a

prevention programme is being developed, which shows an example of transference from research results to clinical practice (http://www.trastornosafectivos.com/v1/suicidio.jsp).

Depression in the General Population

Our team is currently analysing data on the differential impact on health and functioning of subsyndromal symptoms of depression and psychosis. Data for these analyses come from the 2002 World Health Survey, a cross-national study performed by the WHO representing all regions of the world. This sample comprised 257,072 individuals from 68 countries, and we are exploring the hypothesis of a continuum in the impact of depressive and psychotic symptoms on health in the general population, i.e., the relevance of subsyndromal presentations as well as a possible linear increase in the impact of symptoms as severity rises. Some findings from analysis of this database have already been published by other authors[20].

The team has recently obtained funding from the European Union Seventh Framework Programme for two collaborative projects: COURAGE and PARADISE. "Collaborative Research on Ageing in Europe" (COURAGE) evaluates the impact of ageing in Europe through the development of new objective and subjective measures based on a community epidemiological study of different physical and mental long-term pathologies. Due to the ageing of the populations of Europe[21], and health trends such as the decline of fatalities from infectious diseases and better access to health care, impairments and health problems are occurring later in life. There is a need to disentangle the measures of health state, QoL, and well-being of the population within the background of the clear conceptual framework of health provided by the ICF. COURAGE will use this framework to develop measures of health and health-related outcomes for an increasingly aged population. These measures will provide objective and evidence-based prevalence trends, and will relate these to both QoL and well-being outcomes, as well as to the role of health determinants such as the built environment and social networks. In the Spanish sample, there will be a special emphasis on mental and neurological disorders.

The general objective of the project entitled "Psycho-Social Aspects Relevant to Brain Disorders in Europe" (PARADISE) is to compare and harmonise studies, literature, and data collection strategies regarding specific psychosocial problems of people living with brain disorders. Many European studies that include descriptions and assessment of psychosocial difficulties associated with brain disorders tend to focus on single brain disorders or a combination of one or two of them, and do not cover the full range of difficulties that a person with a brain disorder faces[22]. As a result, the information we have at the European level on psychosocial difficulties takes the form of narrow "information silos" that are neither comprehensive nor comparable across disorders unless extensive attempts are made at post hoc harmonisation[23]. The project is going to propose a harmonised protocol and data collection strategy, taking a "horizontal approach", which will make it possible to evaluate the incidence of specific psychosocial difficulties across several brain disorders, rather than a "vertical approach" focusing on the epidemiology of a specific brain disorder. Psychosocial difficulties and

QoL are understood in terms of the conceptualization of health and disability found in the ICF, which has proven itself useful in the MHADIE project.

All of this research will increase the body of knowledge regarding the epidemiology and impact of affective and other mental disorders at a national, European and international level through the development and validation of new evaluation strategies. Furthermore, it will open up new lines of research, evaluation, prevention, and treatment, and will contribute to the design evidence-based health and social policies.

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PAST, PRESENT AND FUTURE OF THE *CLÍNIC* SCHIZOPHRENIA RESEARCH GROUP

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Past, present and future of the *Clínic* schizophrenia research group

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SPAIN

ABSTRACT – The currently available diagnostic and therapeutic tools for schizophrenia are unsatisfactory. There is a clear need for new multidisciplinary treatments and intervention strategies that allow a broad-based approach to the disease. At the Hospital Clínic in Barcelona, the Clinic Schizophrenia Group (*Grup Esquizofrènia Clínic*, GEC) is actively involved in the following lines of research: physical health, neuroimaging, neuropsychology, the genetic, cellular and molecular bases of psychotic disorders, and child and adolescent mental health.

In the area of physical health, it has been observed that life expectancy in patients diagnosed with schizophrenia is 20% lower than in the general population. Sixty per cent of this excess mortality can be attributed to medical diseases: the risk of diabetes mellitus and metabolic syndrome is twice as high in patients diagnosed with schizophrenia as in the general population. In the area of neuroimaging, research has highlighted the existence of brain structure anomalies in patients with psychosis or schizophrenia. In cognition, these patients present global alterations in the areas of memory, attention and executive functions, which range between one and two standard deviations below the mean of the general population and which have repercussions for the their general functioning. In child onset psychosis, younger age has been associated with greater severity and poor prognosis. Finally, in the area of genetic studies the research is based on identifying mutations/polymorphisms that influence etiology and pharmacological response in schizophrenic patients.

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Introduction

Schizophrenia is a severe disorder. Its symptoms, development and neuropsychological profile vary widely, as does the degree of disability it causes. Its prevalence is estimated to be approximately 1% of the general population[1]. It is usually a chronic condition which has a serious impact on quality of life of both the patients and their families. The currently available diagnostic and therapeutic tools are unsatisfactory and there is a clear need for new or improved treatments and intervention strategies. Above all, a multidisciplinary approach is required to allow a global approach to the disease.

At the Hospital Clínic in Barcelona the Clinic Schizophrenia Group (*Grup Esquizofrènia Clínic*, GEC), founded and led by Dr. Miguel Bernardo, possesses a long tradition of research in the neurobiological bases of schizophrenia. The group is recognized as a consolidated research group (2005-SGR00223) by the Catalan government's department of universities and research.

In 2007, in cooperation with other Spanish research centres, the GEC helped to set up REMTAP, the Mental Illness and Affective and Psychotic Disorders Network, which received a commendation from the Spanish Subdirectorate for Networks and Co-operative Research Centres. The following year, the group joined CIBERSAM, the Spanish on-line mental health biomedical research centre. This is a newly formed institution comprising several expert groups working independently in basic and clinical areas but which pursue common research objectives, sharing tools and information, and coordinating projects. CIBERSAM provides a solid infrastructure for research and guarantees the presence of recognized researchers in each of the areas. In turn, collaboration between the members groups allows the design of studies with large samples and high statistical power and favours the pooling and comparison of data.

In recent years, the research carried out by the GEC has focused on five areas: physical health, neuroimaging, neuropsychology, the genetic, cellular and molecular bases

of psychotic disorders, and child and adolescent mental health.

In physical health, the first of these areas, the latest studies have found that life expectancy in patients diagnosed with schizophrenia is 20% lower than in the general population[2]. Recent data suggest that most (60%) of the excess mortality is attributable to medical diseases, especially cardiovascular and metabolic diseases[3]. The risk of diabetes mellitus and metabolic syndrome, well-known factors in cardiovascular disease, is at least double in patients diagnosed with schizophrenia compared with the general population[4].

High levels of certain types of cancer, ophthalmological alterations and consumption of toxic substances have also been reported[2]. The causes of the increase in prevalence and mortality are as yet unknown; some authors suggest an involvement of antipsychotic medication, and others propose that the disease itself is the underlying factor that predisposes to these disorders[5]. The objectives of this area of research are: a) to study the role of schizophrenia (and the role of antipsychotics) in the development of cardiovascular and metabolic diseases; b) to provide a basic structure for medical evaluation of the patients. The most important project currently underway is "Diabetes in neuropsychiatric disorders", organized in conjunction with the University of Maryland, Georgia. This project has produced several publications that show that diabetes may share family risk factors with schizophrenia[6,7].

Many studies have demonstrated the existence of structural brain anomalies in patients with psychosis or schizophrenia and also in their relatives[8-10]. The GEC has ample experience in the field of neuroimaging and has published studies carried out in a variety of populations of patients with schizophrenia: first episodes of psychosis, neuroleptic-naïve patients, patients receiving antipsychotic treatment, chronic patients with deficit or patients with EPS, among others. These studies have used a variety of techniques, especially isotopic methods including perfusion and neuroreceptor PET and SPECT[11-13]. The objectives of the neuroimaging line are to study: a) the functional neuroanatomy of auditory hallucinations; b) temporo-limbic functionalism in emotional neuroactivation; c) the comparison between the neurodevelopmental and neurodegenerative hypotheses; d) the central action mechanisms of first and second generation antipsychotics; and e) the dopamine transporter and the NMDA glutamate receptor. In 2009 this area of research has obtained funding from the Spanish health sciences research fund (FIS) for the project "Apoptosis and progressive neurostructural changes in patients with a first episode of schizophrenia: longitudinal and multimodal neuroimaging and molecular biology study" whose principal researcher is Dr. Eduardo Parellada. The study's main objective is to establish whether apoptotic susceptibility is increased in cultured dermal fibroblasts, as a peripheral model of cerebral apoptosis, in subjects who have suffered a first episode of psychosis/schizophrenia. We will examine whether this first episode is related to a loss of cerebral volume, alterations in the white matter bundles and/or reductions in the levels of markers of neuronal integrity evaluated with structural MR (3D MR), 1HMR spectroscopy and DTI over a two-year follow-up period.

The importance of cognitive alterations in patients with schizophrenia is beyond doubt[14]. Studies show global alterations in the areas of memory, attention and executive functions[15,16] which range between one and two standard deviations below the mean of the general population[17] and have repercussions for the patient's functioning[18].

The neuropsychology research line investigates descriptive and functional aspects of cognition, defining it as an important area of study for the analysis of the neurobiological correlates analysed through neuroimaging techniques. This line develops pharmacological and psychological treatment for rehabilitation, and psychometric instruments adapted to the Spanish population.

Its main objectives are: a) the analysis of cognitive functions in psychosis and schizophrenia; b) the validation of psychometric scales and instruments for research and for the clinical treatment of mental health; c) the study of the effectiveness of psychological rehabilitation treatments; e) the relation between cognitive deficits, course of the disease, disease awareness and risk of relapse; and f) the study of the relationship between cognitive functions and the neurobiological mechanisms analysed with neuroimaging techniques.

Among the evaluations of neuropsychological variables currently underway is the project entitled "Analysis of the effects of cognitive rehabilitation treatment in schizophrenia using functional neuroimaging techniques" (principal researcher Dr. Rafael Penades, FIS PI070258).

One of the areas that has aroused most interest in recent years is schizophrenia of childhood or adolescent onset[19,20], and the study of high risk populations. Schizophrenia in the young is particularly devastating; it affects their schooling and their social relations and may impose severe limits on their future achievements. Early detection and diagnosis of the disease is essential, as is the implementation of treatments that are adapted to the needs of each patient.

Childhood inset psychosis has been associated with greater severity[21] and a higher prevalence of the disease among relatives. Prognosis is also worse[22]. The objectives of this research line are to study: a) the etiology of schizophrenia of adult, early, or very early onset so as to identify the factors that trigger the condition and its evolution during the most active phase; b) the clinical, neuropsychological and therapeutic factors associated with the evolution and prognosis of schizophrenia of early and very early onset, and c) subjects at high risk of schizophrenia and transition to psychosis. In this line of research a particularly important project is "Common and differential psychopathological, neuropsychological and neuroimaging characteristics in children and adolescents of parents with schizophrenia or bipolar disorder" (principal researcher Dr. Josefina Castro-Fornieles) which studies the clinical, neuropsychological and neuroimaging characteristics of patients at a high risk of developing schizophrenia and bipolar disorder in childhood.

Genetic studies are the GEC's last research line. In recent years, a great deal of research has aimed to identify mutations/polymorphisms that influence the etiology and pharmacological response in schizophrenic patients[23-25], but the clinical heterogeneity that characterizes this disease makes its study difficult. Identifying mutations/polymorphisms that affect the onset and development of the illness will allow us to identify high risk individuals, to determine the molecular mechanisms involved, and to design prevention programs. The objectives of this research line are: a) to determine the genes involved in the onset and development of the disease via case/control studies with candidate genes; b) to identify the genes involved in the phenotypic characteristics of the disease and in its clinical variability, and c) to improve the efficacy and the toxic profile of psychopharmacological treatment bearing in mind the individual characteristics due to genetic variations.

This is probably the most active of our research lines at present. In September 2008 the FIS granted funding for the project entitled "Interaction between the genotype-phenotype and the environment. Application of a predictive model in first episodes of psychosis" (2009-2012). This project includes 16 hospitals that are leaders in psychiatric research in Spain, and is coordinated by Dr. Bernardo. The aim of the study is to identify genetic and environmental risk factors and to analyse their interaction in the appearance of a first psychotic episode. A sample of at least 300 patients and 300 controls matched for age, sex and socioeconomic status will be recruited. The study is organized in four modules: general, which will provide a clinical and genetic characterization of the subject; neuroimaging, which will obtain MR and DTI images; neurocognition, in which the patient will be evaluated neuropsychologically; and pharmacogenetics, which records variables referring to the area of pharmacology.

Another example of the development of this area of research inside the Hospital Clinic group is the project entitled "Analysis of the polymorphisms of risk in genome-wide association studies (GWAS) in psychosis", a joint nationwide analysis of SNPs in genetically differentiated populations which have presented highly significant associations with psychosis in GWAS studies. This project is also funded by the FIS, and its principal researcher is José Carlos González Piqueras. It will be implemented in various centres under the auspices of the CIBERSAM.

In recent months we have joined the EU-GEI research project, which focuses on the analysis of the interaction between genes and the environment and its repercussion on the development, severity and course of schizophrenia. This is a European level collaborative study which involves the recruitment of 2500 families in ten different countries.

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THE CIBERSAM UGR GROUP: PROMOTING MENTAL HEALTH RESEARCH IN ANDALUSIA

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The CIBERSAM UGR Group: Promoting mental health research in Andalusia

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SPAIN

ABSTRACT – This paper briefly describes both main research lines and structure of our CIBERSAM University of Granada research group based at Granada University in South Spain. We are a multidisciplinary team working in three different research lines adscribed to two smaller psychiatric research groups. Thus, PSYBAM group includes psychiatrists, biologists and psychologists and focus on both psychiatric phenotype definition and gene-by-environment interactions/pharmacogenetics. On the other hand, the older GAISAM group concentrates on epidemiological and social aspects of psychiatry and its members are psychiatrists and psy-

chologists. We have funding from European, Spanish and Andalusian sources and most of our researchers are based at the Centro de Investigaciones Biomédicas within Granada University.

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Setting and Origins of CIBERSAM UGR

The University of Granada (Andalusia, South Spain) was founded in 1531 and has been traditionally one of the largest and more prestigious universities in Spain. Currently, the University of Granada (UGR) is one of the leading Spanish postgraduate centers in terms of research and teaching as measured by conventional quality indicators. Similarly, the Faculty of Medicine is the leading Andalusian centre and one of the best positioned medical schools in Spain, with its Section of Psychiatry and Psychological Medicine being one of the leading research departments.

The UGR branch in CIBERSAM (Centro de Investigaciones Biomédicas en Red de Salud Mental) joined the network following competitive assessment in 2007. The CIBERSAM UGR group is composed by two research groups in the UGR Section of Psychiatry and Psychological Medicine, namely GAISAM (Grupo Andaluz de Investigación en Salud Mental) lead by Prof. Francisco Torres and PSYBAM (The Psychiatry, Biology and Environment Research group) led by Prof. Jorge Cervilla and Prof. Blanca Gutiérrez. The GAISAM group has traditionally being concentrated in services use based research whilst PSYBAM has focused, also within the epidemiological paradigm, on biological psychiatry research with an special interest in gene by environment interaction, psychopharmacogenetics and psychiatric phenotype redefinition. CIBERSAM UGR is currently formed by three senior members funded by UGR and ten full time researchers funded by either CIBERSAM or via projects obtained by PSYBAM or GAISAM groups. Figure 1 summarizes CIBERSAM UGR structure and research

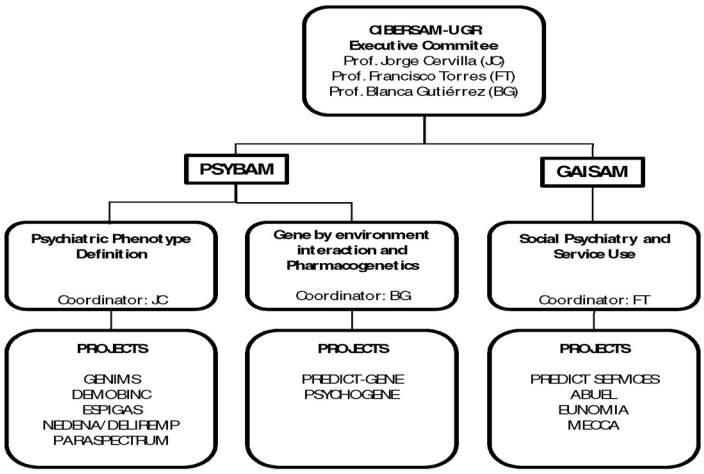

Figure 1. Organization of CIBERSAM-UGR and its main research lines and projects.

lines. CIBERSAM UGR is based at two sites in UGR: The Section of Psychiatry in the Faculty of Medicine (offices) and Biomedical Research Centre (labs). CIBERSAM UGR has formal links with the Institute of Psychiatry and University College and Royal Free Medical School in London, apart from many other international connections such as those represented by the DEMOBINC consortium and the MARISTAN network.

CIBERSAM UGR: Main Research Lines

As mentioned earlier, there are three main research lines on which our group is currently focusing (see Figure 1). All lines are orientated towards epidemiological psychiatry and each line is directed by a senior member of CIBERSAM, two of them (JC and BG) pertaining to PSYBAM research group and the other (FT) to GAISAM research group. PSYBAM lines are psychiatric phenotype redefinition, gene-by-environment interactions and psychopharmacogenetics in psychiatric disorders, whilst GAISAM focuses in social psychiatry and service-use patterns in mental health. Despite this, though, there is an important overlap across research groups as some members in PSYBAM work on GAISAM projects and vice-versa, all being part of the wider CIBERSAM UGR group.

The *Psychiatric Phenotype Definition* line includes a psychosis project and a depression-anxiety project, both of which have been funded by competition at public calls. The rationale beneath this line is that some, particularly psychotic, psychiatric disorders are not efficiently or validly defined and may be potentially misleading both research and clinical practice. The methodology here is to look at empirically tested phenomena elicited from standardized psychiatric examination of patients and explore from an atheoretical viewpoint how mental symptoms cluster and what such cluster correlate with. This may lead to either validation of current nosological entities or to empirical definition of new ones on which an external validation, usually with neurobiological or objective correlates, is elucidated. Main current projects in this line are the DELIREMP project[1] focused in delusional disorder, the NEDENA study[2], the PARASPECTRUM study on paranoid delusions[3], the ESPIGAS study[4,5] and the GENIMS-GAP project on first psychotic episodes currently under data-collection. We also have an ongoing re-analysis of the PREDICT Europe database[6] to explore depression and anxiety phenotypes.

The *Gene-by-Environment Interactions and Psycho-pharmacogenetics* line has its main interest on common affective disorders and psychotic disorders. Hence, depression and anxiety are the focus of the PREDICT-Gene study, funded by a National Research plus Development Plan grant, showing interactions by SERT genotype on the risk effect conferred by stressful life events or sexual abuse[7] as shown on Figure 2. This line also conveys sub-studies on genetic risk for depression[8, 9] with the innovative approach of adjusting genetic associations with depression by potential confounders occurring in large representative samples. More recently, an initial analysis on gene (COMT) by environment (Cannabis Use) interactions in psychotic disorders has produced our first GxE results in schizophrenia[10].

Finally, the *Social Psychiatry and Service Use* line has a long tradition of European collaborative research working on patterns of care[11], rehabilitation and, lately, social predictors of primary care depression as represented by the group's leading study PREDICT-D[6]. Table I shows the PREDICT-D prediction of

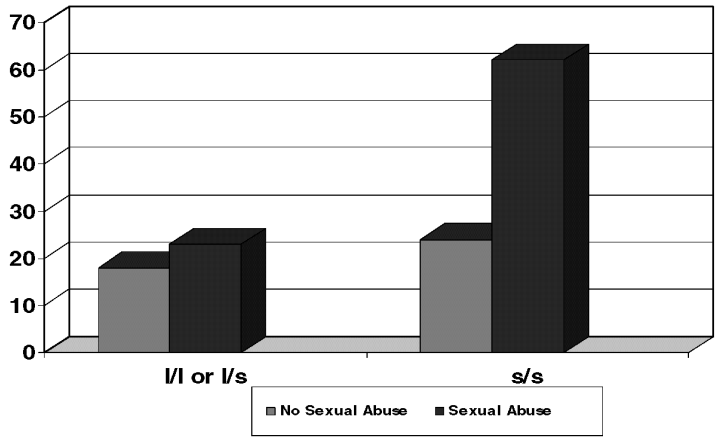

Figure 2. s/s Genotype at the SERT gene modifies the risk effect for depression conferred by previous sexual abuse.

Table I
Predictive variables in the PredictD Model for depression[6]

1. Sex
2. Age
3. Education
4. First degree relative with psychological problems
5. Lifetime depression
6. Difficulties with the paid or unpaid work
7. Physical health
8. Mental Health
9. Discrimination
10. Country

depression package for primary care. This line has had, and continues having, solid financing as has obtained competitive funding for the EUNOMIA, MECCA, DEMOBINC and ABUEL projects, among many others.

Teaching, Clinical Practice and Clinical Research Promotion in CIBERSAM UGR

Senior members in CIBERSAM UGR are deeply involved in both undergraduate and postgraduate teaching. Thus, they are responsible for undergraduate teaching medical students in UGR offering a wide variety of clinical subjects such as Psychiatry, Clinical Neurosciences, Psychosomatic Medicine and Social Psychiatry. Similarly, CIBERSAM UGR members contribute to several postgraduate teaching activities. Hence, we coordinate the Behavioural Neuroscience Module in the UGR MSc degree in Neuroscience and Pain. We also offer PhD supervision and teaching in two UGR PhD programmes PhD in Psychiatry and PhD in Neuroscience, the latter having being recently recognized nationally with a quality mention. At present, we are supervis-

ing over a dozen PhD students from Spain and South America. Some CIBERSAM UGR research members have teaching connections with the Institute of Psychiatry, King's College London, organizing regular Maudsley-based meetings, and/or with South American universities.

Clinical practice, in general adult psychiatry or clinical psychology, is also provided by members in CIBERSAM UGR. We have successfully linked our research activity with such practice having our main links with the Acute Psychiatric Unit in Hospital Universitario San Cecilio. Since recently CIBERSAM UGR hold a contract, via its director, to coordinate the Research Promotion Unit (UNISAM) within the Andalusian Mental Health Programme in the Sistema Andaluz de Salud (SAS). UNISAM is currently responsible for the development of a network of mental health Andalusian researchers who will be involved in prioritized regional research projects to be developed in many SAS mental health clinical resources. Tipically, clinicians who join such project must have attended at least one of the two introductory courses to practical mental health research currently being developed by CIBERSAM UGR members in coordination with the prestigious Andalusian Public Health School.

In summary, CIBERSAM UGR is one of the few groups active in international projects in southern Spain psychiatry and has the objective and the responsibility of promote high quality original research in mental health in Andalusia.

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RESEARCH AT THE MEDICAL IMAGING LABORATORY, CIBERSAM CB07/09/0031

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Research at the Medical Imaging Laboratory, CIBERSAM CB07/09/0031

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SPAIN

ABSTRACT – The Medical Imaging Laboratory is a research group within the Hospital General Universitario Gregorio Marañón. The main research line of the group is focused towards the development and exploitation of medical imaging techniques, including the development of new processing tools for image analysis in clinical and preclinical research. The group has a multi-disciplinary profile and a priority for translational research topics, derived from real problems faced by the clinical specialists. One of the main research areas is the development of technologies for molecular imaging, some of which have been transferred to the industry and are now among the top products of the market. These systems include high-resolution PET, CT and PET-CT. Over the last years the group has developed several software tools to enable quantification of multimodal brain images using morphometric and functional data. Some research applications of these hardware and software tools are illustrated in the paper.

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Resources

The Medical Imaging Laboratory was created in the early 90' as a small group embedded in the general research Department of the Hospital General Universitario Gregorio Marañón at Madrid. Parallel to the enormous expansion in the field of medical imaging, during the past decade the group underwent an exponential growth in human resources (from less than 5 to 35) and technical means. The facilities of the Neuroimaging Research Laboratory include a space of 350 m2 that include offices, electronic workshop, and animal imaging laboratory. The most significant facilities are molecular imaging scanners of several modalities, for preclinical use (high resolution CT, PET, MRI, SPECT, and Optical Imaging). Funding during the last six years has come from more than 30 national or international research projects granted to the group, from public or private programs, as well as from technology transfers to the industry.

Research

The main research line of the group is focused towards the development and exploitation of medical imaging techniques, including the development of new processing tools for image analysis in clinical and preclinical research. The group has a noticeable multi-disciplinary profile and its location within the Hospital warrants an excellent connection with clinicians and ensures a higher priority for translational research topics, derived from real problems faced by the clinical specialists. The multi-disciplinary composition of the group allows for a rapid validation of the results obtained in the research projects, also facilitating the technology transfer to industry. Some of the main research topics of the group in the field of neuroimaging are presented below.

High resolution imaging of laboratory small animals

Molecular imaging techniques applied to animal models are an excellent tool to study pathological processes. One of the main research areas in our group is the development of technologies for molecular imaging, some of which have been transferred to the industry and are now among the top products of the market. These systems include high-resolution positron emission scanners (PET) computerized tomography scanners (CT) and its combination (PET-CT) (Figure 1), nowadays one of the most useful tools for biomedical research in the area of molecular imaging[1,2]. PET enables the monitoring of biochemical processes "in vivo" at a molecular level. This technique has multiple applications in the development of new drugs, in the study of human diseases on animal models or in the characterization of the genomic expression and phenotypical changes caused by genetic manipulation (transgenic, knock-out or knock-in animals).

An ongoing imaging project deals with the cerebral damage produced by the new "design" drugs (MDMA, methamphetamine). The main objective of the study is to combine PET and CT techniques to evaluate the damage to serotonergic neurons and to determine whether there is damage to dopaminergic neurons, taking into account factors such as sex, type of drug and dosage scheme. The two substances selected were MDMA and methamphetamine, the former with a clear preference for the serotonergic system and perhaps for the dopaminergic system; and the latter with a preference for the dopaminergic system[3]. With the help of high-resolution animal PET-CT we can correlate serotoninergic and dopaminergic changes with changes in brain function and with its exact location in the brain. Furthermore, the study aims to determine to what extent the neurons may recover from the damage induced by MDMA.

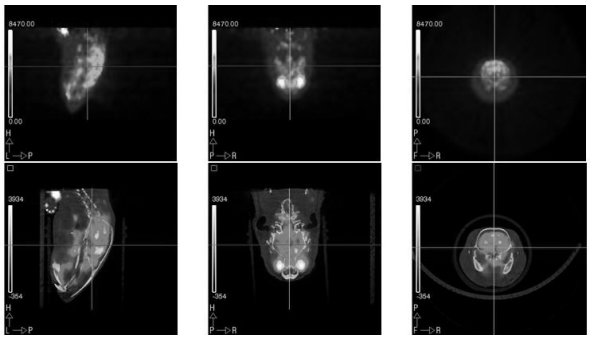

Figure 1. An illustration of molecular imaging. Triplanar view of an 18F-FDG PET rat study fused with a CT of the same animal. Images were acquired with the VrPET/CT, a system developed in our group.

Brain Imaging quantification

Over the last years the group has developed several software tools to enable quantification of multimodal brain images using morphometric and functional data. One of these software tools is based on the Talairach proportional grid system[4,5]. Using this tool we can benefit from the anatomical information of structural images to quantify functional images that have poor spatial resolution, like such as PET or perfusion (cerebral blood volume) scans (Figure 2).

The Talairach quantification tool is an application of the Talairach proportional grid system[6], used as a method for semiautomatic segmentation and analysis of MRI and functional images (PET, or Cerebral Blood Volume maps obtained by MR Perfusion weighted images). The method can be described as a multimodal application where the anatomical information of the MRI is used to build the Talairach grid and a co-registered functional image is superimposed on the same grid. By doing so, the Talairach-normalized tessellation of the brain is directly extended to functional images, allow-

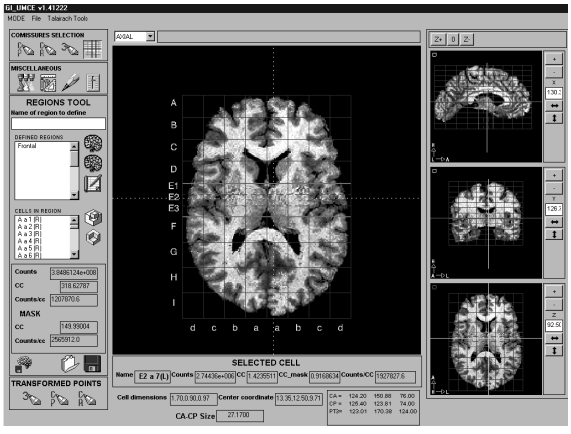

Figure 2. A screenshot of the software tool developed for volumetric and functional quantification of brain images. The triplanar view shows a Talairach grid built upon an MRI and a co-registered PET superimposed for quantification. For each of the 1,065 cells of the grid, volume and metabolic data is obtained for each brain tissue (total or WM, GM, CSF separately).

ing for a convenient regional analysis of volume and activity rates of brain structures, defined in the Talairach Atlas as sets of cells. This procedure requires minimal manipulation of brain geometry, thus fully preserving individual brain morphology. The brain standardization proposed in the Talairach grid system begins with a reorientation centered on the anterior and posterior commissures and the inter-hemispheric plane as the vertical axis, followed by a piecewise linear transformation that produces a tessellation of the brain into a 3D grid of 1,056 cells representing homologous brain regions across subjects. This subdivision of the brain according to the Talairach grid system allowed us to use it as the basis for a segmentation method for inter-subject comparisons, by defining brain regions of interest (ROI) as sets of 3D volume grid cells or 'boxels'. Following this procedure for defining ROI's we have been identified over 20 brain regions, from which we can obtain volume data for each tissue (Gray Matter, White Matter, and CSF), metabolic activity (PET) or perfusion (cerebral blood volume), for the whole brain parenchyma or separately for each tissue. Using this tool, we obtain data for more than 400 anatomical and functional variables[4,5]. This software have been used in numerous publications related to structural and functional alterations of psychiatric patients.

Effect of spatial normalization on voxel-wise studies

In pathologic brains with morphological alterations, the process of spatial normalization, as performed by Statistical Parametric Mapping (SPM) methods, may introduce a confounding effect in the measurement of functional (metabolic) activity data. We have investigated the effect of the spatial normalization of PET images, using MRI and PET studies of schizophrenic patients and controls[7]. Using the Talairach-based segmentation tool mentioned above, and manual segmentation, we measured regional metabolic activity in the untransformed brains and after their spatial normalization. We observed that the spatial normalization has little effect for large ROIs, such as the main brain lobes, even in brains showing pronounced morphological abnormalities. However, smaller structures as the caudate nucleus show a considerable change in metabolic activity values after normalization. This normalization bias is much larger in patients than in controls, and may lead to artifactual differences between both groups if the data are assessed by means of voxel-wise methods (SPM). We concluded that spatial normalization of the PET images of pathologic brains may introduce a potential source of error that should be taken into account in the analysis of functional data, in particular, when studying small brain nuclei as the caudate[7].

Neuroimaging studies in neurogical and mental diseases

In the field of medical imaging, the neurogical and mental diseases are one of the most typical examples of problems which require a multidisciplinary approach. Following a multimodality strategy to describe structural and functional brain alterations, in our research group we make use of the following techniques: structural imaging (MR, CT), for volumetric and morphometric studies; magnetic resonance spectroscopy (MRS), for measurements of some neural metabolites (N-acetil-

aspartate, creatine, choline, mio-inositol); perfusion, to measure microvascularization of cerebral tissue; diffusion tensor imaging, for measurements of White Matter anisotropy and tractography; and PET imaging using 18F-FDG as tracer, for measurement of glucose metabolism as a marker of neuronal activity.

Schizophrenia

The interest of quantitative data extracted from the neuroimaging studies in schizophrenia derives from multiple previous findings of groups of schizophrenic patients who show functional and structural brain alterations (e.g., atrophy of frontal cortex), sometimes related to clinical manifestations (predominating symptoms, evolution, pharmacological response) or to treatment. To generate accurate quantitative data, we measure the volume of the main brain lobes and their tissues (WM, GM and CSF), exploring the structural alterations detectable in chronic and recent onset patients. Among the key findings in our studies, we have found significant clinical and biological differences between treatment resistant and non treatment resistant schizophrenia patients[8]. These differences included greater clinical severity in the treatment resistant sample at baseline, and different baseline anatomical (volumetric) and electrophysiological (response to P300) parameters, together with longitudinal changes in cerebral volumes after treatment with atypical neuroleptics. The structural differences showed a significant degree of sensitivity and specificity, which supports the existence of a distinct subgroup of patients with marked frontal deficits and a poorer response to treatment within the spectrum of schizophrenia[8].

Alzheimer's disease

An early diagnosis of AD and its discrimination against other types of dementias (Lewy, fronto-temporal) are key issues to establish the appropriate treatment, the prognosis and a forecast of the forthcoming social needs of the patient. To achieve an earlier and more reliable diagnosis, a combined used of several imaging techniques have been proposed, with the aim of detecting early changes associated with the disease. In order to detect structural and functional alterations, 18F-FDG PET images are used in combination with four MRI techniques: 1) Anatomical image sequences T1 and T2, for volumetric measurements; 2) spectroscopic studies, to assess the biochemical changes in neurological metabolite markers such as N-acetyl-aspartate, Choline, and Creatine; 3) perfusion studies, to assess the functionality of parenchymal microvasculature and 4) DTI studies, to asses the integrity of white matter tracts. Preliminary results show lower volumes of GM and less blood volume flow in the temporal lobe of patients with severe dementia symptoms compared with patients with mild dementia, suggesting that we can distinguish between different degrees of cognitive impairment at early stages of AD[9].

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TOWARDS THE UNDERSTANDING OF THE GENETIC COMPLEXITY OF FUNCTIONAL PSYCHOSES

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Towards the understanding of the genetic complexity of functional psychoses

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SPAIN

ABSTRACT – One of the main lines of our group focuses on the research of genetic and biological risk factors involved in functional psychosis (schizophrenia and bipolar disorder). Our studies are based on case-control, family and twin designs and are conducted in close collaboration with clinical and basic research groups from other Spanish and European Institutions.

Recent results coming from the *molecular genetics analyses* have been focused on: i) the identification of genetic variability on chromosome 1q in relation to the syndromal definition of functional psychoses, ii) the identification of the interleukin-1 cluster , on chromosome 2q13, as a shared genetic risk factor for both schizophrenia and bipolar disorder, iii) the relationship between this genomic area and functional and morphological brain changes observed by neuroimaging techniques in both disorders, iv) the identification of CNVs related to the risk for psychoses and v) the role of the dysbindin gene in neurocognitive profiles and premorbid adjustment in early onset psychoses.

Our results from the *studies based on prenatal markers of brain instability* have contributed to the identification of three congenital dermatoglyphic risk factors in schizophre-

Other lines of research in our group (G8-CIBERSAM) include: pharmacogenetics, molecular genetics of depression, gene-environmental interaction in affective disorders, twin studies and neurocognition and psychoses proneness. For additional information, please consult http://www.cibersam.es/opencms/opencms/system/modules/es.oneclick.cibersam/elements/jsp/grupo/grupos.jsp

nia including low ab-ridge count, presence of ridge dissociations and presence of abnormal palmar flexion creases.

Gene-environmental interactions have also been explored in schizophrenia and healthy relatives involving the Val158Met polymorphism in COMT gene and cannabis use; these studies have provided evidence of synergism between the Val allele and exposure to cannabis in the causation of psychosis. New projects based on epigenetics are currently conducted in our group in order to understand the genetic complexity of functional psychoses.

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The organization and functional capacity of the human brain depends upon an extraordinary set and sequence of developmental and environmental experiences that influence the expression of the genome. Unfortunately, this sequence is vulnerable to extreme, repetitive, or abnormal patterns of stress during critical periods of brain development that can impair the activity of neuroregulatory systems leading in the long term to profound and lasting neurobehavioral consequences as those observed in patients with functional psychoses.

Functional psychoses include a group of severe complex mental disorders such as schizophrenia and bipolar disorder that are relatively common in all cultures and human populations (*life time risk range 1%-4%*). Although substantial evidence based on family, twin and adoption studies supports the heritability of these disorders (h^2~85%) the nature of the genetic factors involved in their etiology remains still unknown. In this sense, a robust body of evidence suggests that at least a part of these unknown genetic factors may be shared between schizophrenia and bipolar disorders[1]

Although we have improved our understanding of the genetic basis of mental disorders, only 5% of the variance disorder attributable to genetic factors has been well recognized (see Figure 1). Moreover, twin

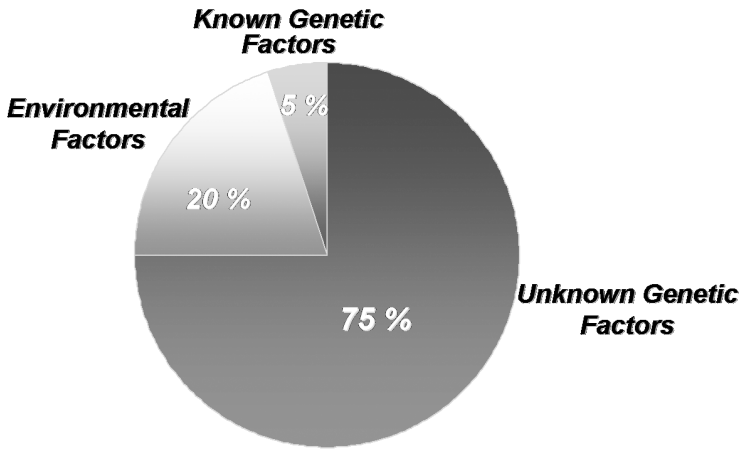

Figure 1. Contribution of the genetic and environmental factors in the expression of the phenotype variability of schizophrenia (Adapted form Pak Sham, 2008, XIVth Biennal Winter Workshop on schizophrenia and bipolar disorder)

and adoption studies have pointed out the important role of environmental factors, especially those associated with prenatal neurodevelopment processes, and to emotional or cognitive stressful life events as well as drug exposure.

Genetic and environmental factors in psychoses

Classical genetic studies and new approaches based on CNVs

Genome-wide linkage studies conclude that there are, at least, 10 different chromosome regions of definitive interest in schizophrenia[2]. One of these is situated at chromosome 1q and studies on this region suggest the possibility of a susceptibility gene for some families of schizophrenic patients[3,4].

Other positional candidate genes (i.e. candidate genes because of their function and their position at the genome) show a high potential in psychosis research. These are the neuregulin-1 (NRG1)[5,6], dysbindin (DTNBP1)[7], the interleukin-1 cluster (IL-1)[8], the D-amino acid oxidase and its activator complex (DAO and G72) and the dopaminergic receptors D1 and D4 (DRD1 and DRD4)[2]. The gene encoding for the Cathecol-O-Methyl Transferase (COMT) has also received considerable attention as a functional candidate gene and in the study of cognitive functions both in patients and healthy individuals[9,10].

Lastly, hundreds of submicroscopic copy-number variations (CNVs) of DNA segments ranging from kilobases to megabases in size have been recently described in the human genome. These structural variants can contain entire genes and their regulatory regions and, although in some genomic regions have no obvious phenotypic consequences, in others can determine the gene dosage. Accumulating evidence indicates that multiple, rare, and recent individual specific CNVs, with major effects on genes from neurodevelopmental pathways, may be involved in schizophrenia aetiology increasing the risk around 15 times in some cases[11,12]. However, this type of rare CNVs can explain a reduced number of cases.

Prenatal markers of neurodevelopmental instability in schizophrenia: the dermatoglyphic studies

Dermatoglyphic abnormalities may constitute enduring evidence of a prenatal insult that occurred before the third trimester of intrauterine life. Fingerprints are formed in the epidermis during this prenatal period coinciding with the neuronal cell migration to the cerebral cortex. During this time, dermatoglyphic morphology can be influenced by environmental factors constituting a *fossilized* evidence of the existence of prenatal instability.

Three congenital dermatoglyphic malformations (low ab-ridge count, ridge dissociations and abnormal palmar flexion creases) carry special interest for research in disorders that are hypothesized to have a neurodevelopmental origin such as schizophrenia and bipolar disorder. Independent studies have reported dermatoglyphic changes in these variables in: i) psychiatric patients compared to controls from the general population[13,14]; ii) family studies including first degree relatives of patients as a proxy for genetic vulnerability[15,16]; and iii) twin studies[17,18]. The fact that genetically identical twins were discordant for dermatoglyphic markers and that first degree relatives presented intermediate rates of dermatoglyphic anomalies between patients

and controls, strongly suggested a mechanism involving an interaction of genotype and environment, whereby an environmental insult influences the expression of genetic liability.

Interestingly, we have also described similar dermatoglyphic patterns in relation to intermediate phenotypes of interest in schizophrenia as schizotypy[19] or in patients with velocardial facial syndrome[20].

COMT and cannabis: A model for the understanding of gene-environmental (GxE) interactions in schizophrenia

There is consistent, albeit preliminary, evidence for GxE interactions from studies using direct molecular genetic measures of genetic variation in psychosis. Recent GxE studies have focused on COMT gene Val158Met polymorphism providing evidence of synergism between the Val allele and exposure to cannabis in the causation of psychosis. The Val carriers were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder years after the exposure to cannabis[21]. Val carriers were also found to display more psychotic experiences in reaction to cannabis use in an experimental challenge study[22] and an experience-sampling study consistent with interaction[23], although both findings were conditional on prior evidence of psychometric psychosis liability.

Other molecular approaches to the understanding of environmental influences in psychoses: Epigenetics

The traditional explanation for phenotypic discordance within MZ twins is the influence of non-shared environmental factors. However, several authors have suggested the possible involvement of epigenetic mechanisms, which result in changes that modify gene expression. Several lines of evidence suggest that such epigenetic factors may influence susceptibility to mental disorders including schizophrenia and bipolar disorder. Although this is a new field of research, there is some evidence for psychosis-associated DNA methylation differences in numerous loci including several involved in glutamatergic and GABAergic neurotransmission[24], brain development[25] and X-inactivation[26].

Phenotypes and endophenotypes of interest in the genetic research of psychoses

Endophenotypes defined by functional and structural neuroimaging

Endophenotypes, or intermediate phenotypes, are quantitative neurobiological traits related to the genetic risk for schizophrenia which, hypothetically, involve simpler genetic pathways than whole clinical phenotypes; this neurobiological traits may avoid the limitations of genetic studies based on a classical categorical definition used in case-control or family designs. In this sense, neuroimaging-defined phenotypes might represent such interesting phenotypes, being enlargement of cerebral ventricles one of the most robust candidate endophenotypes in schizophrenia[27].

Our group analyzed the genetic variability mapped to the Interleukin-1 cluster (chromosome 2q13), where interleukin-1 beta (IL1B), its endogenous antagonist (IL1RN) and other IL-1 family genes are located. An

haplotypic combination in this cluster was associated with an increased risk for both schizophrenia and bipolar disorder[8]. Previous evidence has already shown the importance of IL-1 signalling molecules in neuredevelopmental and neurodegenerative processes, as well as the influence of genetic variability on neuroimaging measures.

Our results showed that genetic variants at IL-1 cluster were associated with an increase of lateral ventricles volume as well as with a differential activation of dorso-lateral prefrontal cortex in schizophrenic patients[28,29]. Likewise, our analyses detected an effect of this genetic variability on the grey matter volume in frontal regions of the brain in bipolar disorder patients[30]. These shared effects of IL-1 cluster on neuroimaging measurements in schizophrenia and bipolar disorder fit with a recent metaanalysis of linkage studies in schizophrenia[2] and linkage studies in bipolar disorder pedigrees[31], since both of them point towards the IL-1 cluster region on chromosome 2q as a shared risk factor for both disorders.

Early onset cases as a phenotype of interest in genetic studies

The greater clinical severity of schizophrenia in childhood and adolescence, the increased familiarity and the clinical and neurobiological continuity with adult forms, have encouraged researchers to investigate genetic factors in this group. This research strategy has emerged as a useful tool to reduce the illness heterogeneity and to increase the power to detect genetic factors that may be more salient in early onset cases.

Among the most relevant findings appear the results on the Neuregulin 1 gene (NRG1) chromosome 8p12. Interestingly, early onset patients carrying the risk variants identified in NRG1 gene showed a poorer premorbid social functioning and a greater total gray and white matter volume in childhood and a steeper rate of subsequent decline in volume into adolescence[32]. These results are the first demonstration of a disease-specific pattern of gene action in the disease.

Another gene that has captured much interest in early onset psychoses is the one encoding the dystrobrevin binding protein 1 (DTNBP1, chromosome 6p22), which influences neurotransmission and so contributes to the cognitive dysfunctions in schizophrenia. Its genetic variability has been related to poor premorbid adjustment, supporting the contribution of this gene to early neurodevelopmental impairment[33].

Recently, a preliminary study based on affected families of Spanish origin conducted in our group, under CIBERSAM coordination, has further described the role of DTNBP1 on both early onset schizophrenia and bipolar disorders. Furthermore, this study has shown an association between some polymorphic markers and poorer cognitive abilities[34].

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A STUDY OF THE SIGNALLING PROTEINS REGULATED BY G PROTEIN-COUPLED RECEPTORS

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A study of the signalling proteins regulated by G protein-coupled receptors

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SPAIN

ABSTRACT – G protein coupled receptors (GPCRs) are the targets for a large number of active compounds including analgesic, antipsychotic and antidepressant drugs. The dysfunction of GPCRs and of the signalling proteins with which they interact, are associated with most of the mental disorders characterized to date. Thus, in order to detect the alterations that are most directly responsible for these pathological states it is essential to increase our understanding of how these regulatory mechanisms operate at the synapse. Using the mu-opioid receptor (MOR) as a model, our studies have defined a series of signalling proteins that are virtually restricted to nervous tissue and which are essential to regulate the stamina of MOR signalling. The Gz-proteins and their regulators RGSZ1/RGSZ2 are good examples of such regulators, as are the RGS-R7 protein subfamily, the HINT-1 protein, etc. We recently identified an association between a series of GPCRs and NMDARs, which can be disrupted by agonists through the recruitment of PKC by free zinc ions generated by the NMDAR/nNOS cascade. These elements participate in the physiology of zinc which is consistently altered in schizophrenia, bipolar disease and major depression. Conclusions: The collaboration between clinical specialists and more basic research should accelerate the discovery of signalling-related genes associated with an increased risk of suffering psychiatric disorders. The knowledge gained will help us to switch from palliative treatments towards preventive or healing therapeutic strategies.

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Our understanding of the elements involved in the internalization and processing of extracellular signals has expanded greatly in the last few years. Functional and gene expression studies have revealed an ever-growing number of proteins that are involved in the regulation of neural GPCRs. By combining behavioural and molecular strategies our group have studied the signalling proteins that co-operate in the processing of agonist-initiated messages. Moreover, we have characterized novel cellular substrates that attenuate or reverse the development of MOR desensitization to morphine. This research will ultimately lead to a better comprehension of the molecular bases of disease, while considering each potential drug target in its full biological context. The experience of our group in the study of MOR regulation in the nervous system is now being applied to explore those receptor systems implicated in the pathophysiology of psychiatric disorders.

The effect of RGS Proteins on GPCR Signalling

The MOR associates with Gi/o/z/q proteins that participate in the propagation of the information carried by its agonists and that regulate the strength of their signals. One of the major advances in our understanding of receptor desensitization in the CNS came about through the discovery of the regulators of G-protein signalling (RGS) proteins. It is now accepted that the potency and duration of the effects initiated at the GPCRs depends on the continuous and efficient re-constitution of the pool of receptor-regulated heterotrimeric G proteins[1]. By rapidly deactivating the Gα-GTP subunits, the RGS proteins help synchronize the presence of agonists at the receptor with the regulation of their effectors. The RGS family is made up of approximately 30 members that mostly act as negative modulators of GPCR-mediated signalling[2] through one of the following mechanisms: acceleration of Gα inactivation by stimulating Gα-GTPase activity; antagonism of G-protein effectors[3]; or the sequestering of Gα-subunits[4]. Functional studies in knock-out animals or local knock-down of target proteins through antisense oligodeoxynucleotide injection have shown that RGS proteins of the RZ, R7, R12 and R4 subfamilies play a crucial role in modulating the effects of opioids, and in the development of tolerance to morphine[4].

The RGS2, RGS4 and RGS8 are all members of the R4 subfamily that are thought to regulate opioid receptor function through the GAP activity of their RGS domains. Moreover, opioid signalling may also regulate RGS expression and function and indeed, RGS4 mRNA is up-regulated by agonist-induced opioid-receptor activation in the rat brain and in other neuronal tissues[5]. This reflects the activity of a negative feedback loop in which opioid-receptor signalling induces the up-regulation of RGS mRNA and the proteins encoded in turn dampen the opioid's signals. Certain RGS members of the R4 subfamily have been linked to the severity of schizophrenia and treatment responsiveness. Indeed, while RGS4 and diacylglycerol kinase, the molecule most commonly associated with bipolar disorder, normally serve to inhibit intracellular signalling via phosphatidylinositol-PKC[6]. RGS2 and RGS5 are associated with the severity of the symptoms of schizophrenia[7].

Recent work from our group has revealed that the RGS-R7 (RGS7, RGS9-2 and RGS11) and RGSZ1/Z2 proteins sequester morphine-activated Gα subunits, thereby promoting desensitization to the action of GPCR agonists[4,8-11]. When antisense technology is

used, all members of the R7 subfamily display a negative regulatory effect on the action of morphine[12]. Besides the potential role of RGS9-2/11 proteins in opioid tolerance, selective expression of an RGS-9 construct in the nucleus accumbens also abolished the exaggerated sensitivity to the reward properties of morphine evident in RGS-9 knockout mice. During chronic morphine treatment, the mRNA expression of RGS7, RGS9-2, and RGS11 increased in most regions of the brain, especially in the striatum and PAG[13]. The expression of these proteins also increased after chronic but not acute morphine administration. RGS proteins of this subfamily are also involved in the genesis of mental diseases. Indeed, reduced levels of RGS9-2 expression in both an animal model of schizophrenia and in post-mortem schizophrenia brains has been observed. These findings provide further evidence implicating RGS9-2 as a candidate gene in schizophrenia[14].

RGS-RZ proteins are also linked to the regulation of MORs. Their activity on receptor-activated Gα subunits reduces the amplitude and duration of morphine analgesia. The impairment of RGSZ1 expression increases the potency of morphine and its effects are notably prolonged[10]. In contrast, knockdown of the RGSZ2 protein initially promotes a sharp increase in analgesia but also it results in the rapid desensitization of some target effectors[11]. These results indicate that RGSZ1 controls only some of the MOR-activated Gα subunits. However, the control of RGSZ2 on these proteins is more extended and when it fails to act, activated Gα subunits over regulate the effectors and promote their uncoupling from the control of MORs, thereby desensitizing these receptors. Sumoylated forms of the RGS-Rz proteins are associated with MORs, and Gαi/z subunits co-precipitate with these sumoylated forms of RGSZ1/Z2[15]. Therefore, sumoylation regulates the biological activity of RGS-Rz proteins, and it is likely to switch their behaviour from that of de-activators for MOR-activated Gα subunits to that of a scaffold protein for specific signalling proteins.

Finally, knock-down of RGS14 (member of RGS-R12 subfamily) increases morphine-induced phosphorylation and internalization of MORs[16]. In this case, morphine produces weaker activation of CaMKII as well as MOR desensitization. Thus, morphine triggers a mechanism mediated by NMDAR/CaMKII to desensitize the MORs in the plasma membrane, and receptor phosphorylation/internalization disrupts this negative feedback regulation[17].

In summary, RGS proteins are essential to regulate GPCR signalling and their dysfunction is increasingly being associated with mental disorders. Most RGS proteins display specificity for a subset of receptor-regulated G proteins, and this characteristic should be therapeutically exploited to selectively regulate post-receptor signalling pathways. Thus, RGS proteins may be useful markers of disease, as well as targets for therapies aimed at regulating the selectivity and efficacy of receptor-targeted drugs, or endogenous neurotransmitters.

The HINT1-RGSZ signalling module in MOR desensitization: the connection with zinc

As stated previously, MOR signalling is coupled to the brain-specific Gz protein as well as its selective regulators, the RGSZ1/Z2 proteins. The protein kinase C-interacting

protein (PKCI), also named histidine triad nucleotide-binding protein 1 (HINT1), acts as an adaptor that connects the cytosolic C terminus of MORs with the cysteine rich domain of RGSZ1/Z2 proteins. As such, HINT1 helps control the activated GαzGTP subunits that may otherwise promote MOR desensitization (see Figure 1). We have shown that the MOR–HINT1–RGSZ signalling module recruits PKCγ in response to morphine with the aid of free zinc ions generated by the NMDAR/nNOS cascade[18]. This PKCγ is then activated, probably by DAG, and participates in the potentiation of NMDAR currents that increase the entrance of free Ca^{2+} and Zn^{2+} ions, and that augment the number and availability of Ca^{2+}-calmodulin complexes. The ensuing activation of CaMKII alters the coupling of MORs to the regulated G proteins and reduces the signalling strength of morphine[18]. It is worth keeping in mind that the antidepressant-like effects of zinc in rodent tests/models of depression are associated with NMDA receptors and the L-arginine/nitric oxide (NO) pathway[19]. Like antidepressants, zinc induces brain derived neurotrophic factor (BDNF) gene expression and the synaptic pool of zinc in the hippocampus augments. Clinical studies suggest the important role of zinc homeostasis in certain psychopathologies and depression, as well as the therapeutic and potential clinical antidepressant activity of this ion. Moreover, serum hypozincemia was associated with depression, which was normalized by effective antidepressant treatment.

Although the PKCI/HINT1 protein is expressed extensively in the mammalian brain, its physiological function in the CNS remains virtually unknown. Interestingly, PKCI/HINT1 has been identified as one of the candidate molecules involved in the neuropathology of schizophrenia in microarray analysis[20] and functional genomic approaches[21]. The expression of this gene is decreased in the frontal cortex of individuals with schizophrenia, suggesting the involvement of this protein in the pathophysiology of the disease. Moreover, systemic administration of agonists that act directly on the DA receptor, such as apomorphine, significantly increased locomotor activity in

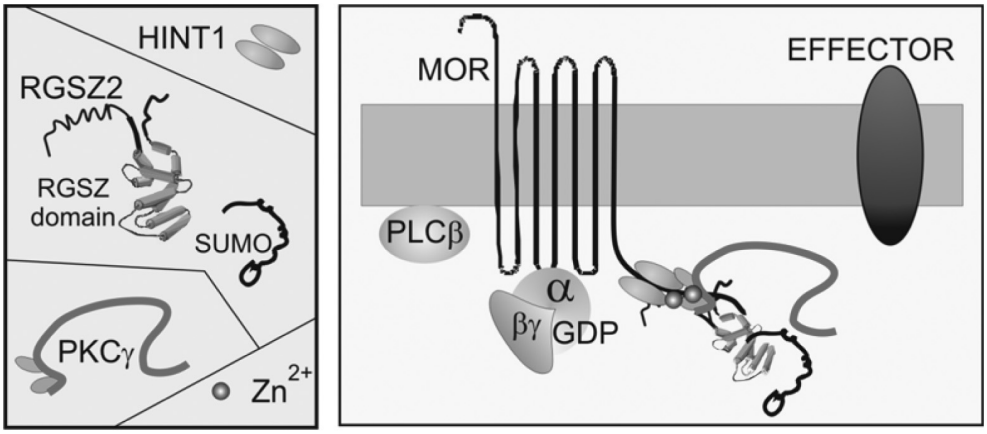

Figure 1. Diagram showing the association between the carboxyl tail of the mu opioid receptor (MOR), the heterotrimeric G protein and the PKCI/HINT1-RGSZ complex, where a series of signalling proteins associate. PKCI/HINT1 binds to the cysteine rich domains of RGSZ. After activation by agonists like morphine the HINT/RGSZ complex binds PKCγ in a zinc dependent manner.

PKCI/HINT1 KO mice[22]. Hence, postsynaptic DA function is augmented in these animals, indicating that the absence of this protein may be associated with a deregulation of postsynaptic DA transmission.

Interaction between GPCRs and *N*-methyl- D- aspartate receptors

Dopamine was the first neurotransmitter system to be implicated in schizophrenia. An important advance in understanding neurotransmitter interactions in schizophrenia was the finding that the hyperdopaminergic state may be a consequence of NMDAR hypofunction. The ability of NMDAR antagonists such as phencyclidine, ketamine and MK-801 (dizocilpine) to exacerbate psychotic symptoms, including the entire range of positive and negative symptoms of schizophrenia in healthy individuals[23], suggested that schizophrenia is related to altered glutamatergic neurotransmission. The theory of NMDA hypofunction in schizophrenia is also supported by novel genetic findings. Several of the recently discovered putative schizophrenia genes may interact with the glutamate pathway by exerting different effects on NMDA receptor mediated transmission[24].

Also, the existing data strongly support the idea that NMDAR fulfils a pivotal role in controlling MOR function in the nervous system (see 17 for review). As mentioned above, negative feedback from the NMDARs contributes to the desensitization of activated MORs[18,25]. Notably, in the absence of the PKCI/HINT1 protein, this loop is broken and morphine sends no activating signals toward the NMDAR. Thus, there is an increased response to morphine that could correspond to the hyperdopaminergic state established as a consequence of NMDAR hypofunction in HINT1 knockout mice[21], as well as in schizophrenia[22].

The goal of systems biology is to understand how genes work together in biochemical pathways and cellular networks. This is especially important in the study of mental diseases since these disorders result from the synergistic interaction of many risk associated genes, none of which have an excessively significant effect. Modern medicine couples psychological therapies with the advances in our understanding of these pathologies and here, the analysis of the neurobiological components involved in mental illnesses is certainly of great relevance. Among the elements involved in these complex processes are the surface receptors, the components of the signalling cascades (G-proteins, RGS-proteins, enzymes, effectors, ionic channels), and those implicated in synaptic plasticity, the modulation of downstream gene expression and the morphological changes in specific brain areas. The work of preclinical groups such as ours will contribute to our understanding of these molecular aspects, providing disease markers as well as a series of candidate therapeutic targets.

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The author(s) declare that they have no competing interests.

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WHY DO BIPOLAR MEN NOT COMPLY WITH TREATMENT? THE SPANISH CIBERSAM DATA

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Why do bipolar men not comply with treatment? The Spanish CIBERSAM data

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ABSTRACT – Compliance with pharmacotherapy for the treatment of Bipolar Disorder (BPD) is necessary to prevent recurrence of affective episodes, which have been associated with increased morbidity risk, treatment non-response, full syndromal recurrence and suicidality. While male gender is one of the specific factors associated with treatment non-compliance in BPD, there have been no specific studies to date on the influence of gender in the adherence to BPD treatment. The objectives of this paper are to describe adherence in BPD in relation with gender in a well-defined catchment area in Vitoria (Spain, CIBERSAM) and the factors associated with it. We use the following methods: patients diagnosed type-I BPD were evaluated in 1994 and began long-term prophylactic treatment. They were followed up for 10 years and underwent assessments at ≤ 8-week intervals to review their morbidity, abuse of alcohol or other substances, hospitalizations, suicide attempts, use and doses of all psychotropic agents, with estimates of adherence to the prescribed, primary mood stabilizing regimen. Bivariate analyses were done to compare compliance between men and women. Logistic regression models were applied to study the factors associated with non-compliance in men. The results show that women were more adherent to the treatment than men. Non-adherent men had higher substance abuse, more mixed and manic episodes and more hospitalizations than men who complied with treatment. Non-adherent women were not married and experienced more suicide attempts.

Conclusions: The findings support the increasing body of evidence that there are important differences in adherence with regard to gender, and that men need special preventive care for manic relapses and special treatment for improving their compliance.

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Introduction

CIBERSAM is a Spanish mental health research network and Santiago Apostol Hospital, Vitoria, is one of its nodes. Research is focused on Bipolar Disorder (BPD) and first psychotic episodes, and includes genetic, neurobiological, epidemiological, clinical, psychopharmacological and psychological investigations. Its first publications concerned psychotic symptoms and diagnosis in BPD[1,2] and also suicide, drug abuse and depressive severity as a prognostic factor of BPD[3]. Another area of special interest is mixed states and rapid cycling[4]. Therefore, one of its major interests is the study of prognostic factors that can be modified in order to improve prognosis in these patients.

One of the main interests in recent years has been the study of adherence to medications in BPD, as this is one of the factors related with outcome that may be modified. Compliance with pharmacotherapy for the treatment of BPD is necessary to prevent the recurrence of affective episodes, which have been associated with cumulative increases in morbidity risks, treatment non-response, full syndromal recurrence and suicidality[3,5-7]. In fact, impaired judgment, rapidly fluctuating moods, and the long-term nature of living with mood instability may affect the ability of a person with BPD to take their medication as prescribed or engage in other treatments to manage the illness[8]. Estimates of non-compliance with medication in BPD range from 12% to 64%, and longer follow-up intervals account for higher rates of non-compliance[9,10]. Lithium, the gold standard treatment in BPD, had a high rate of discontinuation and short-term prescription, with a median adherence time of only 76 days in a six-year follow-up study.

Numerous studies have identified specific factors associated with treatment non-compliance in BPD, including young age, male sex, a lower level of education, being single, comorbid abuse of alcohol and drugs, and excess affective morbidity[6,11]. Although men have been described as being less adherent than women, there are no specific studies on gender differences in the adherence to BPD treatment.

This study investigated adherence to BPD treatment with regard to gender and other factors related with it in a well-defined catchment area.

Method

Subjects

Following the review and approval of the study protocol by the Santiago Apostol University Medical Center IRB in Vitoria, Spain, patients diagnosed type-I BPD were evaluated in 1994 and began long-term prophylactic treatment. They were followed up by the University Health Services, which provide comprehensive psychiatric services

to a Basque regional population of 300,000, independent of economic status, including the only psychiatric emergency and inpatient service in the region. Exclusion criteria were illness or treatment for < 2 years or lack of a family member to participate in the initial and follow-up assessments.

Initially, 78 patients were treated clinically with lithium carbonate as the exclusive mood stabilizing agent, and 72 were followed up for ≥ 5 years. Among the study sample, 71 were followed up from 1994 to 2004 and one committed suicide in year 5. The six subjects excluded from the present analysis were three requiring alternative treatments and three lost to follow-up within 2 years. Study patients starting with lithium monotherapy could receive other adjunctive treatment (most often low doses of antipsychotic agents and rarely antidepressants) during the follow-up, provided that lithium remained their primary mood stabilizer.

Data collection

All study subjects underwent follow-up assessments at ≤ 8-week intervals to review their morbidity, abuse of alcohol or other substances, hospitalizations, suicide attempts, use and doses of all psychotropic agents, with estimates of adherence to the prescribed, primary mood stabilizing regimen. Treatment adherence was rated as good or adequate when ≥ 90% of bimonthly serum lithium assays remained consistently ≥ 0.50 mEq/L, and adherence was verified[12]. This specifically evaluated according to whether subjects took prescribed medicines consistently at the indicated time, only rarely omitted doses (less than once per week), and did not stop taking medicines for more than 1 day in 8 weeks. Treatment adherence not meeting these criteria was considered inadequate or poor[9].

During follow-up and in addition to bimonthly visits, major reassessments were carried out with patients and their designated family observers at 2 and 10 years of follow-up (1996 and 2004).

Data analyses

Our primary aim was to relate the factors associated with pharmacological adherence and gender. We studied adherence in men and women independently in relation to the following factors: substance abuse, marital status, hospitalization (as the episode of depression, mixed mania), suicide attempts, age of disease onset, family history, hospitalizations in prior years, suicide attempts prior to inclusion, years of treatment and episodes during treatment (depression, mixed mania).

Male and female factors of adherence were based on bivariate analyses: *t*-test for continuous variables and chi-square or Fisher's exact test for categorical variables. Data are reported as mean with standard deviations, frequencies or percentages. Two-tailed $p < 0.05$ was required for statistical significance and $p < 0.1$ was required for statistical trend. We performed two logistic regressions with the variables significant in the bivariate analyses.

Results

The sample comprised 72 subjects, and at inclusion the men and women were 44.00 ± 13.65 and 43.57 ± 16.42 years old respectively. During follow-up, 16/72 (22.2%) were considered poorly adherent to lithium treatment, 5 on the basis of low serum lithium levels and 11 by both clinical assessments and assays. The age at onset of BPD

in adherent men was 30 ± 15.38, in adherent women 28.44 ± 11.57, in non-adherent men 24.31 ± 8.31 and in non-adherent women 19.33 ± 2.52. Age at onset was younger in the non-compliant group but differences were only statistically significant in women ($t = 3.773$, $p = 0.002$).

Women were more adherent to treatment than men. 60.61% of men were considered adherent vs. 39.39% who were considered non-adherent. 93.3% of women were adherent to treatment vs. 7.69 % who were not. Men tended to abuse substances more frequently than women ($\chi^2 = 3.819$, $p = 0.051$). Non-adherent men had higher substance abuse than adherent men ($\chi^2 = 3.813$, $p = 0.05$). Substance abuse was not related with adherence in women. Civil status was related with adherence only in women. Woman who were adherent were all married while all the non-adherent women had another civil status ($F = 0.024$).

With regard to BPD episodes, non- adherent men had significantly more episodes, the difference being significant in mixed and manic episodes but not in hypomanic or depressive episodes (Table I). On the contrary, no such effect was evidenced in the women. In relation to hospitalisations non-adherent men had more hospitalizations than compliant men (Table I). In the female groups there were no differences in hospitalisations in relation with compliance, unlike with suicide attempts. Non-adherent women had more suicide attempts ($F = 0.05$) than compliant woman, while there were no differences in the male group.

In logistic regressions (Table II) the dependent variable was adherence to treatment in the group of men, as there were very few non-adherent women. In men the number of admissions for manic episode and the number of mixed hospitalisations were statistically signif-

Table I
Sociodemographic and clinical data

Variable	Men		Statistic	P	Women		Statistic	P
	Adherents (20)	No adherentes (13)			Adherents (36)	No adherents (3)		
Substance abuse	10% (2)	38.5% (5)	$\chi^2 = 3.819$	0.051	2.8% (1)	33.3% (1)	F	0.150
Married	50% (10)	23.1% (3)	$\chi^2 = 2.392$	0.122	75% (27)	0.0% (0)	F	0.024
Hospitalization								
All hosp.	2.00 ± 1.89	6.69 ± 5.17	t = -3.719	0.001	1.91 ± 2.64	4.33 ± 3.79	t = -1.481	0.384
Depression	0.50 ± 1.05	2.46 ± 3.26	t = -2.518	0.017	0.86 ± 1.68	1.33 ± 2.31	t = -0.349	0.758
Mixed	0.25 ± 0.716	1.46 ± 2.57	t = -2.007	0.054	0.39 ± 0.77	0.67 ± 1.15	t = -0.409	0.720
Manic	1.25 ± 1.16	2.77 ± 2.13	t = -2.654	0.012	0.72 ± 1.65	2.33 ± 2.08	t = -1.307	0.310
Suicidal attempts	15% (3)	38.5% (5)	$\chi^2 = 2.361$	0.124	11.1% (4)	33.3% (1)	F	0.056
Age of onset	30.80 ± 15.38	24.31 ± 8.31	t = 1.568	0.127	28.44 ± 11.57	19.33 ± 2.52	t = 3.773	0.002
Episodes								
All episodes	6.11 ± 4.57	12.31 ± 6.0	t = -3.176	0.005	5.72 ± 4.37	7.67 ± 4.04	t = -0.795	0.497
Depression	2.70 ± 2.96	4.77 ± 4.15	t = -1.560	0.135	2.67 ± 2.84	2.33 ± 3.22	t = 0.174	0.876
Mixed	0.60 ± 1.14	2.08 ± 2.72	t = -2.164	0.038	0.92 ± 2.14	1.00 ± 1.73	t = -0.078	0.943
Manic	1.75 ± 1.02	4.08 ± 3.10	t = -3.134	0.004	1.22 ± 1.94	4.00 ± 2.00	t = -2.316	0.129
Hipomanic	1.05 ± 1.50	1.38 ± 1.61	t = -0.599	0.555	0.92 ± 1.13	0.33 ± 0.58	t = 1.523	0.213

Table II
Independent significant factors

	Logistic regression. Hospitalizations		Logistic regression. Episodes	
	Manic	Mixed	Manic	Mixed
OR	2.13	1.64	1.87	1.64
Sig	0.017	0.028	0.022	0.074
CI95%	1.143 - 3.971	1.054 - 2.547	1.095 - 3.206	0.953 - 2.821

icant (Manic p = 0.017 OR = 2.13; Mixed p = 0.028 OR = 1.64). In the other regression the number of episodes of mania was statistically significant (p = 0.002, OR = 1.87) while the number of mixed episodes only had a statistical trend (p = 0.074; OR = 1.64) (Table II).

Discussion

There are important gender-related differences in adherence. First, women are more adherent than men. In our group of men, almost 40% did not comply with treatment, as previously reported[13-15]. On the other hand, non-compliance was very rare in the group of women taking lithium salts in this structured setting, perhaps due to certain factors[16-18]. More men abuse drugs[19] and this abuse was associated with non-compliance in men but not in women. Furthermore, non-adherent men experience more hypomanic, manic and mixed episodes. This could be the cause of non-adherence but also its consequence, and probably both. Interestingly, when we analyzed the independence of variables, severity of the disorder, especially manic episodes, and hospitalizations due to manic and mixed episodes seemed to mediate non-adherence in men. This has not previously been reported in men, although the relationship between men, non-adherence and alcohol and substance abuse is known[8,19]. A cross-sectional study found that severity of disease and manic episodes were related with non-adherence[4,8,10,11,14].

While several studies[10,14,21] have concluded that being married is a factor associated with greater adherence, we found it to be relevant only in the female group. Although the number of non-adherent women was small, it seems that married women are especially responsible thanks to looking after their children and household. Moreover, less compliant women are frequently divorced or single so social factors could be involved[16,22]. In addition, the relationship between suicide attempts and adherence was significant in women but not in men, as previously reported[3,5,6,23,24].

In conclusion, our study found that men do not comply with treatment since they experience more manic relapses and mixed hospitalizations, although relapses are also a likely consequence of manic relapses. Furthermore, it confirms that women are more compliant than men and abuse substances less. It also underlines the association between being married and compliance in women. On the other hand, men may need special preventive care for manic relapses and special treatment for improving compliance.

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THE SAINT JOHN OF GOD MENTAL HEALTH RESEARCH GROUP IN BARCELONA

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SPAIN

ABSTRACT – The group of Sant Joan de Déu-Serveis de Salut Mental is one of the 26 groups that belong to the CIBERSAM, The group is located in Sant Joan de Déu-Serveis de Salut Mental and Hospital Sant Joan de Déu.

We focus our research in two areas: the study of the schizophrenia and severe mental disorders and the epidemiology and social consequences of mental disorders. For example, the group has projects on the cause of patients with a first psychotic episode using neuroimage to understand the mechanism of social cognition, or several clinical trials for treatment resistant schizophrenia.

The group has a bank of donor neurological tissue. The bank has been recognized as a platform inside the CIBERSAM and is fully operative. The materials of the bank one used for own research projects as one directed towards understanding the molecular mechanisms altered in psychiatric disorders that control dendritic development.

The Group has leaded the Spanish study of the ESEMED project, part of the WHO World Mental Health Surveys initiative.

The Group has carried out studies on the treatment of depressive disorders in primary care, analyzing the results of the pharmacological treatments in naturalistic conditions. These studies have been funded by the Catalan Health Technology Assessment Agency and the ETES (FIS). In this line, a multicenter study for resistant depression has been proposed by the REMTAP partners and approved to the last FIS call on independent clinical trials research.

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The group of Sant Joan de Déu-Serveis de Salut Mental is one of the 26 groups that belong to the CIBERSAM (Centro de Investigación Biomédica en Salud Mental), which is funded by the Instituto de Salud Carlos III. The group is also a recognized research group by the Generalitat of Catalunya (AGAUR UNI/1022/2005). It includes 9 doctors, 8 doctoral students, 4 support technicians and clinical collabrators. During the year 2008 the impact factor of the group was 115,729.

The group, which is located in Sant Joan de Déu-Serveis de Salut Mental and Hospital Sant Joan de Déu, started in the year 1997 with two projects funded by the Fondo de Investigación Sanitaria (FIS), which assessed the needs of outpatients with schizophrenia, the consequences of the disorder on carers and families and the role of health services in taking care of patient needs. From these first studies, we have focused our research in two areas: the study of the schizophrenia and severe mental disorders and the epidemiology and social consequences of mental disorders.

The general objective of the group is to relate the biological basis of severe mental disorders with their clinical manifestations, and ultimately social consequences. The final aim is to understand the factors that underlie the phenomenology of the disorders and to improve treatments. The group has several lines of research:

Psychotic disorders

We have finished a prospective study with a prevalent sample of patients with schizophrenia that aimed to define disorder subtypes. The subtypes are defined based on the patient clinical characteristics, neuropsychological and psychosocial functioning, and impairment in neurodevelopmental indicators. It has been a 5 year follow-up study, funded by two FIS grants (97/1275, PI 98/75-03) and one 'Fundació Marató de TV3' grant. Two years ago, the group began to carry out studies using neuroimaging techniques, especially functional MRI, taking advantage of the Hospital Sant Joan de Déu GE Signa1.5T Scan. Several projects continue in this line, the largest being a prospective study of first psychotic episodes (FIS PI051115, Fundación Caja Navarra). This study includes specific objectives on gender differences, the role of drugs at the onset of illness, and social cognition (which includes fMRI). The study will follow a cohort of over 80 people with psychotic disorders attending any service belonging to Sant Joan de Déu – Serveis de Salut Mental (currently, 35 people have been recruited during the last 12 months). This first episode study will continue with a much larger first episode project conducted with 18 research groups from the CIBERSAM.

Existing pharmacological treatments are not effective for all people suffering from schizophrenia. Many people show persistent delusions and hallucinations and the treatment of negative symptoms is still a challenge. We are carrying out clinical trials that try to develop new treatment strategies for individuals with treatment resistant schizophrenia: three projects based on pharmacological treatment, one assessing the combination of two anti-psychotics (amisulpride and quetiapine) for patients showing persistent positive symptoms, another with antipsychotic treatment augmentation with Selective Estrogen Receptor Modulator (SERM) (raloxifene) for negative symptoms and a third one on the role of antidepressants in treating negative symptoms. This last one is a multicentre study with 8 other centres that belong to CIBER-

SAM. Beside these pharmacological studies, there are four on psycho-social treatments: home care, family interventions, cognitive and remediaton treatment and animal assisted therapy. The two first trials have been funded by the American NGO Stanley Foundation and the last four by the *Instituto de Salud Carlos III, Fundació Marató TV3 and Fundació la Caixa*. All the studies are totally independent from pharmaceutical industry. We will keep carrying out projects of treatment for resistant schizophrenia.

We are also developing new lines of investigation of cognitive disorders in schizophrenia (e.g. memory, source monitoring), and their relationships with clinical symptoms.

The group created a bank of donor neurological tissue, which started with the project "Intracellular transduction signal mechanisms in the prefrontal cortex" funded by the *Fundació Marató TV3*, conducted with Dr. Mengod from the *Consejo Superior de Investigaciones Científicas* (CSIC). Dr. Mengod conducts basic research of the brain. The bank has been recognized as a platform inside the CIBERSAM and is fully operative. A relevant aspect of the bank is that donnors assessed with clinical and neuropsychological questionnaires when they volunteer as donnors. The recent incorporation of Dr. Ramos, thanks to the funding from the CIBERSAM, will initiate a new line with the tissue samples. Dr. Ramos is a post-doctoral researcher who has been carrying out projects on the neuronal development in a rodent experimental model at the University of Harvard. The starting project is directed towards understanding the molecular mechanisms altered in psychiatric disorders that control dendritic development (Marie Cuire IRG (2007) D/53057, MICINN-BFU2008-01103).

Mood disorders

The Group has leaded the Spanish study of the ESEMED project, part of the WHO World Mental Health Surveys initiative. The Spain-ESEMED study is a general population epidemiological study with more than 5.500 interviews in Spain and 23.000 in Europe. As a continuation of the project, through the funding obtained by the SANCO program of the European Union, we continue the analyses and publication of results (previously the study was funded with grants from the V EU FP QLG5-CT-1999-01042, the FIS PI052855E and the MCyT). Besides being disseminated through scientific publications, the data of this study have been used for in the "Strategy in Mental Health of the National System of Health 2006" of the Ministry of Health, and for health plans of several Autonomous Communities. A new project on the use of epidemiological data for mental health priorities and planning has been also funded in the 2008 SANCO call.

The Group has carried out studies on the treatment of depressive disorders in primary care, analyzing the results of the pharmacological treatments in naturalistic conditions. These studies have been funded by the Catalan Health Technology Assessment Agency and the ETES (FIS). In this line, a multicenter study for resistant depression has been proposed by the REM-TAP partners and approved to the last FIS call on independent clinical trials research.

During 2009, we are starting two new epidemiological studies funded by the European Commission on the prevalence of mental disorders in special populations, the elderly (COURAGE project that evaluates not only mental but also physical health and disability) and the SCHOOL-CHILDREN (children of schooling age).

Health services research

The group has an extensive research track in the evaluation of services and sanitary processes. Dr. Haro was the coordinator of the Network RIRAG (G03/061), that stands for Research Network of Outcomes Applied to Management in Mental Health and Disability. The projects have focused in the comparison of the mental health services between regions and countries (European project EPCAT) and cost analysis (project PSICOST). More recently studies on the treatment adequacy of the depressive disorders in Spain and in Europe have been carried out (PI 03/10109).

The group has also conducted different research studies funded by CATSALUT. They were about the availability of the mental health resources in Catalonia as well as the use of new technologies for mental health care evaluation and planning. During 2006 the group lead a study on the assessment of the dependency in people with mental disorders and intellectual disabilities, funded by the Catalan Government.

Child and Adolescent Mental Health

The group has recently incorporated child and adolescent mental health inside the lines of research. The first project is a study on first psychotic episodes, and patients older than 7 years are included. Dr. Dolz, already a member of the group, is heading this area and works in the Maternity and Children Hospital of Sant Joan of Deu. Dr. L. San has recently joined the group which will foster research in this area.

Social aspects related to mental health

Since the impact of the disorder goes beyond the patient and affect relatives and society in general, our group has been interested in the psychosocial consequences of mental disorders and how to reduce them. Two projects funded by the FIS about the Family Burden in schizophrenia and the assessment of a family intervention have been finished (FIS 98/75-03; FIS PI0212721). Three other studies that assessed social stigma in schizophrenia have been done. One of them based in communitary intervention to reduce stigma in adolescents, another about the assessing of self-stigma in patients. Recently the FIS has funded a project on the validation of a scale for the assessment of stigma in people with schizophrenia. Another study that assesses social stigma in schizophrenia is ongoing.

Currently we are starting a study about mental health of homeless in the city of Barcelona. This project is funded by private foundations and has the support of the Generalitat de Catalunya.

Gender aspects of mental health

The study of gender is specifically included in the projects. Besides, some studies focus on gender differences. For example, one study linked to the clinical trial about augmentation with Selective Estrogen Receptor Modulator (SERM) analyzes the role of estrogens as determinants of the differences between men and women in schizophrenia. Another study is being conducted to determine the gender differences in the patterns of use of mental health services (PI06/90233). The AGAUR (from the Catalan Government) funds a study on the detec-

tion of the psychological risk of the victims of domestic violence. Susana Ochoa and Judit Usall members of the group funded the Catalan Work Group on Women and Mental Health that has organized two Congresses on Gender and mental health and has the support of the Societat Catalana de Psiquiatria, and during 2009 have organized the seconds Congress on Gender and mental health in Catalonia.

The group is also interested in the development and validation of scales. Several funded projects (FIS, CIBERSAM, *Fundació Seny…*) allow from the development of new scales. For example: IRAOS scale (prodromical assessment of patients with schizophrenia), Link's scale (stigma assessment), CANFOR (needs of patients with mental problems who are in a forensic unit), Dorothea Orem (scale for assessment of nurse needs), SUMD for affective disorders, SDLS (scale for assessment of quality of life for people with schizophrenia), and Beck's scale for insight (for patients with schizophrenia).

The recognition by the AGAUR of the Network of Community Nursing in which our group also participated is the base for the planning of new intervention projects, some of which are receiving funding.

The bibliography includes some recent publications of the group.[1-25]

Acknowledgements

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DEPRESSION AS A NEUROINFLAMMATORY CONDITION. LESSONS FROM CLINICAL DATA AND ANIMAL MODELS OF STRESS

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Depression as a neuroinflammatory condition. Lessons from clinical data and animal models of stress

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SPAIN

ABSTRACT – Studies carried out with some stress protocols show a pro-inflammatory response in brain and other systems characterized by a complex release of several inflammatory mediators such as cytokines, transcription factors, prostanoids and free radicals. Such response contributes to cell damage during several neuropsychiatric diseases related with stress (posttraumatic stress disorder, major depressive disorder, anxiety disorders, schizophrenia). In particular, data from the clinical arena associate an increase in proinflammatory mediators with major depression. This review considers the current status of knowledge of stress-induced inflammation in brain. Interestingly, anti-inflammatory pathways are also activated in response to stress, constituting a possible endogenous mechanism of defence against excessive inflammation. The possibility of pharmacological modulation of these pathways to prevent neuroinflammation and subsequent brain damage in stress and in stress-related neuropsychological conditions is also reviewed. This dual response deserves further attention in order to understand pathophysiological changes and possible new therapeutic approaches of stress-related neuropsychopathologies.

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Introduction

First studies on the possibility of increased inflammation in depression were carried out during the early 90's. Three studies of Maes and co-workers[1-3] concluded that the immune cell profile of several groups of minor, simple major and melancholic depressed patients are different from controls, and point towards the existence of a systemic immune activation during depression. Although the level of some proinflammatory cytokines –interleukin 6 (IL-6) and IL1beta (IL-1β)– were not statistically significative higher due to methodological limitations in 1992, further studies[4] demonstrated increased levels of several cytokines, also including tumour necrosis factor alpha (TNFα). Sixteen years later, there is a substantial body of evidence associating an increase in proinflammatory mediators in major depression. Furthermore, there is now evidence that effective antidepressant treatment largely attenuates inflammatory changes[5]. However, after a detailed revision of many articles[6], it must be noted that not all studies have found an association between inflammation and the pathogenesis of depression, and individual factors such as gender, body mass index, personality and severity of the disease must be taken into account. One of these probably confounding factors is the individual response to stress. In fact, during a similar period of time (last 20 years), there are also evidences supporting that similar inflammatory changes also occur in milder forms of the depressive disorder spectrum and also in individuals subjected to stress.

Stress produces an inflammatory response in central nervous system (CNS) and in periphery. The relationship between stressful events and the onset of depression is well documented[7] as well as the incapacity to initiate or regulate the response to a stressor as a critical factor in the pathophysiology of various stress-related pathologies such as depression, anxiety or post traumatic stress disorder (PTSD)[8]. In humans with major depression higher basal cortisol plasma levels have been described as well as higher corticotropin-releasing factor (CRF) levels in cerebrospinal fluid (CSF) than in control patients. Some authors described this as a status of hipercortisolism in depressed individuals[9]. One of the main objectives of our research group is the study of neuroinflammatory pathways in the pathogenesis of stress-related neuropsychiatric diseases.

In this short review, we focus on changes in intra- and inter cellular messengers in brain induced by stress. We present results from different experimental models used in our laboratory and by others, analyzing mechanisms and discussing consequences of these alterations.

Neuroinflammation

Inflammation is a complex set of co-ordinated mechanisms governed by the interaction of multiple specific mediators such as cytokines, prostaglandins, chemokines, substance P, etc, that generate non specific physiological responses including hypothalamus-pituitary-adrenal (HPA) axis activation, fever and sickness behaviour[10]. When localised, it can be considered as a protective mechanism to contain injury or infection. However, when inflammation is excessive in intensity (over expression or over activity of several mediators) and time (inefficient resolution) it becomes harmful and exacerbates numerous diseases.

The CNS is able to respond to peripheral inflammatory stimuli and to constitute a local inflammatory response called *neuroinflammation* in spite of the brain-blood barrier. Circulating or endothelial cytokines can trans-

duce a signal to neurons via substances such as nitric oxide (NO) or prostanoids; these are synthesized by the inducible isoforms of the nitric oxide synthase (NOS-2 or iNOS) and cyclooxygenase (COX-2) whose transcription is induced by IL-1 among other cytokines. However, cytokine receptors are expressed constitutively throughout the CNS and neurons, astrocytes, microglia and oligodendrocytes can themselves produce inflammatory mediators[11]. The key features of CNS inflammation include: glial activation, oedema, major histocompatibility complex (MHC) expression, systemic acute phase response protein synthesis, complement activation, accumulation of pro-inflammatory cytokines, expression of NOS-2 and COX-2, expression of adhesion molecules and accumulation of free radicals and prostaglandins[10].

There is extensive evidence that inflammation within the CNS contributes to many acute and chronic degenerative disorders and some psychiatric diseases (i.e. depression, PTSD and schizophrenia)[11].

Main agents in stress-induced CNS inflammation

Glucocorticoids

In CNS, glucocorticoids (GCs) have been identified as regulators of diverse processes such as neurogenesis, neuroinflammation, neurodegeneration, memory, learning and mechanisms of adaptation. While GCs affect behaviour and cognition undoubtedly the most specific function of GCs in the brain is feedback inhibition of the HPA axis after stress exposure[12].

GCs are considered anti-inflammatory, immunosuppressive and immunomodulatory under standard conditions[13]. However, in recent years the classic view that glucocorticoids are universally anti-inflammatory has been challenged at a variety of levels, mainly in the CNS. Thus, in the brain, GCs can even be pro-inflammatory at the level of cell extravasation and migration as well as inflammatory messenger[14].

Numerous studies have demonstrated that stress conditions (high levels of GCs) induce release and accumulation of pro-inflammatory mediators such as NO, prostanoids, cytokines and activation of nuclear transcription factor NFkB[15]. In addition, some studies show that microglial proliferation (a useful indicator of neuroinflammation) after stress exposure is mediated by a glucocorticoid and glutamate receptor dependent mechanism[16].

Glutamate

One of the initial processes that take place in the stress response is the release of excitatory amino acids (glutamate and aspartate) in some brain areas[17]. As early as 20 minutes after the onset of immobilization, there is an immediate and sustained release of glutamate and aspartate into the synaptic cleft that reaches excitotoxic levels. The increased extracellular glutamate binds to its ionotropic N-methyl-D-aspartic acid (NMDA) receptor whose over-activation causes a continuous excitation of neurons, inducing further glutamate release, ATP depletion and a dramatic increase in intracellular Ca^{2+} levels, which eventually leads to neuronal death.

Pro-inflammatory cytokines

Many studies show that exposure to acute stressors (immobilization, inescapable tailshock, escapable tailshock and footshock) can potently increase the expression of IL-1β in the central nervous system (CNS).

This IL-1β contributes to some of the responses that occur during stress such as monoamine and glucocorticoid release, cognitive impairments and "depressive-like" behaviours[18]. TNF-α is one of the central mediators of tissue inflammation and has been implicated in the pathogenesis of stress response[19], being this release dependent on glutamate. The release of TNF-a also accounts for stress-induced NFkB activation and NO accumulation in the brain. Some other cytokines, such as IL-6 are increased after stress exposure in plasma and brain.

Nuclear factor *kappa* B (NFkB)

Activation of NFkB is one of the earliest events in the stress-inflammation response. It controls the transcription of many of the acute phase proteins and inflammatory genes[20]. Actually, stressors in humans and animals induce an increase in NFkB in the cell nucleus as well as elevations of noradrenaline and GCs[20]. We demonstrated experimentally for the first time that stress activates NF-kB in the brain. This occurs very early after the beginning of stress[21] and later studies showed this activation in humans too, after with psychological stress (free speech and a mental arithmetic task)[22].

NFkB produces the expression of genes responsible for the accumulation of oxidative/nitrosative and inflammatory mediators that finally contribute to cell damage or generate reversible or, in chronic conditions, even irreversible cellular damage. This makes NF-kB a very interesting new target for a therapeutic approach. Two main sources of oxidative/nitrosative mediators and inflammatory damage after stress dependent of NFkB are inducible NO synthase (iNOS), which produces NO and peroxynitrite, and cyclooxygenase-2 (COX-2), which produces prostanoids.

Therapeutic possibilities to reduce neuroinflammation in stress and depression

During the last years, an enormous scientific effort has been done to understand neuroinflammation in animal models of depression, including the use of specific pharmacological tools to reduce the increased levels or function of glucocorticoid hormones, excitatory aminoacids, cytokines, iNOS and COX2[23]. However, one of the most promising approaches is to use one of the defence mechanisms that allow organisms to adapt and survive to stress. In particular, certain prostaglandins derived from the differential activation of COX isoforms, a mechanism considered as a possible endogenous regulator of the inflammatory response in neurodegenerative conditions.

One of these prostaglandins is the anti-inflammatory prostaglandin 15-deoxi-prostaglandin J_2 (15d-PGJ_2), a structural, non enzymatic derivative from the prostaglandin D_2. This prostaglandin is the proposed endogenous ligand for the *gamma* isoform of the subfamily of peroxisome proliferators activated nuclear receptors *gamma*, PPARγ. These receptors have been directly implicated in the regulation of the inflammatory response in numerous animal models of neuropathologies associated with inflammation. In particular, the use of PPARg agonists in models of stress is a promising approach due to its anti-inflammatory effects[24].

In conclusion, inflammation is a key player in the effects of stress and in the pathophysiology of depression (Figure 1). Thus, the search of new anti-inflammatory drugs is crucial and among all the targets involved in inflammatory stress response, probably PPARg ligands are the most promising as novel drug targets.

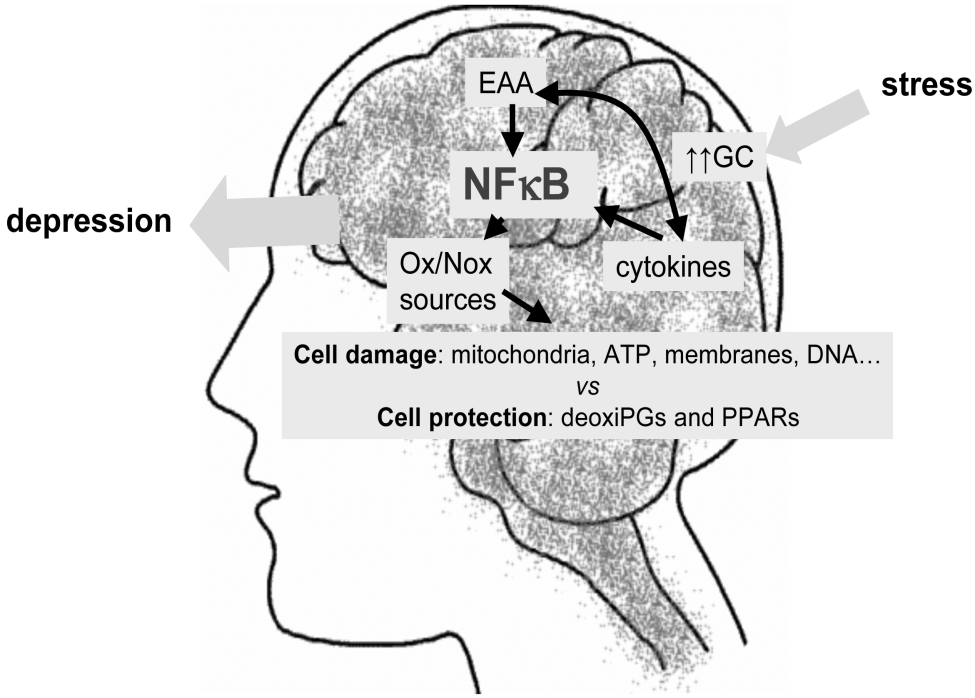

Figure 1. Main inflammatory pathways in stress-induced depression.
GC: glucocorticoids; EAA: excitatory amino acids; Ox/Nox: oxidative and nitrosative enzymatic sources.

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STUDIES IN PSYCHOSOMATIC PSYCHIATRY AND IN GERIATRIC PSYCHIATRY: THE ZARAGOZA EXPERIENCE

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Studies in psychosomatic psychiatry and in geriatric psychiatry: The Zaragoza experience

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ABSTRACT – In the context of international interest in the psychiatric comorbidity in medical patients; and the growing international concern for dementia and depression in the elderly population, the Zaragoza Group of CIBERSAM has carried out a series of studies of increasing complexity. The objective of this paper is to describe this trajectory. We describe five generations of studies completed, the inspiring philosophy and results in both lines of research. We have standardised a series of assessment instruments and have documented, in a series of studies, the high prevalence and the negative implications of undetected, untreated psychopathology, including an excess mortality rate in depressed patients.

We have also described in cross-national studies the state of the art in psychosomatic psychiatry in Europe, and have developed original methods and instruments for the early detection of "complex" medical patients.

In geriatric psychiatry, we have completed cross-national studies both in dementia and depression, and have reported epidemiological data which are considered to be interna-

tional reference in the field. The ZARADEMP Project includes now analytical, causal data as well as information on risk factors and early markers of the diseases. Conclusions: Translational research and studies including neurobiological bases of psychopathological disturbances should now be the priority to advance in elucidating causes and mechanisms of disturbances observed. CIBERSAM provides the adequate structure to complete high quality collaborative research.

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Introduction and Background

The Zaragoza Group, the co-ordinating group of Area IV ("Other pathologies") within CIBERSAM is a multidisciplinary team with a psychiatric nucleus. It is considered to be expert in the fields of both psychosomatics/liaison psychiatry and geriatric psychiatry, and has developed five "generations" of studies of increasing complexity.

The first "generation" studies started in the 1970s, when standardisation of assessment instruments was imperative in Spain. An important number of international instruments were validated: Mini Mental Status Examination, GHQ-28, Eysenck Personality Questionnaire, Geriatric Mental State-AGECAT, Montgomery-Asberg Depression Rating Scale, Hamilton Anxiety Rating Scale, Euro-D Scale for the elderly, etc. An original interview to assess psychiatric morbidity in medical patients, the Standardized Polyvalent Psychiatric Interview or SPPI, was also developed[1]. The second "generation", epidemiological type studies in different medical populations started once the appropriate instruments were available. The public health interest of this research was summarized in a specfic chapter in a WHO supported book[2]. It was followed by the third "generation", studies in large representative samples of both medical patients[3] and community samples of the elderly[4]. The fourth "generation" refers to large, multicentre, trans-national European studies in both fields[5-7], funded by the EU Biomed Programmes; and we are now involved in the fifth "generation", which includes collaborative studies with other CIBERSAM groups, has incorporated biological aspects, and is aiming at translational research.

Research in Line I: Psychosomatics/Liaison Psychiatry

This line of research follows strategic plans formulated in 1977, when a new Psychosomatics and Liaison Psychiatry (PLP) Unit was organised at Zaragoza University Hospital[8]. We argued strongly for the advantages of epidemiological type research in this field[9], and soon documented the high prevalence and characteristics of psychiatric disturbances in medical settings; and the negative implications of undetected, untreated psychopathology, work that was summarised in a WHO supported book[2]. Contributions to endocrine disorders resulted in an invited chapter in a book recently awarded the First Prize, in the Mental Health catego-

ry, by the British Medical Association[10]. The Zaragoza Primary Care Study has also contributed to the international literature, documenting, for example, differences between somatisers and psychologisers[3]; or the fact that "each medical diagnosis doubles the probability of a comorbid psychiatric disturbance")[11].

The Zaragoza group has been one of the main contributors to the European Consultation-Liaison Workgroup (ECLW), which has done seminal work in describing the state of the art in EU countries[5]. Original documentation instruments were developed[12], and studies were completed in 13 countries and 90 hospitals reporting, for example, that referral rates from medical departments (1.4%) are much lower than the expected morbidity rate; that referred patients have a length of hospital stay double or triple the expected hospital standard, or that service provision is strongly influenced both by the specific approach and by the amount of staff in PLP Units[13]. These studies led to the original view of "complex patients", and subsequent studies developed both an original European system for "quality improvement" in PLP Units and the COMPRI (complexity prediction instrument)-INTERMED (interdisciplinary medicine) method, an innovative model for the early detection of "complex patients" (with physical and psychiatric comorbidity) in need of an early treatment plan awarded a Honourable Mention by the American Academy of Psychosomatic Medicine in the 2001 Dorfman Journal Paper Award[14]. The Zaragoza group has extended the use of the COMPRI-INTERMED method[15], and is now involved in a new study endeavouring to document the empirical bases for organising the first "Combined Medicine-Psychiatry Inpatient Unit" in Spain.

These experiences supported the successful application to the Carlos III National Institute of Health (ISCIII): The Spanish "National Research Network for Liaison Psychiatry/Psychosomatics" (REPEP) was approved and the co-ordinating node is in Zaragoza. Strategies similar to CIBERSAM were implemented, which attracted the interest of the American Academy of Psychosomatic Medicine, resulting in an invited paper[16]. The REPEP Study, a consensus research project, was considered to be crucial to this strategy: in the context of a "continuity of care" model and in support of the working hypothesis, this is the first multicentre study (7 hospitals, 3,300 patients invited to participate) documenting the negative outcome of comorbid depression detected at the time of hospital discharge. Approximately 20% of patients (with an average of 5 medical diagnoses and mean age of 74 years) were depressed; compared to controls, cases of comorbid depression have poorer quality of life at follow-up (in primary care); more disability; and a poorer outcome (60%) including an excess mortality rate (submitted).

Hypotheses related to differential characteristics of depression in medical patients are now being investigated, along with their health economic implications. Innovative, evidence-based efficacy intervention studies should now be designed to treat this kind of depression. Furthermore, a new sub-line has emerged to study probable causes of the premature death in depressed patients. An original "Bio-Psycho-Social Autopsy" Interview, BPSA has been developed[17]. In this initial stage, a case-finding design similar to the REPEP Study will be implemented to detect cases of depression that eventually die (Figure 1). Hypothesised causes of death include biological dysfunctions (including cytokine deviations and endothelial dysfunction), but also psychosocial causes such as "self-abandonment" and stressful life events.

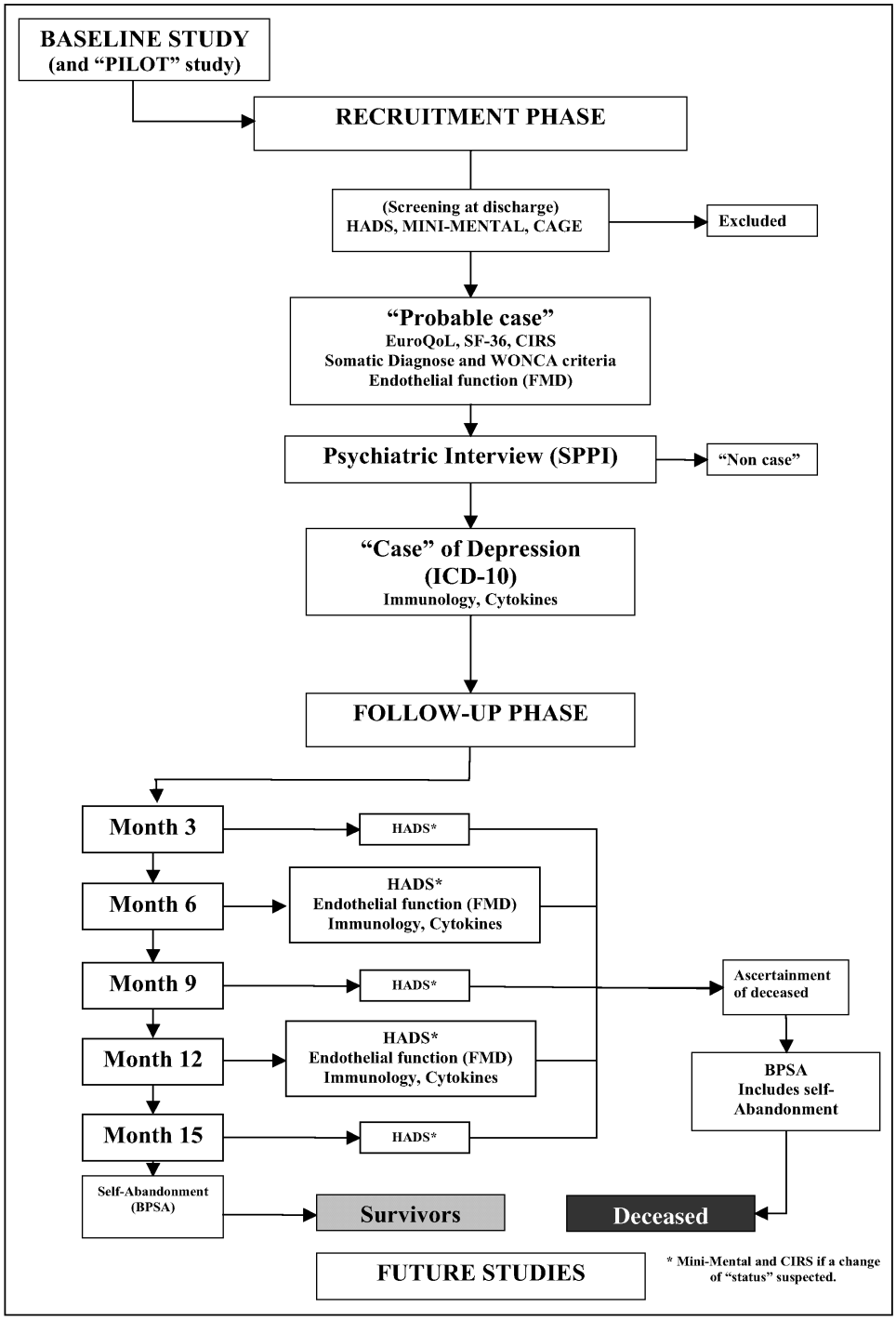

Figure 1. Algorithm of the FamiDep Project, to study probable causes of premature death in depressed patients.

The transfer of knowledge generated by this line of research is reflected in invited chapters in relevant Spanish (Farreras (ed), Medicina Interna, Masson, 2000) and American (Levenson (ed), Textbook of Psychosomatic Medicine, APP, 2005) textbooks of medicine.

Research in Line II: Geriatric Psychiatry

Our experience in psychiatric epidemiology, as well as the relative priority we believe should be placed on research in the elderly, determined our commitment to Line II, the study of dementia, depression and somatic comorbidity in the general population. The Zaragoza Study ("ZARADEMP 0") was the first one of its kind in Spain and in Southern Europe[4]. It provided data on the prevalence of morbidity, including Alzheimer's type dementia (ATD), which have been transferred to the National Health System (report to the Aragon government). It also documented an intriguing overlap of dementia and depression, generated nosological hypotheses, and influenced the design of the following studies.

The Liverpool-Zaragoza Study[18] initiated a series of cross-cultural studies and influenced the design of subsequent European enquiries, including the EURODEM and EURODEP Studies. The latter was the largest cross-national study yet conducted (ten European groups, 25,000 individuals) on descriptive/analytical epidemiology of depression in the elderly population. Its main articles documented cross-national differences in the prevalence of disorder; the relationships of depression with cognitive disturbances, and with physical morbidity; and the influential role of religious practice[7].

Data from "ZARADEMP 0" also contributed to the first EURODEM series of studies documenting the prevalence and associations among dementias across Europe[6]. More ambitious studies were designed for the second series: eight European cities participated, and 44,336 individuals were assessed in this first, originally designed cross-national study on the epidemiology of ATD and other dementias, Parkinson's disease, and stroke. North-South geographical differences in the incidence of dementias have been documented[19,20]. More importantly, it was the first study on the risk factors of dementia in "incident cases". This series of international studies is the reference standard in the field and has influenced European and international policy in relation to predictions and organisation of services (OECD Report, 2002).

The ZARADEMP Project was designed in this context (Figure 2). It is a longitudinal, four-wave epidemiological study, the main objectives being to document the incidence of dementia, depression, and psychiatric morbidity; to study early markers and/or risk factors of both dementia and depression in incident cases; and to test hypotheses related to associations between psychiatric and somatic morbidity. In the baseline, cross-sectional study (Wave I), a stratified, representative sample of individuals aged 55 and over (n = 4,803) was assessed in a two-phase, case finding procedure. Then, the cohort of non-dementia individuals has been followed up in four waves (Wave II, III, and IV), approximately every two and a half years[21].

The following is a summary of the most relevant results reported to date. Contrary to some expectations, the prevalence of dementia by age group has not increased since the previous decade; on the contrary, an intriguing decrease of the prevalence in men has stimu-

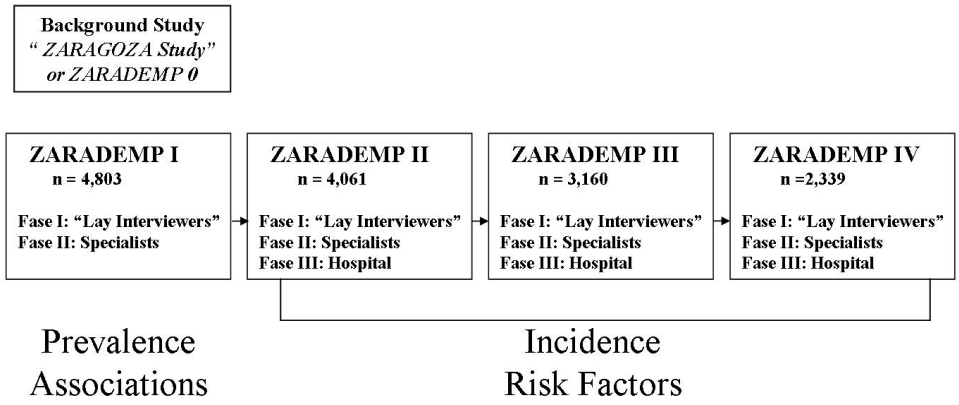

Figure 2. Longitudinal design of the Zarademp Project.

lated environmental hypotheses, including hypotheses related to the Spanish Civil War[21]. The prevalence of non-cognitive symptoms in cases of dementia living in the community is very high (90.1%), and negative-type symptoms, including a Geriatric Mental State (GMS) "apathy-related symptom cluster" has powerful specificity in distinguishing from non-cases. On the basis of this study, we have argued strongly in favour of the inclusion of non-cognitive psychopathological symptoms in the concept of dementia[22]. Furthermore, support has been found for the hypothesis that specific non-cognitive psychopathological symptoms predict incident mild cognitive impairment (MCI), but different symptoms predict incident ATD[23].

The ZARADEMP Project has also contributed to the "Multicentre Spanish Study on Ageing" and to studies in the elderly for doctoral theses that should be reported in the international literature: risk factors in "first episodes" of depression (incident depression); epidemiology of dementia in rural populations; the role of alcohol consumption as a risk/protective factor for ATD; epidemiology of sleep disorders; use of medication and psychiatric morbidity; or epidemiology of disability. Ongoing and projected studies with other university departments and/or CIBER structures related to the ZARADEMP Project include a project on the "Intelligent Home" for the disabled elderly with physical-psychiatric disability; genetic studies in ATD with non-cognitive psychopathology; and strategic plans to develop a research department in the planned Alzheimer's disease centre in Zaragoza.

Bridges between the lines of research

This research experience in two rather independent lines provides ample opportunity to share hypotheses and protocols. Studies of depression in medical patients (psychosomatics, line I) are an example of this, and we have found support for a hypothesis related to the effect of old age on the prevalence and characteristics of psychopathology (submitted; psychogeriatics, line II).

In the opposite direction, the ZARADEMP Project (line II) has provided the opportunity to test "psychosomatic" hypotheses (line I). A positive and statistically significant association has been found between somatic and psychiatric morbidity in the elderly; the concentration of this comorbidity in a sector of the population is consistent with Hinkle and Wolff's traditional conjectures about "vulnerability" to illness[24]. Furthermore, a preferential association of psychiatric morbidity with stroke has been found, and new analysis are now endeavouring to better explain this association, in a combined project with R. Robinson and Iowa University.

In a different study within ZARADEMP, a bidirectional association has also been found between diabetes and depression. In the first study reported in the international literature using both formal psychiatric criteria and a prospective, population-based design, diabetes was associated with an increased risk of prevalent depression, but also of incident (first episode) depression[25]. The inverse association might be even more intriguing from the "psychosomatic" perspective: the depression documented during the baseline of the project doubles the risk of incident diabetes documented in the follow-up waves (submitted).

New and future projects

The CIBERSAM philosophy coincides with our 5th "generation" of studies emphasising neurobiological, collaborative, and translational research. We are prepared to contribute to CIBERSAM with the Zaragoza fields of expertise. For example, knowledge of organic depression and elderly depression might well fit with experience from other groups in Area II (depression). Similarly, the knowledge of cognitive disturbance, apathy, and other negative symptoms should be the main contribution from Zaragoza to the ongoing study on first episodes of psychosis (Area V of schizophrenia). In addition to psychogeriatric experience, the Area IV we co-ordinate includes expert groups in the fields of child and adolescent psychiatry, as well as in adult psychiatry. Therefore, the influence of the vital course, at different ages, on the different pathologies, is one of the research priorities. Moreover, on the basis of strategic plans that have already been approved, immediate, co-ordinated projects in which Zaragoza should take a leadership role include a recently funded project on the epidemiology of "complex" patients on general hospital floors and implications for organisation of services; the project to develop a Spanish version of an apathy scale; and a longitudinal study on depression in patients with cardiovascular pathology.

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THE RESEARCH GROUP IN BENITO MENNI CASM: RECENT FINDINGS FROM IMAGING STUDIES

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The research group in Benito Menni CASM: Recent findings from imaging studies

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SPAIN

ABSTRACT – The focus of the research group in Benito Menni CASM is on imaging studies in schizophrenia and other major psychiatric disorders. In this article we describe our recent functional imaging findings in schizophrenia, which suggest that there may be dysfunction of the default mode network in the disorder, specifically failure to de-activate during cognitive task performance. We also describe other ongoing studies which are investigating functional imaging abnormalities underlying schizophrenic symptoms such as formal thought disorder and affective flattening, and the structural and functional imaging correlates of cognitive impairment in the disorder. We report on new imaging methods under development by our group and summarise future research directions.

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Background

Benito Menni CASM has a longstanding tradition of supporting research, and this culminated in the establishment of a dedicated research unit in 2005. The unit is part of the CIBERSAM research network and has also received support from other sources includ-

ing the European Research Commission, AGAUR, FIS and other Spanish Government grant bodies. Collaborations exist nationally, especially with other CIBERSAM groups, and internationally (Cambridge and Newcastle in the UK, Munich and Vienna in Europe and Melbourne, Australia).

The focus of the unit is the biology of major psychiatric disorders, ie schizophrenia, bipolar disorder and major depression. We investigate these primarily using functional neuroimaging, which we combine with structural neuroimaging, neuropsychology and detailed clinical evaluation with the aims of a) delineating patterns of brain abnormality in major psychiatric disorders, and b) relating brain abnormality to aspects of the psychopathology of these disorders, such as symptoms and cognitive impairment. A further objective is to develop new methods of imaging analysis. In the last three years we have acquired structural, DTI and functional imaging data on over 100 chronic schizophrenia patients, approximately 80 patients with affective disorder and corresponding numbers of controls. We have also scanned approximately 40 first-episode psychosis patients from the geographical area adjacent to Barcelona. Here we report on some of the group's functional imaging findings to date.

Functional imaging in schizophrenia

As part of a study which aimed to examine both prefrontal and basal ganglia function in schizophrenia –i.e. to test the hypothesis that it is a 'frontostriatal' disorder[1]– we carried out an fMRI study during performance of a working memory task (the n-back task) in 32 chronic schizophrenia patients and 32 well-matched normal controls[2]. Similar to other studies we found that the schizophrenia patients showed significantly reduced activation in a network of brain regions including the dorsolateral prefrontal cortex (DLPFC). An unexpected additional finding, however, was a large cluster of apparent hyperactivation in the medial prefrontal cortex bilaterally. This 'hyperfrontality' was in a similar area to that found in a recent meta-analysis of other studies using the n-back task[3], although the authors noted that this area was not activated in either patients alone or the controls alone. Further analysis revealed that the apparent hyperactivation in our study was not due to intrinsically greater activation in the schizophrenia patients, but instead reflected a failure to de-activate in the medial frontal/anterior cingulate cortex (which, as a result of the subtractive nature of the contrasts between patients and controls, manifested as relatively greater activation – see Gusnard[4]). The areas of activation and de-activation we found are shown in Figure 1.

Whitfield-Gabrieli *et al.*[5] have recently reporte closely similar findings in a study of 13 schizophrenia patients in the early phase of illness, again using the n-back task. Although, in our study, there was no evidence of an association between failure to de-activate and any aspect of the clinical picture, in Whitfield-Gabrieli *et al.*'s[5] study the degree of failure to deactivate was associated with both the severity of positive and negative symptoms in the patients. They additionally found that failure to deactivate was seen to a lesser but still significant extent in unaffected first-degree relatives of the schizophrenia patients.

The cluster where we found failure to deactivate in schizophrenia corresponds to one of the two main nodes of the so-called default mode network[4,6]. This consists of a network of brain regions which are active at rest but deactivate during performance of a wide range of cognitive tasks. It includes two prominent midline regions, the medial

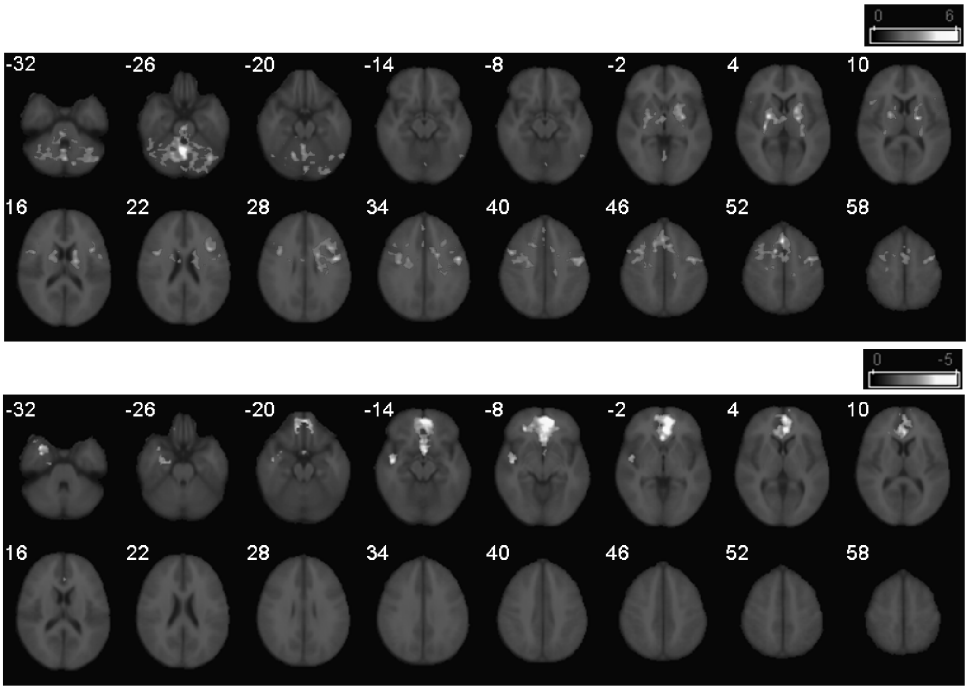

Figure 1. Brain regions showing significant differences between schizophrenia patients and controls during performance of the n-back task (2-back vs baseline contrast). Upper figure depicts areas where controls activated more than patients, lower figure shows the converse (areas where patients activated more than controls). The schizophrenia patients showed significantly reduced activation in the cerebellum, basal ganglia and right thalamus, and in a set of connected frontal regions stretching bilaterally from areas around the frontal operculum to both precentral gyri and supplementary motor areas, reaching some sections of the right middle lateral prefrontal cortex. The patients also showed failure of de-activation relative to controls in an area extending over the gyrus rectus bilaterally, related fronto-medial structures, and the anterior cingulate gyrus. There was a second, smaller and weaker cluster of failure to de-activate affecting parts of the right hippocampal complex and neighbouring anterior temporal regions. The right side of each image represents the left side of the brain. Colour bars indicate Z-scores from the group level analysis. Data reproduced from Pomarol-Clotet *et al.*[2]

prefrontal cortex anteriorly and the posterior cingulate cortex/precuneus posteriorly. The default mode network is believed to be involved in a variety of functions such as self-reflection, self-monitoring, and recall of personal experiences, and has been argued to be central to maintaining one's sense of self[7] and/or monitoring the external environment for unexpected events[8].

Clearly, failure to de-activate in the default mode is a potentially significant finding in schizophrenia. We are currently undertaking further studies at different stages of the disease and using tasks other than the n-back working memory task.

Functional imaging in relation to psychopathology

Irrespective of the recent evidence for default mode network dysfunction in schizophrenia, hypofrontality continues to be an important functional imaging abnormality, which, despite positive and negative findings in differ-

ent studies, is supported by meta-analysis[3,9]. It has been proposed that hypofrontality is a brain correlate of the negative symptoms of schizophrenia[10]. Liddle[11] has also proposed that frontal dysfunction – perhaps in regions of the prefrontal cortex related to response inhibition – could also underlie the symptom of formal thought disorder (FTD). There is some, but not unanimous, evidence that FTD is associated with poor neuropsychological performance on tests of frontal lobe function. However, to date few studies have examined this relationship between FTD and frontal lobe dysfunction from the perspective of functional imaging, and their results have not been consistent (for a review see McKenna[12]).

We have carried out a combined neuropsychological and fMRI study comparing intellectually preserved schizophrenia patients with and without FTD and with controls. Preliminary results indicate that the patients with FTD showed more evidence of impairment in executive function; however, the differences, while significant were not marked, and the patients with FTD also showed more impairment on some non-executive tasks. On the other hand, fMRI during performance of a working memory task, the patients with FTD showed less activation in prefrontal areas than those without FTD.

Executive impairment is a core aspect of schizophrenic cognitive impairment. However, little is known about the brain correlates of cognitive impairment in schizophrenia. De Vries *et al.*[13] found that a small series of schizophrenic patients with marked cognitive impairment showed no more evidence of structural brain abnormality on CT than in schizophrenia as a whole, but there were strong suggestions of resting functional imaging abnormality. More recently Wexler *et al.*[14] have found evidence that cognitively impaired schizophrenia patients show more white matter abnormality, but not grey matter abnormality, compared to cognitively intact patients. We have recently investigated structural and functional brain differences between 18 cognitively impaired schizophrenia patients (defined on the basis of performance below the 1st percentile on standard executive or memory tests) and 23 patients with memory and executive function in the normal range (Ortiz-Gil *et al*, submitted). The two patient groups did not differ on structural measures, but the cognitively impaired patients show less activation in dorsolateral and other prefrontal cortical areas than the cognitively intact patients during performance of a working memory task.

We are also investigating the neural substrates the impaired responsiveness ('affective flattening') seen in schizophrenia. In an fMRI study designed to examine how cognitive analysis could influence facial emotional recognition schizophrenia patients in comparison to healthy subjects, we have evaluated the neural substrate of the performance of two emotional recognition task, an intuitive emotional and a more cognitively demanding task. In contrast to controls, we found that schizophrenia patients invariably adopted a cognitive approach, based in a feature-based analysis when identifying facial affect and failed to activate the amygdala in the intuitive task[15]. A more focused analysis in the amygdala response found that schizophrenia patients showed similar amygdalar activation to controls during the initial stage of emotional processing, but this activation decreased during the later stage. Conversely, they showed lower accuracy scores than controls in the first part of the block, but similar scores in the latter part. These findings suggest that schizophrenia patients have an initial automatic emotional response but, in order to solve the task, they need to switch to a compensatory cognitive strategy consisting of a feature-based analysis of the emotional faces (Salgado-Pineda *et al.*, submitted).

New methods for the analysis of magnetic resonance images in psychiatry

In recent years we have been working on the development of new tools to extract relevant information from magnetic resonance images from several modalities. On the one hand, we have developed statistical models to quantify several parameters of interest in diffusion imaging and to assess their reliability as well as methods for the selection of the best tensor model (DTI approach) to describe white matter structure in different parts of the healthy and injured brain[16]. In addition, we have developed new methods to quantify the local orientation distribution function (ODF) of white matter tracts[17-19] by means of high angular resolution diffusion images (HARDI). These ODF maps and those provided by DTI have been used to create and characterize global patterns of structural brain connectivity with the concurrently use of graph theory, network analysis techniques and advanced tractography algorithms[20].

On the other hand, we have been working extensively on methods to quantify brain connectivity from functional magnetic resonance images (fMRI). We have applied several statistical tools for that purpose, including multidimensional scaling[21,22], wavelets[23] and, to a larger extend, frequency related methods[21,24-26] (See Figure 2). These brain connectivity measures have been useful for

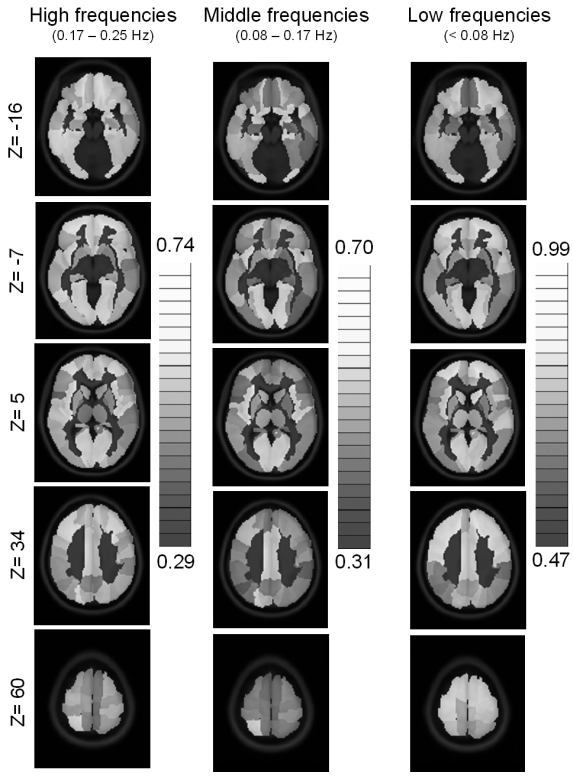

Figure 2. Levels of resting state functional connectivity in the healthy brain as given by a frequency based mutual information measure. Results are shown through a parcelation of the brain in 90 regions. Extracted from the original work published by Salvador *et al.*[24].

more complex descriptions of brain organisation based on what is known as "small world networks"[21,23].

Apart from bringing new knowledge on the dynamics of the healthy brain in the resting state and while performing cognitive tasks, we are using these new tools to study schizophrenia and other major psychiatric disorders.

Future directions

As noted above, we are initiating studies to further investigate the finding of default mode network dysfunction in schizophrenia. Importantly, Whitfield-Gabrieli *et al.*[5] found evidence that failure to de-activate in schizophrenia was associated with increased connectivity between the medial prefrontal cortex and other parts of the default mode network. We are therefore planning to examine this finding in more depth using the novel connectivity techniques developed by our group. Also, failure to de-activate the default mode network in schizophrenia has only been found in studies using working memory tasks. However, in normal subjects the default mode network deactivates in response to a wide range of cognitive tasks. We therefore plan to undertake studies to determine whether failure to de-activate in schizophrenia is also seen with other tasks, both executive and non-executive. We are also investigating the relationship of failure to deactivate to genetic polymorphisms identified in schizophrenia. Studies examining default mode network function in schizoaffective disorder, bipolar disorder and major depression and are also underway in collaboration with other CIBERSAM groups.

Future projects in the area of the neuroimaging of schizophrenia include: functional imaging of hippocampal function in the disorder using a virtual reality spatial navigation task and further studies of emotional responsiveness in relation to symptoms like affective flattening. Concerning other disorders we are developing a clinical and neuroimaging study of delusional disorder. We are also planning a study of the neural correlates of euthymic cognitive impairment in collaboration with other CIBERSAM groups.

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COMPARATIVE ASSESSMENT OF CURRENT ANTIDEPRESSANTS EFFICACY AND SEARCH FOR NEW TARGETS AND STRATEGIES FOR THE TREATMENT OF DEPRESSION

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Comparative assessment of current antidepressants efficacy and search for new targets and strategies for the treatment of depression

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SPAIN

ABSTRACT – Depression is a multifactorial disease with a high prevalence worldwide. Despite the advances in drug discovery and therapeutic options there are still multiple shortcomings that need to be improved. In this context, the main work of our research group has focused mainly in three different approaches. Firstly, we have applied and developed methods to obtain evidences about comparative efficacy and safety among competing antidepressants. Secondly, we have analyzed gene expression patterns in the post-mortem brain of depressed patients as well as in different animal models of depression. The aim of this approach was to find genomic alterations related to depression that may constitute new targets for the development of antidepressant drugs. Finally, we have as-

sessed the use of selective α_2-adrenoceptor antagonists in order to improve or accelerate the therapeutic benefits of the antidepressant treatments actually used.

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Introduction

According to the World Health Organization, depression is a chronic, recurring and potentially life-threatening disease that affects about 121 million people worldwide. Moreover, it has been predicted that, by 2020, depression will be the second largest health burden following only heart diseases. Despite the existence of several pharmacological treatments for depression they are far from ideal. On the one hand, antidepressants must be administered for weeks or months to obtain clinical improvements, and the side effects are still a serious problem even with the newer medications. On the other hand, it has been estimated that 30-40% of the depressive patients do not respond adequately to antidepressant therapy, and fewer than 50% show full remission after treatment. In this context, the work of our research group has focused mainly in three different approaches: 1) a comparative assessment of currently used antidepressants efficacy and safety, 2) the search for new targets in depression in order to develop new antidepressant drugs, and 3) the study of new pharmacological strategies to potentiate the efficacy of the actual antidepressants.

Comparative assessment of antidepressants efficacy and safety

One of the many problems currently faced by a clinician attending a depressed patient is to try to decide on the most appropriate treatment to prescribe by following evidence-based guidelines. With a plethora of such guidelines to interpret them adequately and implement appropriately their recommendations the clinician needs to master at least[1] some psychometric issues regarding outcomes measurement and selection, and[2] the general methodology of meta-analysis which ought to be the main support, as the highest level of evidence, of those guidelines.

Fortunately the psychometric issue does not seem to present major problems since the most usual clinician-rated symptomatic scales to assess depressed mood are highly correlated[1,2], and the main on-going issues relate with the usefulness of shorter versions or the use of patient-reported outcomes to inform the clinical practice[3]. However more stress should be put on the clinical relevance of categorical reported outcomes by using standardized criteria such as clinical response, remission, and discontinuation on treatment for any cause. We strongly think such criteria should replace gains since baseline as primary outcome criteria in randomised clinical trials (RCTs) because of their advantages regarding proper interpretation for both clinicians and patients[3,4].

In part because of the extension in the last decade of the concepts underlying evidence-based Psychiatry, and also due to the appearance of no-cost friendly programs to perform meta-analysis, the weighted combination of effect sizes from independent RCTs (or in other words the overall replication of findings) has changed from being a quasi-esoteric

method privative of some initiates to a normal, and even abused, technique in the armamentarium of clinical researchers[5]. As a consequence it has also been filtrated to the clinician who hopefully will currently search for appropriate systematic reviews and meta-analysis to learn about the best treatment currently available for his patient condition. In our world of evidence-based Psychiatry that task ought to be straightforward. However the real situation is far from being so plain. Certainly there is now a wealth of RCTs to inform clinical decisions, and since the beginning of the 21st Century the problem of publication bias –at least regarding industry supported RCTs– has ceased to exist because of independently of being subject to peer publication or not, the summaries of RCT protocols and further main outcomes must be compulsory registered in public domains. However, in the case of depressive disorders, the main available evidence continuous to be the comparative efficacy and safety of antidepressants versus placebo. Unfortunately, much less information exists on the comparative efficacy among competing antidepressants with the same or different pharmacological profile. Thus there is an odd situation where we have at our fingers a wealth of high quality information but, many times, not the kind of information explicitly required to make a therapeutic decision. Accordingly, part of the work of our group is devoted to apply and develop methods to inform, as reliably as possible, about comparative efficacy and safety among competing antidepressants when the required head-to-head comparisons do not exist. For such task we used extensions of the classical methods of two-arm meta-analysis to accommodate correlated multi-arm comparisons within the framework of indirect and network comparisons. Some methodological articles of our group have already appeared[4,6,7] and we look forward to extend our specific research lines to wider translational horizons in the hope of unifying clinical, methodological, and basic research within a coherent framework in the depression area.

Search for new targets for the treatment of depression

It is generally accepted that approximately 50% of the risk for depression is genetic. However, the specific genes underlying the aetiology of this disease have not yet been identified. Our group has developed a research line to analyze gene expression patterns in the post-mortem brain of depressed patients as well as in different animal models of depression.

For an initial approach, a group of post-mortem brain samples of depressed patients were compared to well-matched control subjects using DNA microarrays. Of a total of 22000 explored sequences, significantly altered expression was found for 229 sequences. In the brain samples of patients with depression 82 sequences showed an increased expression when compared to the control group. Conversely, expression was reduced in 147 sequences[8]. Some of the altered sequences identified had been previously associated with depression, like some genes involved in exocytosis processes, glutamatergic neurotransmission activity or glial activity. The altered genes with interest as putative therapeutic targets or molecular markers for treatment and diagnosis of depression are being validated by Western-blott and quantitative real-time polymerase chain reaction (qRT-PCR) techniques.

Animal models involve a unique tool for the study of the pathophysiology of depression and for the evaluation of the therapeutic efficacy of new antidepressant drugs. Using

microarray technology and qRT-PCR for analysis of messenger RNA levels in rat brain cortex, we compared the expression patterns of three different animal models of depression. The models used were acute treatment with reserpine (5 mg/kg i.p.), chronic treatment with corticosterone (18 mg/kg/day for 15 days, subcutaneously implanted pellet), and olfactory bulbectomy. Gene ontology analysis showed that significant gene changes were clustered primarily into functional neurochemical pathways involved in apoptosis and neuronal differentiation[9]. However, only two of these genes (complement component 3 and fatty acid-binding protein 7) showed differential expression levels in all the three models studied[9]. Moreover, some of the genes classically related to human depression were differentially expressed in at least one of these animal models[9]. These results demonstrate that the three models, in spite of showing differences in their gene expression patterns, share modifications in neuronal signalling pathways. Finally, these findings suggest that the corticosterone model is the one which most closely resembles the changes found in postmortem human brains of depressed subjects.

New strategies for the treatment of depression

The administration of several classes of antidepressant leads to an enhanced noradrenergic neurotransmission. Central noradrenergic transmission is regulated by inhibitory α_2-adrenoceptors (α_2-ARs) expressed on locus coeruleus, somatodendritic neurones and on axon terminals. Thus, the activation of these receptors induces an inhibition of noradrenaline (NA) release in the brain. In this context, it has been described that depression is associated with a selective increase in the high-affinity conformation of the α_2-ARs in the human brain[10,11]. This enhanced α_2-AR activity could be involved in the deficit in noradrenergic transmission described in the aetiology of depression. Moreover, the delay in the appearance of clinical improvement with antidepressants could be due to activation of inhibitory α_2-AR autoreceptors by the increase of the synaptic monoamine levels at the first stage of treatment. In this way down-regulation of α_2-ARs has been proposed as the principle action of antidepressant treatment and desensitization of α_2-ARs has been demonstrated after chronic treatment with different antidepressant drugs as desipramine and clorgyline[12]. In the therapeutic context of this hypothesis, the use of selective α_2-AR antagonists appears to be a new and effective pharmacological approach to the treatment of depressive disorders. Taking this theory into account, the work of our research group has focused in two different areas.

In a first line we have developed and pharmacologically characterized a new family of (*bis*)guanidine and (*bis*)2-aminoimidazoline derivatives ('twin' and 'half' molecules) as potential α_2-AR antagonists. Some of these new compounds have demonstrated not only to behave as α_2-AR antagonists but also to be able to increase NA levels in the rat brain[13-15].

On a second approach, we have evaluated whether the combination of a NA selective reuptake inhibitor (reboxetine) or a serotonin selective reuptake inhibitor (citalopram) with an α_2-AR antagonist (RS79948) represents a more effective strategy than the antidepressant alone to enhance noradrenergic transmission. Our results showed that the blockade of the tonic inhibitory effect mediated by α_2-ARs accelerates the enhancement of noradrenergic transmission obtained following long-term antidepres-

sant treatment[16]. These data suggest that α_2-ARs antagonists might be useful adjuncts to currently used antidepressant drugs in augmentation or acceleration strategies.

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INCREASED DENSITY OF 5-HT2 RECEPTORS AND 3H PAROXETINE BINDING SITES IN BIPOLAR DISORDER

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Increased density of 5-HT2 receptors and 3h paroxetine binding sites in bipolar disorder

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SPAIN

ABSTRACT – Although the serotonin system has been implicated in the physiopathology of bipolar disorder, the findings reported are not conclusive. The few studies carried out to date use heterogeneous methodologies with small samples and do not control confounding factors such as pharmacological treatment. The present study analyses pre-synaptic 3H paroxetine binding sites and post-synaptic 5HT2 receptors in platelets of patients with bipolar depression and mania. We use the following methods: Case-control design, including patients with bipolar disorder type I, current depressive episode or current manic episode, not receiving pharmacological treatment that might interfere in the study. We found increases in the density of 3H paroxetine binding sites in manic episodes and in the number of 5-HT2 receptors in bipolar disorder in both mania and depression. We did not find significant alterations in the affinity constant. There was a correlation between suicidal ideation and the duration/severity of the affective episode, but there was no significant relationship with the rest of the clinical variables, either past or pre-

sent. Conclusions: These results suggest the existence of a serotonin dysfunction in the physiopathology of bipolar disorder.

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Introduction

The Psychiatry Department of the Bellvitge University Hospital belongs to CIBERSAM (Centro de Investigación en Red de Salud Mental, Instituto de Salud Carlos III). This is a Spanish mental health research network and our group is one of its nodes. Research is focused on Affective Disorders (Unipolar and Bipolar), OCD (Obsessive-Compulsive Disorder) and first psychotic episodes, and also includes neurobiological (neuroimage, neurochemistry and neurophysiology) and clinical therapeutic studies.

Among the neurochemical systems, the serotonin system is the one that has been studied the most in affective disorders, especially in unipolar depression[1]. Reduced serotonin activity has been associated with increased susceptibility to developing a major depressive disorder and suicide risk[2]. Research on this subject has also been carried out by our department[3,4].

The few studies conducted to date in the context of bipolar disorder suggest the existence of a serotonin dysfunction in the physiopathology of the illness. At the genetic level, associations with the areas of the genome related with the serotonin system have been reported[5,6] though the results are not conclusive[7,8].

Most studies of the serotonin system in the context of bipolar disorder have analysed neurochemical alterations in cerebrospinal fluid and plasma. One of the most consistently replicated findings in bipolar disorder is the reduction in the concentrations of 5HT metabolites, especially in bipolar depression but in mania as well[9]. Several alterations have been reported in the response to serotonin agonists in the hypothalamus-hypophysis axis, such as a blunting of the prolactin response in both mania and bipolar depression, and a reduction of the cortisol response in euthymia[10].

The study of the serotonin uptake system in platelets is a promising approach. The few articles published to date suggest a reduction in the pre-synaptic uptake system in bipolar depression, although the results are not conclusive[11,12]. In mania an increase in the density of the serotonin uptake system has been found[13,14] but this finding has not been replicated in all the studies conducted to date[15]. The studies carried out have followed heterogeneous procedures and have not adequately controlled the factors that may interfere in the results, especially psychopharmacological treatment.

3H paroxetine is a powerful, specific inhibitor of the uptake of 5-HT and therefore a ligand that is well suited to the study of the 5-HT transporter complex[16]. 3H paroxetine binding has not been analysed in bipolar disorder, although Marazziti & cols[17] studied this parameter in 25 patients with psychotic symptoms (21 bipolar) and reported a reduction in the overall sample in comparison with the control group[17]. Re-

duced 3H paroxetine binding has also been reported in seasonal affective disorder[18].

The 5-HT_2 receptor is a post-synaptic receptor whose characterization, in association with the study of pre-synaptic markers, represents a good functional equivalent of the serotonin system[19]. This receptor is one of the most frequently studied in affective disorders, above all in unipolar depression, but it has hardly been investigated in the context of bipolar disorder. To date, only one study has examined its density and affinity, in a sample of 29 manic patients and 29 controls using 125I-ketanserin as a radioligand[20]. Fourteen of these patients were evaluated two weeks after the start of treatment with lithium and then five weeks after returning to the previous functioning levels. The authors did not find significant differences in Bmax and Kd values between manic patients and controls, or between the values at baseline, after two weeks, or at the moment of functional recovery.

In summary, very few studies have been conducted of the serotonin uptake system in platelets of patients with bipolar disorder. The results obtained to date are interesting but controversial. This study analyses pre-synaptic 3H paroxetine binding sites and post-synaptic 5HT2 receptors in platelet membranes of patients with bipolar disorder type I. This is the first study to apply a homogeneous design for both bipolar depression and mania in patients who have not received psychopharmacological treatment.

Methodology

The sample comprised patients with bipolar disorder type I, (current depressive episode or current manic episode according to DSM-IV criteria) attended consecutively at the Psychiatric Service of the University Hospital of Bellvitge between 1998 and 2006. The study was cross-sectional with a case-control design. We prepared an ad hoc questionnaire containing sociodemographic data and past and present clinical variables. Patients who had received previous psychopharmacological treatment that might interfere with the neurochemical study were excluded. Informed consent was obtained from all patients prior to inclusion in the study. Controls were matched for sex and age and were studied at the same time of year in order to avoid seasonal variations. The techniques used to prepare the membrane and the study of the radioreceptors of paroxetine and 5HT2 followed the standard procedure for these analyses[20].

The statistical assessment of the results was performed using the *Statistical Package for Social Sciences* (SPSS) version 10.01. The differences between means of dichotomous variables were compared using the Student test for independent samples if the quantitative variables were normally distributed, and otherwise with the *Mann-Whitney U test*. The differences in means between the qualitative variables of more than two categories were compared using analysis of variance in the qualitative variables that were normally distributed, adjusting for the control variables. The *Kruskal Wallis test* was used in the variables that were not normally distributed. The correlation between normally distributed biochemical variables and other quantitative variables was performed using the *Pearson correlation*, and the non-normally distributed variables were studied using *Spearman's rho test*. The level of significance was set at 0.05 (confidence intervals of 95% for the difference of means studied).

Results

The initial sample comprised 70 patients (35 bipolar depression; 35 mania) and 40 controls. The mean age of patients was 38.5 years, and there was a slight predominance of women over men (52.9% vs 47.1%).

A diagnostic latency of almost 8 years was found in the sample: the mean age of the first episode was 26.7 years and the mean age of diagnosis was 34 years. The mean time of evolution of the illness was 12 years. The most frequent form of onset was depression (above 60%). Ten per cent of patients presented a history of rapid cycling and slightly more than half presented previous suicide attempts. In 60% the illness followed a seasonal pattern and around 35% had previously presented psychotic symptoms. In 11.4% of patients the index episode was the first.

Among the depressive episodes, most were severe without psychotic symptoms (71.4%), melancholic (80%) and with an evolution of more than 40 days since the onset of symptoms. The mean baseline scores on the HDRS were around 37 and the mean initial GAES score was slightly above 36. Of the manic patients, 31.5% presented psychotic symptoms, most of which were consistent with mood (28.6%). The mean time of evolution of the hyperthymia episode was 22 days and the mean baseline scores on the Young and GAES scales were 37 and 39 respectively.

Significantly higher Bmax values for the 5-HT2 receptors were found in all patients than in controls. No other differences were found in the rest of the parameters studied (Table I). Manic patients also presented significantly higher 3H-paroxetine Bmax values than controls, though none of the other biochemical parameters presented significant differences. Table II compares the serotonin alterations in the depressive and manic episodes.

No correlations were found between the serotonin parameters studied and past and present clinical variables, with the exception of suicidal ideation and duration-severity of the episode. Patients with previous suicide attempts presented significantly lower 3H-paroxetine Bmax values than patients without previous suicide attempts. A significant negative correlation (0.01) (bilateral) was found between the number of the 3H paroxetine binding sites and suicidal ideation during the index episode, evaluated by the score of item 4 on the Hamilton Scale ($r = -0.682$ $p < 0.001$; $r = -0.0624$ $p < 0.001$).

Table I
3H paroxetine binding sites and 5HT-2 receptors in patients and controls

		Patients (n = 70)		Controls (n = 40)		
		Mean	SD	Mean	SD	
3H-paroxetine	Bmax	1345.79	404.40	1251.97	232.66	n.s.*
	Kd	0.06	0.07	0.06	0.01	n.s.**
5HT-2	Bmax	134.04	70.47	81.47	20.39	P < 0.01***
	Kd	0.75	0.28	0.70	0.16	n.s.**

SD: Standard deviation
Bmax: fmol/mg proteins. Kd: (nM/l)
n.s.* = No significant differences between patients and controls (T-Test)
n.s.** = No significant differences between patients and controls (Mann-Whitney U)
*** = significant differences between patients and controls (Mann-Whitney U)

Table II
Serotonin function in bipolar depression and mania

		Depression (n = 35)		Mania (n = 35)		
		Mean	SD	Mean	SD	
3H-paroxetine	Bmax	1124.66	350.48	1566.91	329.21	P < 0.01*
	Kd	0.05	0.01	0.07	0.01	n.s.**
5HT-2	Bmax	145.14	87.03	122.94	47.43	n.s.**
	Kd	0.72	0.29	0.78	0.27	n.s.**

SD: Standard deviation
Bmax: fmol/mg proteins. Kd: (nM/l)
* = significant differences between patients and controls (T-Test)
** = no significant differences between patients and controls (Mann-Whitney U)

In bipolar patients, the 3H-paroxetine Bmax values presented significant differences in relation to the time of evolution of the episode and the Hamilton and Young initial scores: negative in the case of time of evolution and the Hamilton initial score, and positive in the case of the Young initial score. No significant differences were observed in the rest of the variables studied.

Discussion

We found an increase in the density of the 3H paroxetine binding sites in manic episodes and an increase in the number of 5-HT2 receptors in bipolar disorder in both mania and depression. The absence of specific studies in this field makes these findings particularly relevant. To our knowledge, this is the largest study of pre-synaptic and post-synaptic serotonin markers carried out to date in naïve type 1 bipolar patients.

The increase in the 3H paroxetine Bmax in mania corroborates previous findings that manic episodes, at least in their initial stages, may be associated with an increase in serotonin neurotransmission in bipolar patients[21]. Several authors have associated the existence of increased plasma concentrations of 5HT with psychotic disorders, irrespective of the specific diagnosis[22,23]. Our findings provide at least partial support for considering mania as a psychotic disorder; however, these other studies cannot be compared directly with ours, because they evaluate different aspects, use different methodologies, and propose hypotheses from different perspectives. Authors such as Marazziti & cols[17] observed a reduction in 3H paroxetine Bmax values in a sample of patients with psychotic symptoms which included a high percentage of bipolar patients[17]. Our results do not support this finding, but the heterogeneity of the sample in Marazziti's group makes it difficult to compare the two studies.

The classical studies of the serotonin uptake system present results that do not always coincide and in fact present methodological limitations. Our results corroborate those of most previous studies[13,14] but not those of a study with a very small sample (7 patients) most of whom were receiving stabilizing treatment[15].

We found increased Bmax of the 5-HT2 receptors in bipolar disorder in both manic and depressive episodes. These results do not support those of the only previous study published to date, which used a different methodology and allowed pharmacological treatment[20]. The increase found in the number of

5-HT2 receptors in bipolar disorder supports the hypothesis of a hypersensitivity of the central post-synaptic receptors secondary to a failure in the regulatory mechanisms of pre-synaptic uptake as a physiopathological mechanism in affective disorders[24].

Clinical limitations of our study include the sample size, the exclusion of other clinical subtypes and the matching of the control group, which was only approximate. Using the platelet model to study the central functioning of the serotonin system may be another limitation.

However, the increases in the density of the 5-HT2 receptors and in the number of 3H paroxetine binding sites in bipolar disorder type I are relevant findings and may help to broaden our understanding of the interrelation and complexity of neurobiological models.

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ANIMAL MODELS IN PSYCHIATRY: CONCEPTUALIZATION AND PRECLINICAL MODELS OF DEPRESSION

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Animal models in psychiatry: Conceptualization and preclinical models of depression

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SPAIN

ABSTRACT – Psychiatric diseases in general and mood disorders in particular, are difficult to model in animals since the subjective nature of the core symptoms appears to preclude objective observation of behavioural changes. A suitable animal model of a psychiatric condition must fulfil three core criteria: share patho-physiological characteristics with the human disease (*face validity*); measure accurately the behavioural and biochemical manifestations of the disease (*construct validity*); and symptoms improve with medications that improve those seen in afflicted humans (*predictive validity*). Also, it is well known that genetic and environmental factors play a key role in psychiatric disorders. Genetic animal models of these disorders represent an important direction for research, and are widely used to explore the role of different genes in brain mechanisms. In this review we explore the conceptualization of animal models in psychiatry and their extension to the different animal models of depression in particular. Conclusions: Animal models are necessary for the advancement of knowledge of the neurobiological mechanisms underlying psychiatric disorders. They are also very useful for exploring new therapeutic alternatives. However, a correct interpretation and conceptualization of a particular state in animals is essential for them to be considered animal models of a human illness. A model should be a useful system for studying another system, not simply a reduction or a simplification.

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Introduction and conceptualization

Animal models are essential in the investigation of the mechanisms underlying human disease and in the design of new therapies. However, modelling complex multi-syndrome psychiatric illnesses such as major depression has been, and is still, one of the main objectives of psychiatric research. One of the reasons for this is that depression is defined clinically as a pathological complex of psychological, neuro-endocrine and somatic symptoms that cannot be reproduced in animals, and especially in rodents. Only certain measurable animal behaviours have been shown to be relevant in human depression. In this paper, we will focus on the utility of current models and the research strategies for investigating novel targets relevant to depression-like symptoms in mice. The review is divided into three parts. First, we discuss the different criteria used to validate an animal model and some of the more pressing issues associated with studying behavioural models of depression. Second, we describe some of the more widely used murine models of depression and/or models for the screening of antidepressant activity, and finally we discuss other relevant issues to modelling depression specific to genetically modified mice and their utility in the study of molecular pathways associated with depression and the mechanism of action of antidepressant treatments.

The animal models have been used in psychiatry throughout history, mainly because they are practical biological systems that help us understand more complex ones, such as those in humans. To evaluate the validity of an animal model, many criteria have to be explored. The validation of animal models in psychiatry has been classically considered under four conceptual categories: *Reliability* and different types of validity: *Construct validity, face validity* and *predictive validity.* Undoubtedly, the more types of validity a model satisfies the greater its value, utility and relevance to the human condition. However, it should be pointed out that some semantic issues seem to exist between some authors[1,2]. This makes the evaluation of the models more difficult. In the present review we will refer to these terms following these definitions: 1) *Construct validity* is defined as the accuracy with which the test measures that which it is intended to measure[1].For example, a study might want to measure depression status by the degree of anhedonia. This measure is one of the symptoms clinically described in depression status, but whether it would constitute a valid measure of the overall syndrome is difficult to assure. 2) *Face validity*[3] is assessed by the similarities between the model and the disease. That is, how well it apparently resembles the human depressive state. It refers to the phenomenological similarity between the behaviour exhibited by the animal model and the specific symptoms of the human condition. For example, because the pharmacotherapy of depression typically requires chronic drug treatment to obtain a full response, for a model to have face validity it must respond to chronic treatment. This point will be discussed below, but this is the main weakness of tests like the forced swimming test (FST) and the tail suspension test (TST) in mice. 3) *Predictive validity* in psychopharmacology is determined mainly by the animal's response to therapeutic drugs. It is assessed by whether a model correctly identifies antidepressant treatments without making errors of omission or commission, and whether potency in the model correlates with clinical potency[2]. 4) *Reliability* refers to the consistency and stability with which the variables of interest

are observed, and is relevant to both independent and dependant variables[1].

The terms *animal model of depression* and *animal test for the screening of antidepressant activity* are frequently used as synonyms in the literature, although they have intrinsically different meanings. An animal model of depression should possess the three most important validities: construct, face and predictive, e.g., the chronic mild stress model mimics depressive disorder to a high degree. However, other very popular models do not satisfy all of these criteria but are considered useful tools for the screening of new drugs. The most relevant examples of tests for antidepressant screening are the FST and the TST which have a very high predictive validity but poor face and construct validity. Their high predictive validity and reliability has led them to be considered cheap, quick and very useful tools for investigating novel drugs relevant to depression-like symptoms in rodents. In the current paper we will be pointing out the differences between animal models and tests for screening.

Rodent strain is another important parameter to consider when trying to design a new paradigm or set up a model. Important differences exist between strains of rodents that can clearly condition the result obtained. Proof of this is the wide range of literature available on this point[4-7]. Differences can occur in a wide variety of behaviours, e.g., baseline immobility scores in control animals in the FST or TST, or lack of sensitivity to clinically used antidepressant treatments. A remarkable example of this last point is the lack of sensitivity of the majority of animal models of depression to selective serotonin reuptake inhibitors (SSRIs) treatment[8-10]. One attempt to improve the lack of sensitivity of animal models of depression to serotoninergic antidepressants is the modified FST in rats, which will be described in detail below. Sex differences have also been described. Differences in sensitivity between male and female mice were revealed by some studies, depending on the strain used[9,10]. Therefore, strain and gender are two important factors to consider when modelling depression disorder. The current paper will not review such differences but we strongly recommend that those researchers who want to tackle behavioural studies in depression or other psychiatric diseases bear them in mind.

Animal models of depression

Depression is one of the psychiatric disorders which is most widely investigated pre-clinically. These studies have been possible thanks to the fact that there are several models that meet the criteria for an "animal model in psychiatry". Unfortunately, none of following models must be considered a standard model of depression, but all of them provide useful information about different aspects of depression disorder and they help us study the neurobiological mechanisms implicated in depression as well as being able to detect new therapeutic approaches to this disorder.

Behavioural Despair Model

Forced Swimming test

The FST, together with the TST, is one of the most common tests used for initial screening of an antidepressant drug. The FST was described by Porsolt in 1977[11] in rat and later was adapted to mouse[12]. The rationale in both species is the same. Animals are placed individually into glass cylinders

containing water, and the duration of immobility during the testing period is evaluated. An animal is judged to be immobile when it remains floating in the water making only the movements necessary to keep its head above the water. Many hypotheses have been advanced to explain the physical adaptation that is the immobility response observed in the FST and TST (see below). The immobile posture in the context of the FST was originally coined 'behavioural despair' by Porsolt (1978)[13], largely based on the assumption that the animals have 'given up hope of escaping'. In other words, immobility represents a failure to persist in escape-directed behaviour. Other investigators have contended that the behavioural responses comprise an evolutionary preserved coping strategy[14] in which immobility behaviour represents the psychological concept of "entrapment" described in clinical depression[15-17]. Thus, the development of immobility disengages the animal from active forms of coping with stressful stimuli[17]. Others have suggested that this immobility may be analogous to the clinical observations that depressed patients often lack sustained expenditure of effort reflected in a pronounced psychomotor impairments[18]

Immobility behaviour is reversed by acute antidepressant treatments in mice and semi-acute treatment (3 doses) in rats. As mentioned before, this is the main weakness of this model and the TST. One of the main advantages of these tests is their ability to detect a very wide spectrum of antidepressants, discriminating antidepressants from neuroleptics and anxiolytics[19-21]. In the 90s, a modification of the FST in rats was developed which is able to correlate specific behaviours with modifications in the monoaminergic system[22]. Catecholaminergic agents like desipramine and bupropion increase climbing-type behaviour, whereas SSRIs and serotonin (5-HT) related compounds increase swimming-type behaviour[22,23] in addition to decrease immobility behaviour. This adaptation of the classical model represents a further step in the identification of the neurotransmitter systems implicated in depressive-like behaviours.

Both the FST and TST are dependent on a motor readout. So, it is very desirable to test spontaneous motor behaviour to discard those animals with severe motor phenotypes or pharmacological side effects in motor behaviour may give misleading information in these tests.

Like the TST, the FST was essentially validated retrospectively based on the effects seen with clinically effective antidepressant agents. This fact would imply that the FST and TST should perhaps be more appropriately considered models of antidepressant action rather than models of depression per se. Self-evidently, as we mentioned before, it is most desirable that an experimental paradigm can detect depressive like behaviour in addition to antidepressant-like behaviours.

Tail Suspension Test

The TST is theoretically similar to the FST. Since its introduction 24 years ago, the tail suspension test has been used as a model for assessing antidepressant-like activity, in most cases in mice[21, 24] although an adaptation of the model exists for rats[25]. In this test, the mice are suspended by the tail for 6 min and the amount of time they spend immobile is manually or automatically recorded[26]. Similar to the FST, a great battery of antidepressants have reversed the immobility time[24, 27]. However, in general, SSRIs are more effective in the TST, whereas other atypical agents (rolipram, levopro-

tiline) reduce immobility in the FST but result inactive in the TST[28]. Furthermore, the TST avoids any possible confusion induced by hypothermic exposure, which may be problematic in the FST, especially if a targeted gene is involved in thermoregulatory processes. Furthermore, the TST also circumvents the need of the mice to swim, which may be relevant for examining the effects of certain genetically modified animals where motor coordination may be compromised. Thus, the TST is more commonly used to study transgenic animals than the FST. However, some commonly used inbred strains, such as C57Bl/6, are not ideal for use in the TST as they have a tendency to climb their tails.

Pharmacological models

The first models developed for depression were pharmacological models. These models are based on bioassays for specific neurochemical actions of antidepressants. They originated from the monoaminergic theory of depression that proposes that "depression is due to a deficiency in one or another of three monoamines, namely 5-HT, noradrenaline (NA) and or/dopamine (DA)". Indeed, one of the earliest pharmacological models in depression was the reserpine effects reversal test, designed by Costa in 1960[29]. It was the first attempt to screen imipramine-like drugs and led to the isolation of desipramine and the demonstration of its antidepressant effect. Reserpine, an antipsychotic and antihypertensive drug, acts by blocking the vesicular monoamine transporter, which transports free NA, 5-HT, and DA from the cytoplasm of the presynaptic nerve into vesicles for subsequent release into the synaptic cleft. The unprotected neurotransmitters are then metabolized by monoamine oxidase (MAO) and therefore never reach the synapse. The consequence of reserpine administration is marked catalepsy, hypothermia and ptosis[29]. Last two symptoms are reversed by monoamine oxidase inhibitors (MAOIs) and different classes of antidepressants[30]. This model has been considered to have poor predictive validity in general, so, it has been used as a screening test of antidepressant drugs rather than an animal model of depression. A similar pharmacological model is the administration of 5-hydroxytryptophan (5-HTP), a precursor of 5-HT, but this model is considered more a test for 5-HT reuptake inhibitor potency[31] rather than a model of depression. Another common pharmacological model is the psycho-stimulant withdrawal test. This model causes depressive-like symptoms and is sensitive to antidepressant drugs. Psycho-stimulant withdrawal decreases locomotor activity in rats. Several antidepressants have reversed locomotor activity[32] and certain tryciclic antidepressants, such as imipramine, are effective in this model[33].

Brain lesion models

The bilateral destruction of the olfactory bulbs creates a chronically altered brain state with complex changes in behavioural, neurochemical, neuroendocrinological and neuroimmunological parameters, many of which are comparable to those seen in patients with major depression[34]. Thus, the olfactory bulbectomy in rodents has been proposed to represent a model for chronic psychomotor agitated depression. It also has a high predictive and construct validity[35]. The major behavioural change in this model is a hyperactive response in a brightly illu-

minated open field arena. Other changes in corticosteroid levels in plasma and serotoninergic dysfunction, which mimic major depression in some patients, have been described. These changes are reversed by chronic, but not acute, antidepressant treatments[36,37] such as the tricyclic antidepressant (TCA) imipramine[38]. Other antidepressants, such as the mixed inhibitors of the reuptake of 5-HT and NA, milnacipran and venlafaxine, reduce olfactory bulbectomy activity in the open field test too. Interestingly, a recent study has demonstrated that bulbectomized mice showed significantly increased brain-derived neurotrophic factor (BDNF) in depression-related brain areas such as the hippocampus and frontal cortex[39]. This clearly disagrees with the neurotrophic hypothesis of depression, which postulates that a loss of neurotrophic factors is directly involved in the pathophysiology of depression, and that their restoration may be the result of the therapeutic efficacy of antidepressant treatment[40-43].

Chronic models of stress

Social Isolation Model

There is evidence that early life events influence brain development and subsequent adult behaviour and play an important role in the causation of certain psychiatric disorders such as depression. Indeed, rats isolated at 16-18 days of age display high hyperactivity levels when compared to those of group controls[44]. Furthermore, it has been reported that behavioural differences between isolated and non-isolated rats is abated by acute treatment with TCAs, such as amitriptyline and desipramine[45].The model has strong predictive validity but paradoxically, isolated animals show greater persistence in operant tasks[46]. Similarly, neonatal handling reduces emotional reactivity and susceptibility to learned helplessness. The handling procedure reduces helplessness behaviour, with a decrease in the number of escape failures, an increase in the number of avoidance responses and a decrease in the escape latency in the shuttle-box after induction of learned helplessness. In addition, handling during infancy decreases the number of fecal boli in an open field test, which suggests that the level of emotivity in adulthood is reduced. It is suggested that handling in infancy improves behavioural adaptation to the environment, including enhanced adaptive response to stress[47,48].

Chronic Mild Stress Model

In this model, animals are submitted to a series of mild randomized chronic stressors (food and water deprivation, stroboscopic illumination, grouped housing) for at least 2 weeks. Animals submitted to chronic mild stress display a number of behavioural, biochemical and physiological changes, reversed by chronic but not acute antidepressant treatment[49]. This model reproduces more accurately the real clinical situation, where antidepressants are only effective after two or three weeks.

Since the initial studies this model has been validated as a model of depression because it assembles the three necessary types of validity to be conceptualized as a model in psychiatry. The construct validity of the chronic mild stress model derives from the evidence that it causes a generalized decrease in responsiveness to rewards because the animals display anhedonia, which is a core symptom in depressive disorders. It possesses face validity because it causes the appearance of many other symptoms of major depressive disorder, such as a decrease in sexual and aggressive

behaviours, locomotor activity and rapid eye movement (REM) sleep latency and it increases the number of REM sleep episodes and loss of body weight[50]. Finally, the predictive validity of the chronic mild stress model is established due to the fact that many studies have reported that a wide range of chronic antidepressant treatments reversed the stress-induced anhedonia. These include TCAs (imipramine, desipramine, amytriptiline) and SSRIs (citalopram, fluoxetine, fluvoxamine)[51,52]. However, an important drawback to be considered in this model is the poor inter-laboratory reproducibility.

Learned Helplessness Model

Another important example of a model of depression is the learned helplessness model, because "helplessness" is another symptom of depression. Learned helplessness is a psychological condition in which an animal has learned to act or behave helplessly in a particular situation (e.g. exposure to repeated uncontrollable shocks). In this situation animals develop escape, cognitive and reward behaviour deficits and this behaviour is reversed by short-term treatment with antidepressants[53]. This model is one of the most robust for the screening of new antidepressant treatments[54-56]. However, it is often criticised because it involves strong stressors, although the animals recover a few days after the cessation of shocks and symptoms are reversed by acute antidepressant treatment (3 days of treatment).

Genetic models

The advent of transgenic technology in mice has had a dramatic impact on all the fields in biomedical research, including the neuropsychopharmacology. Indeed, the generation of knockout (KO) mice lacking specific proteins has become an invaluable tool to predict whether mice with a neurotransmitter dysfunction, both in transporters or receptors, are more predisposed to developing depression-like behaviour. However, care must be taken when using knock-out mice, as compensatory changes can occur owing to the life-long ablation of a protein, and, in fact, such alterations may result in the behavioural phenotype. More recently, inducible and site-specific knock-out mice have been generated, which enables the role of proteins to be assessed in adult mice, negating the compensatory effects. Similar strategies can also be used to knock-in specific genes, which lead to an over-expression of the protein. All of them represent a powerful tool to study the role of specific proteins in depression.

The first KO studies were obviously those related to the monoaminergic system like the 5-HT transporter (SERT) and receptor, which are molecular targets of TCAs and SSRIs. In SERT KO mice, a decrease in basal corticosterone levels[57] was reported and the effect of some SSRIs like fluoxetine was blocked in the TST, whereas the effect of NA reuptake inhibitors was conserved[58]. Furthermore, $5HT_{1A}$ and $5HT_{1B}$ receptor KO mice showed more alterations in anxiety-related behaviours than depression-like behaviours. Another attempt to study depression in genetic models was the manipulation of the noradrenergic system, including its binding sites and carriers. Several studies have reported that NA transporter-KO mice display less immobility following social stress than a control group in a model of depression[59].

The glucocorticoid receptor (GR) is a ligand-activated transcription factor that binds with high affinity to cortisol and other glu-

cocorticoids. A number of studies have considered the possibility that the number and/or function of GRs are reduced in depressed patients, so mice with GR mutations have been studied[60]. GR-KO mice die perinatally but GR-heterozygotes display increased helpless behaviour and stress causes higher corticosterone levels in plasma[61]. So, GR-heterozygote mice could be considered a model of the predisposition to developing depressive episodes after stress.

In recent years the successful administration of short-interfering RNA (siRNA) in vivo has opened the possibility of selectively down-regulating a target gene in a temporal and spatial fashion[62]. One example of this approach is the paper from Thakker and colaborators[63] where SERT-siRNA was infused into the ventricular system, decreasing significantly the SERT mRNA levels in the raphe nuclei. The animals showed an antidepressant-related response in the forced swimming test. This technique is similar to that of antisense oligonucleotide administration, but to date siRNA does not appear to be associated with the side effects of the former. Furthermore, it would overcome the potential developmental adaptations and genetic compensation that may mask the establishment of a clear phenotype in genetically modified animals (knockouts).

Conclusions and perspectives

In this review we have first tried to explain the importance of animal models in psychiatry and we have focused our review on the most used animal models of depression and/or tests for the screening of antidepressant activity. As stated above, animal models in psychiatry, and specifically in depression disorder, are extremely difficult to model because of the multi-facetal aspect of the illness. However, despite their intrinsic limitations, the full potential of animal models of depression has not yet been realized and they represent an under-explored opportunity for drug development. Especially because models such as FST, learned helplessness and olfactory bulbectomy are to test drugs that increase the monoaminergic neurotransmission. Thus, it remains uncertain if other non-monoaminergic mechanisms will be detected by the current models of depressions. The correct conceptualization of the meaning of a model in psychiatry may help to understand the process and to refine or design new models able to reveal the therapeutic potential of a broad range of compounds. Furthermore, new genetic approaches are giving us relevant information about the signalling pathways. All these different approaches will provide us a greater understanding of the pathophysiology of major depression and, hopefully, will lead us to the development of safer and more effective antidepressants.

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Table I
Classical animal models used to modelize human depression

Table 1						
MODEL	**TYPE**	**Face**	**Construct**	**Predictive**	**Description**	**References**
Behavioural Despair	Forced swimming test	-	-	+	Animals are placed individually into glass cylinders containing water and the duration of immobility is recorded Immobility behaviour is reversed by antidepressant treatment One of the most used test to screen antidepressant activity and discriminate antidepressants from neuroleptics and anxiolytics Used in rats and mice	11,12,19,20,21
	Modified forced swimming test	-	-	+	FST with modifications: increasing the water depth to 30 cm from traditional depths of 15–18 cm, using a time sampling technique to rate the predominant behavior over a 5-s interval Used to assess the role of monoamines in antidepressant action: Catecholaminergic agents (noradrenergic and dopaminergic) increase climbing-type behaviour and SSRIs and 5-HT related compounds increase swimming-type behaviour Used in rats	22,23
	Tail suspension test	-	-	+	Animals are suspended by the tail for 6 min and the amount of time they spend immobile is recorded Acute antidepressant treatment decreases immobility behaviour One of the most used test to screen antidepressant activity. Furthermore, one of the most used test to study genetically modified animals Used mainly in mice	24,25,27
Brain Lesion Model	Olfactory bulbectomy	-	+	+	Removal of the olfactory bulbs in rodents shows a variety of behavioural, neurochemical and neuroimmunological parameters: increase open field activity and nocturnal hyperactivity, modify BDNF levels in hippocampus and prefrontal cortex Some of these changes are reversed by chronic antidepressant treatment Used in rats and mice	34,36,37,39
Pharmacological Model	Reserpine	-	-	-	Reserpine acts by blocking the vesicular monoamine transporter (NA, 5-HT, and DA) from the cytoplasm of the presynaptic nerve Its administration causes hypothermia and ptosis reversed by different classes of antidepressants Used in rats and mice	29,3
	5-HTTP	-	-	-	It provides a rapid and accurate index of SSRIs potency in vivo Used in rats and mice	31
	Psychostimulant	-	+	+	Psychostimulants increase the functional activity of central monoaminergic and cholinergic systems It causes a decrease in locomotor activity reversed by different classes of antidepressant Used in rats and mice	32,33
Chronic Stress Model	Social isolation	-	-	+	Animals isolated at 18 days of age display hyperactivity Hyperactivity is reversed by acute antidepressant treatment Used mainly in rats	44,45
	Chronic mild stress	+	+	+	Animals submitted to different randomized chronic stressors display anhedonia, decrease sexual and aggressive behaviours and loss of body weight These changes are reversed by chronic antidepressant treatment Drawback: poor reproducibility inter-laboratories Used in rats and mice	49,50,51,52
	Learned helplessness	-	+	+	Animals submitted to inescapable shocks subsequently display deficits in escape, cognitive and reward behaviours Reversed by acute antidepressant treatment (3 days of treatment) Used in rats and mice	53,54,55,56

Abbreviations: BDNF: brain-derived neurotrophic factor; DA: dopamine; FST: forced swimming test; MAOIs: monoamine oxidase inhibitors; NA: noradrenaline; SSRIs: selective serotonin reuptake inhibitors; 5-HT: serotonin; 5-HTTP: 5-hydroxytryptophan; TCAs: tricyclic antidepressants; +/-: presence / absence of face, construct or predictive validity.

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PSYCHOSIS, PERSONALITY, PSYCHOPATHY AND DOPAMINE: FROM CLINICAL SYMPTOMS TO MOLECULAR ASPECTS

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Psychosis, personality, psychopathy and dopamine: From clinical symptoms to molecular aspects

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SPAIN

ABSTRACT – The 12 de Octubre-PARG-CIBERSAM Research Group has been constituted under the direction of Tomás Palomo. From initial studies on the dopaminergic system carried out in the United Kingdom, the group has developed clinical research projects on different psychiatric disorders and personality traits in which alterations of this system play a central role. Thus, the 12 de Octubre-PARG-CIBERSAM Research Group has focused on psychotic disorders, addictions and dual diagnosis, and impulsive and psychopathic personality traits. Complementing their clinical approach, the group has studied the neuropsychological, neuroimaging, neurophysiological and molecular genetic aspects of these disorders.

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The 12 de Octubre-Psychosis and Addictions-CIBERSAM Research Group (12Oct.-PARG) was set up under the direction of Tomás Palomo continuing his early work on the dopaminergic system and mental disorders carried out in the United Kingdom. These first studies focused on dopaminergic hypersensitivity[1] as the basic substrate of schizophrenia[2] and of the mechanisms underlying addiction, moving from basic to clinical research in translational studies[3] following an original revision of the dopamine hypothesis of schizophrenia[4] (Figure 1). The group has continued deepening understanding of the dopaminergic system and its involvement in psychotic and addictive disorders, and, in relation to these, of personality disorders and impulsivity. In the past ten years, the group was established, based on the clinical work carried out at Hospital Universitario 12 de Octubre and its catchment area (around 1 million inhabitants), with other areas having been added recently. This group has carried out intensive research including neuropsychological, neuroimaging and genetic studies which will be described in this article. Basic translational research which showed that stimulation of the dopaminergic system leads to dopamine sensitization[5] has been taken up again with the development of animal models to study sensitization of dopaminergic circuits involved in impulsivity, learning, personality disorders, and the onset and progression of hyperdopaminergic states as the basis for psychotic phenomena.

This article summarizes some representative examples of the clinical research that has been carried out by the 12Oct.-PARG, with special reference to clinical, neuroimaging and genetic studies that are currently underway related to psychosis and addiction related personality disorders.

Psychotic disorders

Research on psychosis and schizophrenia therefore stems from the above cited late 1970s studies on dopaminergic sensitization in animals and patients, and has constituted the cornerstone on which both Psychiatry Depart-

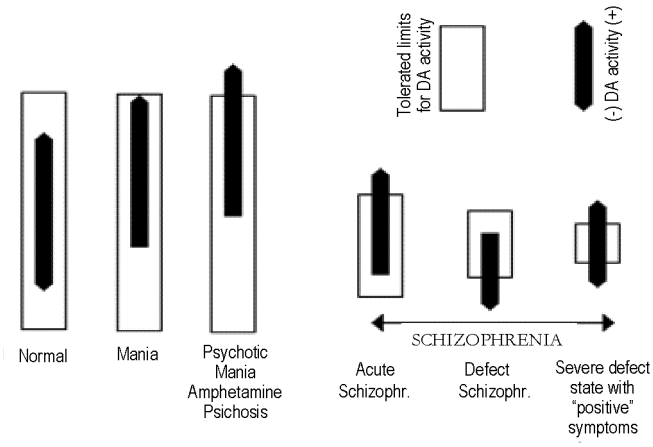

Figure 1. Postulated tolerance limits for dopamine (DA) activity in schizophrenia and other conditions.

ment research in the Hospital Universitario 12 de Octubre and the establishment of the 12Oct.-PARG were based. With respect to humans, research has been carried out on the causes (genetic vulnerability), pathogenesis, psychopathology (negative and neurocognitive symptoms), course (progressive deterioration/neurodegeneration) and treatment (typical and atypical antipsychotics, especially clozapine), from a dopaminergic perspective. A range of different techniques have been used in these studies, including neuroimaging (PET, structural and functional MRI, spectroscopy), neuropsychology, neurophysiology (P300 wave, prepulse inhibition) and genetic studies (of polymorphisms directly or indirectly related to the dopaminergic system).

Vulnerability for Schizophrenia and Cognitive Functioning

From an etiological perspective, the 12Oct.-PARG has mainly focused on genetic vulnerability studies of polymorphic associations of dopamine-related genes, and on studies of addiction as an environmental vulnerability factor and as a complication of psychosis and schizophrenia.

Cognitive decline and abnormal cognition are cardinal symptoms of schizophrenia. It is thus not then surprising that risk factors for schizophrenia are also involved in cognitive dysfunction. We have therefore studied both the genetic contribution and the neuropsychological, neuroimaging and neurophysiological endophenotypes related to cognitive functioning.

Regarding genetic vulnerability for dopamine dysfunction in the etiology of schizophrenia, we have studied both the DRD2 gene for the dopamine D2 receptor and the gene that codes for catechol-O-methyltransferase (*COMT*), an enzyme responsible for the availability of dopamine at prefrontal synapses.

Studying the C957T single nucleotide polymorphism (SNP) of DRD2 gene, we have shown that homozygous carriers of the C allele have a greater vulnerability to develop schizophrenia providing additional evidence that genetic variation at the DRD2 gene plays an important role in the vulnerability to schizophrenia[6]. We also found also that healthy carriers of the CC genotype for the C957T SNP of the DRD2 have a poorer prefrontal cognitive performance than non-CC subjects[7].

The involvement of the COMT gene is still controversial. When we studied the G674A (Val108-158Met) SNP we found a trend toward an association between the Val/Val genotype and schizophrenia[8]. Increasing the sample size and genotyping another SNP (C610G) of the COMT gene has enabled our group to confirm this association. Since COMT activity is sexually dimorphic, we recently carried out two independent studies in homogeneous samples of male and female Spanish schizophrenic patients. In males, we found an association between the homozygous Val genotype and the disorder, which resembled a recessive model ($P = 0.022$; odds ratio [OR] = 1.67). This overrepresentation Val homozygotes is at the expense of a decrease in heterozygous individuals, whilst the Met homozygotes showed no differences when controls and patients were compared. As a consequence, the heterozygous genotype in this sample had a protective effect ($P = 0.03$; OR = 0.65) and a strong deviation from Hardy-Weinberg equilibrium in male patients was observed ($P = 0.006$). In addition, a 2-SNP haplotype analysis (rs4818-Val158Met) confirmed that there is an overrepresentation of the different homozygous Val genotypes in the male schizophrenic sample. Regarding females,

we did not find any statistically significant association between COMT SNPs and schizophrenia. In the light of this we suggest that the Val158Met SNP is involved in risk and protective genotypes for schizophrenia in Spanish males[9].

The cannabinoid system was also explored for genetic vulnerability factors, given its relationship with the dopaminergic system. Allele 4 of the (ATT)n microsatellite located in the 3' region of the cannabinoid receptor 1 gene (CNR1) was found to be a protective factor against schizophrenia, independently of substance use[10,11].

Looking for vulnerability markers related to dopamine, in collaboration with Lourdes Fañanas CIBERSAM group, we have expanded the analyses of the genetic contribution of the IL-1B gene (IL-1 cluster, chromosome 2q13) wich codes for interleukin-1beta (IL-1beta). This cytolcine plays a key role in dopaminergic differentiation and dendrite growth in developing cortical neurons to brain functional changes and to structural abnormalities in schizophrenia. Our results suggest that hypofrontality reported in some schizophrenic patients might be explained, at least in part, by this functional polymorphism at IL-1B gene[12]. As well as COMT gene differences described above, other genetic variants with influence on brain functionality may account for the neurocognitive heterogeneity observed in schizophrenic patients.

Recently the 12Oct.-PARG has started an ambitious project (FIS08/0514) to study the relationship between cognitive deficits and psychosis in schizophrenia and bipolar disorder from the standpoint of a common dopaminergic dysfunction, using clinical, neuropsychological, neurophysiological, neuroimaging and molecular genetic approaches.

Pathogenesis and disease progression. Neurodegeneration

The group has also investigated the etiopathology of psychosis using neuroimaging. In this respect, complex techniques (volumetric MRI, MRI spectroscopy, PET) were used in initial projects to study the putative role of neurodegeneration in schizophrenia. The first results obtained confirmed early volume loss of prefrontal gray matter fitting a logarithmic model[13], and N-acetyl aspartate spectroscopy data suggested the need for alternative approaches to the neuronal hypothesis (involving glia, neuropile) in order to explain the histological substrate of this volume loss[14]. In a different study, IL-1B and IL-1RN genes, involved in neurodevelopment and neurodegenerative processes, were analyzed in schizophrenics, in collaboration with the Lourdes Fañanas CIBERSAM group. Patients the carrying VNTR-allele*2 of the IL-1RN gene showed a significant enlargement of both left ($P = 0.002$) and right ($P = 0.01$) ventricles. Sex and illness duration were controlled for in the analyses. Our results, though preliminary, suggest that the IL-1RN gene might contribute to the ventricular volumetric changes observed in schizophrenic patients[15].

Combining volumetric and functional techniques added complexity to the results obtained by the group, with findings indicating that volume loss and dorsolateral prefrontal cortex hypoactivity were not clearly correlated in initial stages of the disorder[16], and suggesting the need to explore brain areas that had not been much considered previously, especially the visual cortex[17].

Atypical Antipsychotic Treatment and Clozapine

The group's findings regarding treatment include the important differences observed

in structural, functional and spectroscopic neuroimaging between patients treated with typical and atypical antipsychotics. Of special interest was the finding that lymbic/prefrontal circuit hyperactivity and visual circuit hipoactivity were corrected after administration of atypical antipsychotics, especially clozapine[18], together with a reduction (albeit incomplete and varying according to the drug used) of cortical grey matter deficits[19]. Based on these results, a new project (FIS06/0219) is currently underway in which clozapine is used to treat first-episode psychosis with the hypothesis that it will lead to an improved clinical and neuropsychological course, and to prevention of the expected atrophy in the first few years after illness onset.

Dual diagnosis

The clinical interest of the 12Oct.-PARG in addictive disorders and their relation with the dopaminergic system led them to investigate the comorbidity between psychosis and substance use disorders (SUDs), that is, dual diagnosis. In this respect, the group has studied the clinical and sociodemographic differences between psychiatric inpatients with and without dual diagnosis[20]. Cognitive function in schizophrenia and its relationship with psychotic symptoms when SUD history is considered has also been studied. Thus, correlation between PANSS negative scores and Wisconsin Card Sorting Test performance was found in schizophrenic patients without SUD history, but not in dually diagnosed schizophrenic patients[21]. Regarding dual diagnosis from a genetic perspective, the group is studying common vulnerability factors for both psychosis and SUDs (FIS 08/0529).

Personality traits and disorders

The same, striatal-meso-cortico-limbic, dopamine circuits, that are involved in the dopamine hypothesis of psychosis and schizophrenia underlie the mechanisms of impulsivity and addictive disorders. On the other hand, the 12Oct.-PARG has a well established tradition in the study and treatment of these disorders. Therefore, continuing with the dopamine system, the group has been studying both in animals and humans the dopaminergic basis of impulsivity, addiction and comorbid personality disorders. Here we present some of the research carried out by the group, focusing especially on impulsivity, attention-deficit-hyperactivity-disorder (ADHD) and antisocial/psychopathic disorders. In studying comorbid vulnerability we have focused on genetic polymorphisms directly or indirectly related to the dopaminergic system, as we did for psychoses.

Attention-Deficit-Hyperactivity Disorder (ADHD)

Starting from previous studies on alcoholic populations, the group has evaluated impulsivity as a personality trait in alcoholic patients from a clinical[22], neuropsychological[23] and neurophysiological[24,25] perspective. In order to avoid the possible confounding effect of substance use, impulsivity was also studied in pathological gamblers. Neuropsychological tests as well as self-administered questionnaires indicated a high level of impulsivity in both alcoholic patients and pathological gamblers, especially in those with childhood ADHD history[26]. Using the Wender-Utah Rating Scale, an instrument for retrospectively diagnosing ADHD validated in Spanish population by our group[27], we found that around one-third

of alcoholic patients[28], and a similar proportion of pathological gamblers[26], had a history of childhood ADHD.

These results contributed to a better understanding of the clinical characteristics of these patients, and led to the search for genetic markers of vulnerability. We found an association between ADHD and genetic variants of *CNR1* in alcoholic patients[29], where variants with a greater number of repetitions of the (ATT)n microsatellite were overrepresented among patients who had a history of childhood ADHD. Furthermore, the number of repetitions of the microsatellite was correlated with WURS scores, indicating that the effect was quantitative in nature. Research on ADHD genetics is ongoing with the genetic mapping of the locus/loci involved in ADHD in Spanish families (Alicia Koplowitz Foundation Research Grant 2007-2009).

Dissocial personality disorder and psychopathic traits

Regarding personality traits and disorders, the use of the concept of psychopathy has improved the capacity for defining patients with antisocial disorders and has enabled the group to identify more homogeneous populations for the study of candidate genes. Psychopathy is characterised by egoism, lack of remorse or guilt, callousness and lack of empathy. These subjects are also impulsive, aggressive, and some may become delinquents. Psychopathy many of the traits of Factor-1 items in Psychopathy Check List (PCL-R) closer to ICD adult Dissocial Personality than to DSM Antisocial Personality.

The 12Oct.-PARG has described an important association between antisocial behaviours and the *Taq*IA SNP in alcoholic patients[30]. Regarding psychopathy, psychopathic traits were evaluated by the Hare's Psychopathy Checklist revised (PCL-R). The genotype distribution indicates there is a relationship between the *Taq*IA SNP, CNR1 and FAAH endocannabinoid genes and PCL-R's Factor 1 in alcoholic patients (Figure 2). This relationship seems to be additive and independent and might be responsible for 11.4% of the variance in this PCL-R subscale[31]. Our results suggest the implication of the dopaminergic and endocannabinoid systems in those processes leading to the comorbidity of alcoholism and antisocial behaviour.

Looking more specifically for links between dissocial personality and dopamine interactions we found a strong interaction between *Taq*IA and the C957T SNP of the DRD2 gene, both in locus 11q 22-23, such that the simultaneous presence of the risk genotypes for both polymorphisms, but not of each one individually, was associated with a greater prevalence of dissocial personality disorder and psychopathic traits (PCL-R) (Figure 3). Therefore the *Taq*I-A polimorfism of the ANKK1 gene and the C957T of the DRD2 gene are epistatically associated with psychopathic traits in alcohol-dependent patients[32]. The coincidence of both polimorphisms suggests a possible potentiation of dopamine activity: an increase in dopamine synthesis (*Taq*IA1) and a secondary increase in D2 receptor number (C957). However, although this study suggests an interaction between the novel kinase expressed by the *ANKK1* gene and the dopaminergic D2 receptor, the ANKK1 protein has not been identified as of yet, leading the group to start a basic research project with the objective of characterising this kinase in order to define the biological substrate underlying the *Taq*IA SNP genetic association findings (FIS 08/0529).

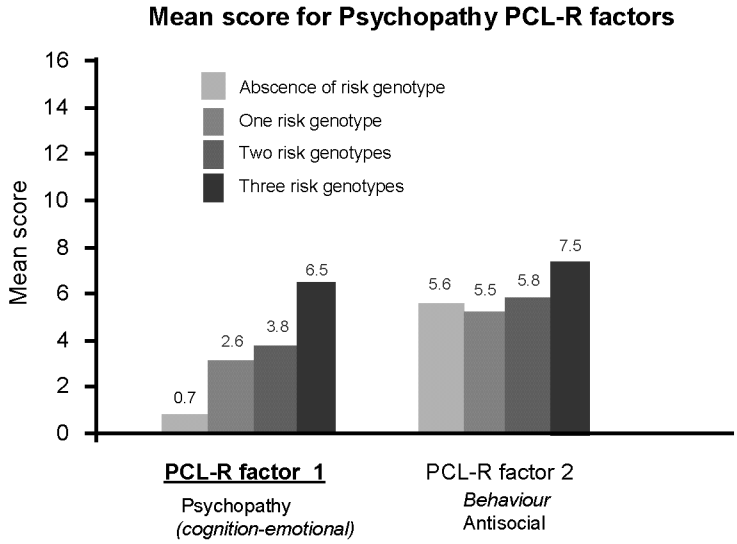

Figure 2. Polymorphisms for genes ANKK1, CNR1 and FAAH, contribute independently (4.1%, 3.8%, 4.1%) and additively (11.4%) to phenotype Factor 1 (psychopathic traits) total variance.

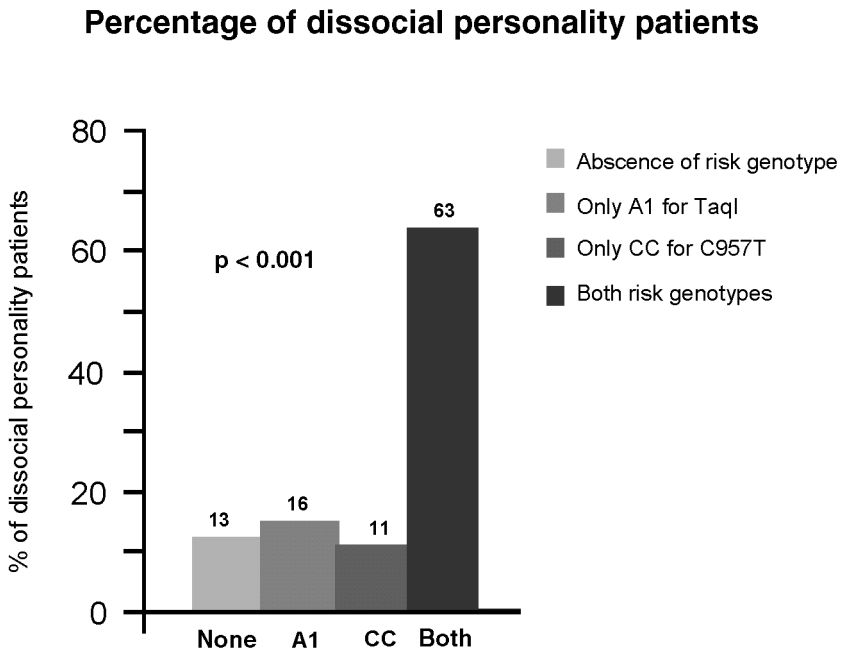

Figure 3. Percentage of individuals with dissocial personality. Epistatic relationship, between polymorphisms *Taq*I-A1 + of ANKK1 gene and C957T of gene DRD2. Increased risk for Dissocial Personality only when both polimorphisms are present.

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LONG-TERM EFFICACY OF ANTIDEPRESSANTS: ANALYZING BRAIN ADAPTIVE MODIFICATIONS

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Long-term efficacy of antidepressants: Analyzing brain adaptive modifications

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SPAIN

ABSTRACT – The regulatory changes induced by chronic antidepressants on the different brain signalling process has been the subject of study in our group. We here review some of the results on this topic. On one side, our efforts have been addressed to the study of the coupling of 5-HT_1 receptors to G proteins: we have demonstrated that 5-HT_{1A} autoreceptors are selectively desensitized by chronic fluoxetine, suggesting that this could be one of the reasons of the delayed response of antidepressants. A functional desensitization of 5-HT_{1B} receptors has been also found. On the other hand, we have focused on the mechanisms involved in neural proliferation, studying two possible new targets: a) the endocannabinoid system, as we have observed a functional up-regulation of CB_1 receptor functionality in an animal model of depression (olfactory bulbectomy), reversed by fluoxetine; and b) the Wnt-β-catenin pathway: an up-regulation of the expression of β-catenin in hippocampus, in parallel with an increase of cell proliferation, has been observed in the hippocampus of rats treated with venlafaxine. Taken together, these results provide valuable information about the involvement of transductional pathways in the mediation of the effects of antidepressant drugs.

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Depressive disorders are debilitating diseases with a high life prevalence[1]. The molecular mechanisms underlying the therapeutic action of antidepressant drugs (ADs) are not fully clarified: those most commonly used present as an immediate mechanism of action their ability to increase serotonin (5-HT) and/or norepinephrine (NE) brain levels. Since the initial introduction of MAOI and tricyclic compounds, several pharmacological groups have been progressively incorporated to the therapy of depressive disorders: in this regard, selective inhibitors of 5-HT reuptake (SSRI) have represented a relevant landmark in the field. Dual NE and 5-HT reuptake inhibitors (SNRI) are a new alternative, still in the frame of monoaminergic acting drugs[2]. A huge number of compounds, exploring other non-monoaminergic mechanisms[3], are currently in development, although still without a clinical demonstration of efficacy.

Although the increase in monoamine levels is a short-term consequence of ADs, all these drugs need to be administered for at least 2-4 weeks to produce a significant clinical improvement. This lag is considered to be necessary for brain adaptive processes to occur[4-6]. It has been classically suggested that these long-term processes could be related to progressive changes in aminergic neurotransmission. In the recent years, other non-exclusive neurobiological theories propose that the functional efficacy of ADs could involve modifications in various signaling pathways regulating cellular plasticity and survival, leading to trophic responses[7].

The evidence that available ADs treatments exhibit a limited efficacy and a slow onset of action suggests that this therapy has not yet reached their upper limit. Therefore, further research on new targets, in addition to increase our knowledge about the mechanisms underlying the antidepressant effect, will likely result in the discovery of drugs with higher level of clinical efficacy profile of response and faster onset of action. In the last decade, our group has been interested in the analysis of the intracellular mechanisms that are modified by chronic antidepressant treatments. This research has been mainly carried out in normal animals, but some studies in animal models of depression as well as in postmortem brain samples of depressed patients have also been carried out.

Methods

In the studies reviewed below, we have used a number of experimental procedures (radiometric labeling, western blot, immunohistochemistry, enzyme quantiation, electrophysiology, behavioural approaches) in order to analyze in deep the involvement of intracellular mechanisms in the long-term response to antidepressants. We will not describe here in detail the different methodological approaches, that are fully reported in the original articles[8-11].

Adaptive changes of monoaminergic systems: The case of 5-HT$_1$ receptors

5-HT-mediated neurotransmission is still one of the main identified targets for antidepressant action. Chronic administration of ADs results in regulatory changes of the different 5-HT receptor subtypes, which could be of relevance for the clinical response. 5-HT exerts its actions through at least 14 different receptor subtypes, the 5-HT$_1$ family, associated to G proteins, is present in high densities through the central nervous system. In this regard, our group has devoted considerable effort to analyze the modifications induced by ADs on the

transductional mechanisms associated to the two main 5-HT_1 receptor subtypes: 5-HT_{1A} and 5-HT_{1B}. Indeed, the efficacy in coupling to G proteins by means of [^{35}S]GTPγS binding autoradiography has been one of the subjects of our study[8]. This technique provides anatomical and functional information since activation of G-protein-coupled receptors upon agonist binding can be detected, and at the same time, the location of activated receptors can also be visualized. [^{35}S]GTPγS binding autoradiography is based on the increase in guanine nucleotide exchange at G-proteins upon agonist stimulation. The nucleotide exchange process can be observed by measuring the binding of [^{35}S]GTPγS, a GTPase-resistant analogue of GTP.

As it is illustrated in Figure 1A, chronic treatment with the SSRI fluoxetine (10 mg/kg, 21 days) induces a differential response in the level of stimulation of [^{35}S]GTPγS binding, depending on the rat brain area analyzed: a significant desensitization is observed in the dorsal raphe, while non-significant changes occur in the remaining areas examined (i.e. hippocampus). 5-HT_{1A} receptors over the dorsal raphe are presynaptic and act as autoreceptors controlling the neuronal discharge. A desensitization of 5-HT_{1A} autoreceptors following AD treatment has been also found in vivo studies, including electrophysiological recordings[8,12,13]. Our results demonstrate that this fluoxetine-induced desensitization of 5-HT_{1A} autoreceptors occurs at the G protein level. This finding is of special interest taking into account that it has been repeatedly suggested that this desensitization may be critical for the delayed onset of the antidepressant effect of SSRI[5].

With respect to 5-HT_{1B} receptors (Figure 1B), our studies reveal a general response of decrease in their G protein coupling ability throughout the rat brain (caudate-putamen, substantia nigra). These studies, carried out on naïve rats, are in agreement with recent studies of our group that show that this tendency to the decrease in 5-HT_{1B}-dependent functionality is also present in a established animal model of depression (olfactory bulbectomy) in some (substantia nigra, -22.7%; dorsal raphe, -31.0%, $p < 0.05$) but not all (caudate-putamen) areas (unpublished). The

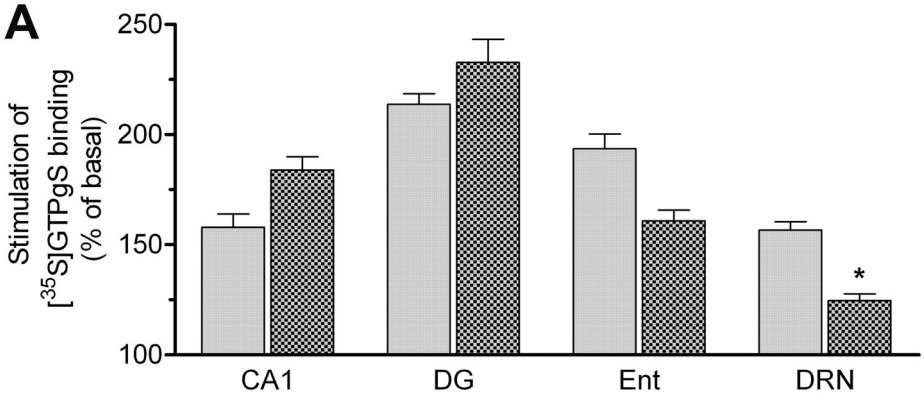

Figure 1A. Effect of chronic fluoxetine treatment (10mg/kg/day, 21 days, p.o) on 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding induced by 8-OH-DPAT (10 μM). A significant desensitization is observed at dorsal raphe (DRN) autoreceptors, but not at postsynaptic receptors (CA1); gray for control and pointed pattern for treated.
CA1: CA1 field of hippocampus; DG: Dentate gyrus; Ent: Entorhinal cortex; DRN: Dorsal raphe nucleus (*$p < 0.05$, *Student t-test* unpaired data).

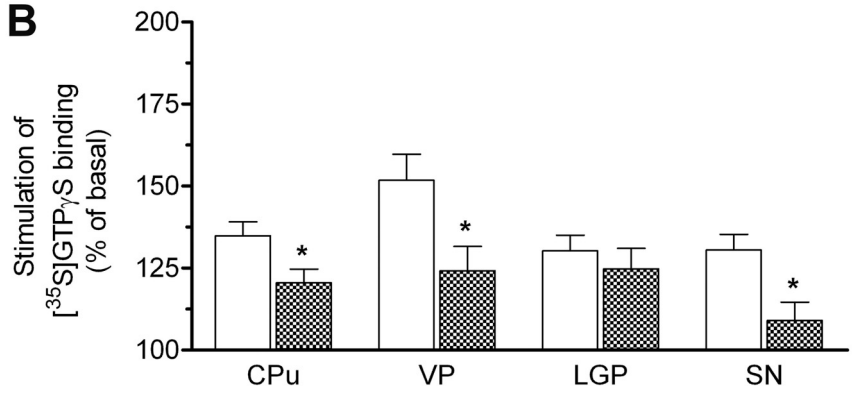

Figure 1B. Effect of chronic fluoxetine treatment (10mg/kg/day, 21 days, p.o) on the 5-HT_{1B} receptor-mediated stimulation of [^{35}S]GTPγS binding induced by 5-HT (10 μM) in coronal sections of the rat brain. A pattern of decrease is observed following fluoxetine; white for control and pointed pattern for treated.
CP: caudate putamen VP: Ventral pallidum; LGP: Lateral globus pallidus; SN: Substantia nigra (*$p < 0.05$, *Student t-test* unpaired data).

tendency to the functional desensitization of 5-HT_1 receptors can be explained in terms of regulatory response to the increase in the levels of synaptic 5-HT[14], due to the acute inhibition of the reuptake process. Although an exact correlation between these changes and the degree of efficacy of ADs is difficult to establish, it is tempting to speculate that these adaptive modifications in 5-HT-mediated signal transduction are required for the clinical response of these drugs.

Is there a role for the endocannabinoid system in the treatment of depression?: The olfactory bulbectomy as a model

Bilateral olfactory bulbectomy (OBX) in the rat is widely used as an animal model of depression, as these animals exhibit a number of behavioral, neurochemical and structural changes that are reversed by chronic ADs administration[15]. As current data suggest that brain endocannabinoid (EC) signalling, mainly through CB1 receptors, might be involved in the long-term adaptations induced by ADs, we have used this model to clarify this issue[11]. As shown in fig. 2A, an increased CB_1 receptor –mediated [^{35}S]GTPγS binding induced by the reported agonist WIN 55,212-2 in the prefrontal cortex of OBX animals was found: chronic fluoxetine fully reversed this increase. Interestingly, previous studies have demonstrated an elevated CB_1 receptor –mediated [^{35}S]GTPγS binding in cortical samples from depressed patients[16]. Our results, in addition to validate the OBX as a model of depression, strongly support the involvement of EC signaling in both depression and antidepressant mechanisms, as it is illustrated by the absence of modifications in the animals receiving chronic fluoxetine. In this regard, it has been shown that CB_1 receptor knock-out mice exhibit enhanced depressive-like behaviours[17] and, consistently, acute low doses of cannabinoids produce antidepressant-like effects in rodents[18,19] likely via promoting hippocampal neurogenesis[20]. Nevertheless, further studies are required in order to fully clarify the role of EC system in depression.

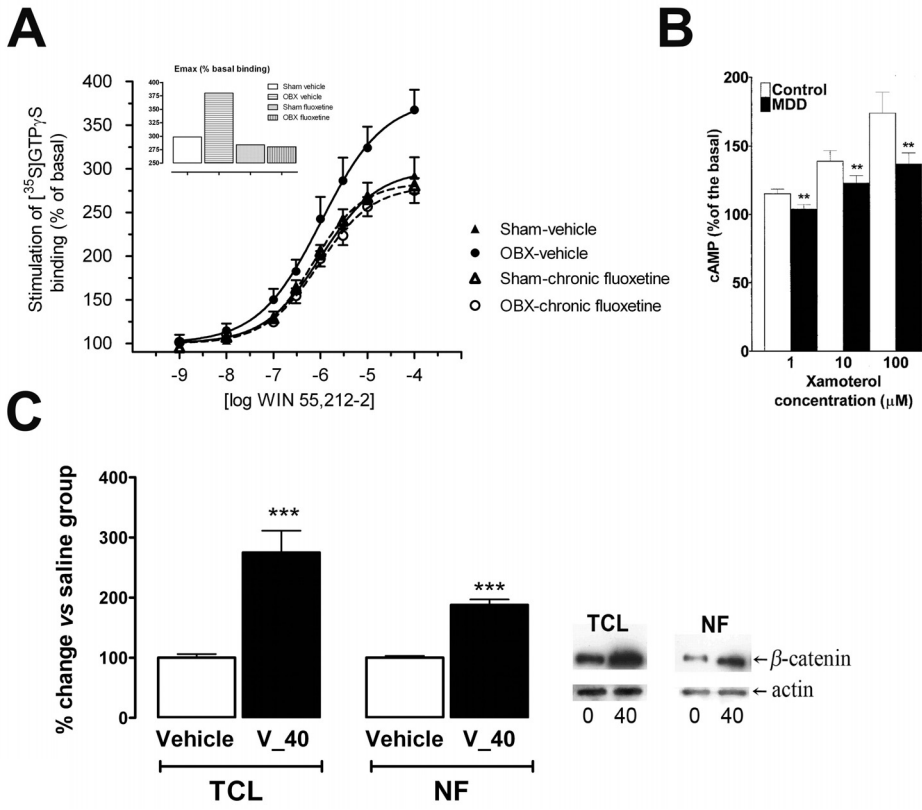

Figure 2. **A.** Effect of OBX (olfactory bulbectomiced rat) and chronic treatment with fluoxetine (10 mg/kg/day, 14 days, minipumps) or vehicle on CB_1 receptor-mediated stimulation of [^{35}S]GTPγS binding induced by WIN 55,212-2 (10μM) in rat prefrontal cortical membranes. Note that chronic fluoxetine reversed the increased functionality of CB_1 receptors induced by OBX (inserted graph). Data represent the mean ± SEM. Modified from Rodriguez-Gaztelumendi *et al*., 2009. **B.** Effect of increasing concentrations of the specific β-adrenoceptor agonist xamoterol (1, 10, and 100 μM) on cAMP (cyclic adenosine monophosphate) levels (expressed as mean ± SEM of the percentage of increase over the basal) in crude membranes from postmortem human frontal cortex of control (open bars) and major depression disorder (closed bars). $^{**}p<0.01$ *post hoc* paired t test after repeated-measures analysis of variance. Taken from Valdizán *et al*., 2003. **C.** Effect of chronic venlafaxine (40 mg/kg/day, 14 days, minipumps) treatment on the expression of main effector proteins of Wnt and AKT/PKB signaling pathways. Graphs represent relative densitometry levels of β-catenin in treated animals as a percentage of these proteins in saline group animals (mean ± SEM). Venlafaxine treatment increases β-catenin immunoreactivity in TCL (total cell lysate), and NF (nuclear fraction) of rat hippocampus in Western blot studies. Densitometric measurement levels were normalized to actin protein amounts.

Modulation of neural plasticity circuitry: Supporting a trophic response for antidepressants

In the last few years, the interest about the mechanisms of action of antidepressants has moved from the receptor level to the intracellular signaling cascades[21]. In this regard, the cAMP-CREB transduction pathway has been consistently implicated in the long-term effects of antidepressants. Studies carried out in postmortem samples from depressed patients have resulted in contradic-

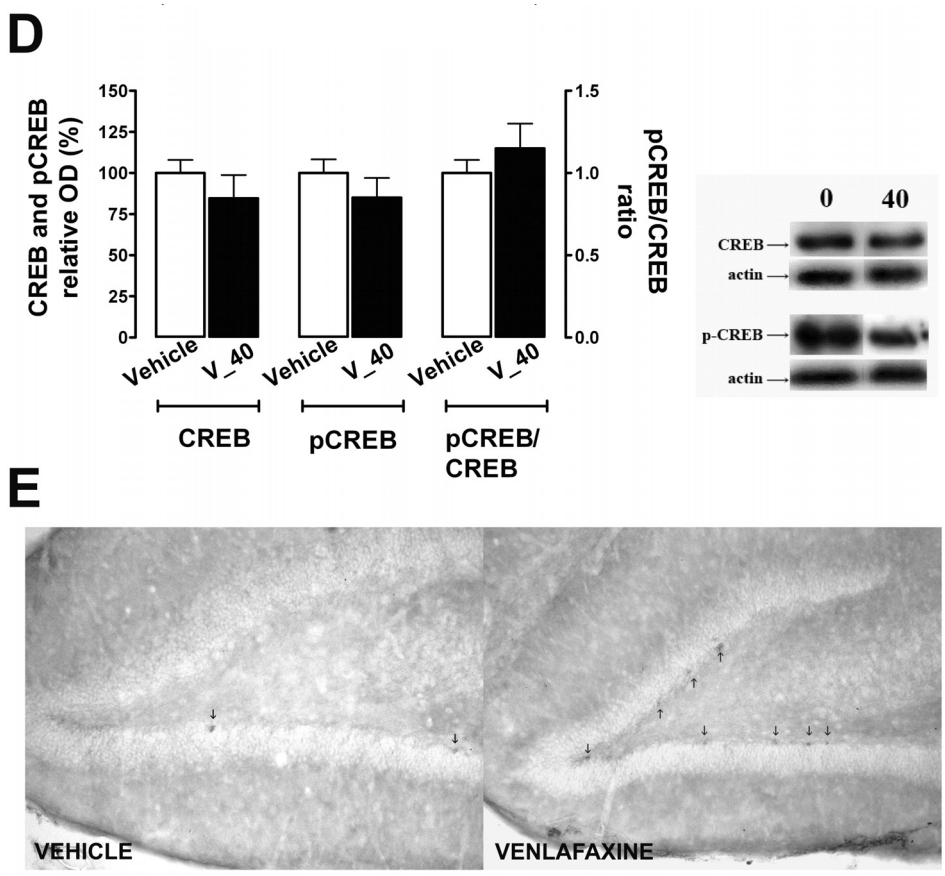

Figure 2. (cont.) **D.** Effect of chronic venlafaxine (40 mg/kg/day, 14 days, minipumps) treatment on the expression of CREB and pCREB. Graphs represent relative densitometry levels of CREB and pCREB, and pCREB/CREB ratio related to the vehicle group (mean ± SEM) of nuclear fractions from rat hippocampus from saline and venlafaxine treated animals in Western blot studies. Densitometric measurement levels were normalized to actin protein amounts.
E. β-catenin immunohistochemistry in the subgranular zone (SGZ) of the hippocampus of adult rat from vehicle and venlafaxine (40 mg/kg/day, 14 days, minipumps) treated animals. β-catenin positive cells were labelled using DAB as a chromogen. Cresyl violet was used as counter-staining. The number of β-catenin positive cells in the SGZ is significantly increased after chronic treatment with venlafaxine.

tory results[22]: We have also addressed this issue, finding no significant change in the basal activity of the enzyme (adenylate cyclase) in brain samples from a well characterized group of depressed patients, with respect to matched controls[9]. However, we found a significant lower response to β_1-adrenoceptors agonist-stimulated AC activity in the major depression group ($p < 0.01$) (see Figure 2B).

It is now well documented that chronic AD treatment enhances cell proliferation in adult rodent subgranular zone (SGZ) of hippocampus and that the time required for the differentiation and maturation of newborn neurons correlates well with the appearance of clinical response to the AD treatment[23]. In line with the new trophic hypothesis, we have addressed in detail the modifications induced by the chronic administration of the

SNRI venlafaxine (40 mg/kg, 14 days) on two intracellular proteins involved in neural plasticity: in addition to the expression of CREB and pCREB, widely suggested to be involved in AD-induced cellular changes, we have also analyzed the expression of β-catenin, an emerging candidate to play a key role in neuroproliferative processes. Although the involvement of CREB and pCREB expression in the cellular responses induced by antidepressants is widely accepted, the nature of this modulation appears to depend on several factors (type of antidepressant, doses, route of administration) and contradictory data have been published[24,25]. We have found no modification in CREB and pCREB expression in the hippocampus of rats treated with venlafaxine (figure 2D). In contrast, preliminary data from our lab appear to indicate that chronic fluoxetine does up-regulate pCREB in the rat brain.

Wnt-β-catenin cascade regulates the hippocampal neurogenesis in the adult brain. Activation of the canonical Wnt pathway leads to the inhibition of GSK-3, allowing β-catenin to be translocated to the nucleus, where activates transcription of target genes. We have demonstrated that chronic venlafaxine induces a significant increase in the expression of β-catenin in the SZH (Figure 2E): an increase in cell proliferation, quantified by BrdU immucytochemistry, is observed in the same animals[10]. Western blot (Figure 2C) and immunoelectron microscopy studies have demonstrated an increased presence of β-catenin (+88.0 ± 9%, western data) at the nuclear level[10]. These results suggest that the hippocampal proliferative effect of chronic venlafaxine, only evident at a dose that inhibits both 5-HT and NE reuptake systems, requires a strong activation of intracellular signaling through Wnt[26], probably resulting in an increase of the expression of cell cycle regulator genes.

Conclusion

In conclusion, our group is focusing its efforts in the analysis of the modulatory changes occurring on the monoaminergic neurotransmission following antidepressant treatments, and on the modification of those involving neuroplastic and proliferative pathways. We are also interested in the possible interactions between these two types of responses. These studies may contribute to the development of new therapeutic targets for the depressive disorders, which is the ultimate goal of all our work.

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NEUROPLASTICITY AND DEPRESSION: FIRST DEPRESSIVE EPISODES STUDIES (FIDES)

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Neuroplasticity and depression: First Depressive Episodes Studies (FIDEs)

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SPAIN

ABSTRACT – Neuronal plasticity may have a critical role in the pathophysiology of *Major Depression*. A variety of genetic, endocrine and environmental factors involved in the development of depressive disorder exert a high influence in neuroplasticity/neurogenesis processes, which in turn might be crucial in recovery from episodes and prognosis of the illness. We use the following prospective-longitudinal study with patients with a first episode of MDD. Included will be 30 patients matched with 30 healthy subjects by age, gender and IQ. Four modules will be established: Clinical (demographics and clinical variables); Neuroimaging (3T MR imaging acquisition); Neuropsychological (cognitive assessment); Biochemical (DNA extraction; BDNF plasma levels; telomere length and telomerase activity; salivary cortisol determination). There will be a baseline assessment and after 1 and 2 years. Expected results: To establish relation between how patients affected

of a first episode of depression get access to the health care system and to specialized services for early recognition and treatment and neurochemical, neuroanatomical and neuropsychosocial markers. The combination of different factors involved in the pathophysiology of depression will allow us to establish pragmatic models of prediction of the therapeutic response by neuropsychobiological profiles. Conclusions: Carrying out a project where the patients will be detected, diagnosed and treated at the very beginning of the illness will help on the one hand to determine what clinical, social or psychological variables might be related to antidepressant response, and on the other hand, this approach will reduce the costs of no treating the depressive episode as soon as possible.

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Major depressive disorder (MDD) is usually an episodic condition that remits with treatment or the passage of time; often, there are recurrent episodes over the course of a lifetime. Many patients respond well to standard treatments for depressive. For others, however, depression can be a persistent and highly disabling condition, and has been predicted to be the second most important contributor to burden of disease in 2020[1]. It is accepted that in MDD the response to the first treatment can determine the evolution of the illness[2]. The significance of first episode in schizophrenia has demonstrated to be a key factor to determine the course of this disorder[3]. But the long-term implications of early diagnose and treatment of depressive first episodes have not been deeply addressed yet. Previous studies have reported that a longer no-treatment interval in a given depressive episode entails higher risk of chronicity[4,5]. Even though the course of the illness is influenced by the initial response to treatment, the number and the duration of previous episodes[6], it is still not possible to assert that by diagnosing and treating appropriately a first episode will improve the prognosis and will revert or avoid neuroanatomical alterations.

Dysfunction of neuronal plasticity o remodelling may contribute to the pathogenesis of mood disorder[7]. Human post mortem and animal studies suggest a correlation of neuroplasticity with recovery from depressive episodes[8]. Many in vivo neuroimaging investigations have detected reduced hippocampal volumes in patients with MDD. Most of the studies suggest that excitotoxic damage may occur to the hippocampus after prolonged exposure to glucocorticoids and may result in long-lasting cellular alterations in this region. Data from volumetric imaging studies highlight the fact that clinical parameters of patients, such as early history, family history and burden of syndromal and subsyndromal depressive illness, may make an important contribution to hippocampus size. The results for other brain regions are inconsistent but mainly it has been reported enlarged amygdala volumes and reduced volumes of the anterior cingulate and the prefrontal cortex, suggesting alterations in the frontolimbic network. Frodl *et al*.[9] have recently reported that patients showed higher volume decline in the anterior cingulum, left amygdala, and right dorsomedial prefrontal cortex and bilaterally in the hippocampus over a 3-year follow-up. These data suggest that neuroplasticity changes occur as a result of stress- and depression-related factors.

Several clinical studies on MDD have shown that blood brain-derived neurotroph-

ic factor (BDNF) –a factor used to index neuroplasticity– is associated with depression response, supporting the notion that depression improvement is associated with neuroplastic changes. BDNF plays an important role in facilitating neuronal outgrowth of stem cells of hippocampus. The neurotrophic hypothesis proposes that stress associated increases in cortisol can lead to impaired neurogenesis in the hippocampus, which might then result in depressive symptoms. BDNF levels increase in MDD patients during antidepressant treatment[10], reversing, at least partially, the reduced hippocampal and other frontolimbic volumes[9].

Additionally, chronic psychological stress is associated with cellular damage measured by peripheral blood mononuclear cell (PBMC) telomere length (a putative marker of cell aging) and telomerase activity. Simon and colleagues[11] found shortened PBMC telomeres in patients with depression, bipolar disorder and/or co-morbid anxiety disorders. Interestingly, glucocorticoids can also lead to downregulation of telomerase activity and to shortened telomeres. PBMC telomeres dynamics might depict CNS ones (especially in mitotic cells such as hippocampal stem cells), thus to become a promising marker of neurotoxic processes involved in depression.

Genetic factors can influence brain changes due to stress and other neurotoxic processes. Hippocampal volumes are found to be associated with polymorphisms in the promoter region of the serotonin transporter (SLC6A4) in patients with MDD. Met-allele carriers of the BDNF (Val66Met) polymorphism had smaller hippocampal volumes in both patients and healthy controls when compared with homozygous Val-allele carriers. Polymorphisms of the 5-HTTLPR and 5-HT1a receptor are associated with increased amygdala activation investigated with functional MRI in patients with MDD[9]. Another approach employed in this area of research is the mapping of gene variations to specific behavioural traits, such as neuroticism. Sen *et al*.[12] found that investigating a BDNF coding variant (Val66Met), Val allele was associated with neuroticism as a vulnerability factor for depression. The short promoter region of the serotonin transporter polymorphism has also been linked to anxiety-traits such as neuroticism and harm avoidance[13]. Recent findings support the view that the 5-HTTLPR is associated with a major neuroendocrine stress system[14]. Interestingly, altered hippocampal volume, BDNF Val66Met polymorphism, and neuroticism have each been implicated in the etiology of major depression[15].

According to these hypotheses, the cognitive deficits described in depression may be related to impairments in neurogenesis. Neuropsychological studies reliably report deficits in hippocampus-dependent recollection memory that may not abate during euthymia. Also, the dorsolateral prefrontal cortex abnormalities have accounted for the executive dysfunction displayed in depressive disorder, either in the acute phase or inter-episode. Functional imaging studies implicate frontotemporolimbic circuit changes in patients with MDD, but the results of these studies are variable with respect to observed changes in the prefrontal cortex and limbic system. Despite these converging lines of evidence suggesting that both brain areas are important in the pathophysiology of MDD, including studies that suggest that there may be structural changes in these regions, virtually nothing is known about whether appropriate early treatment of MDD, i.e, at onset of the disorder, can alleviate or even reverse some of these changes.

The importance of these possible mediators in the pathophysiology of depression and the in the course of the disorder remains largely speculative at this moment. It is still not clear to what extent all these approaches for pathogenesis and treatment of depression reflect the situation in patients. State-of-the-art neuroimaging postprocessing software might provide new information to shed light on these previous results in order to determine morphometric, functional and anatomical characteristics of the onset of the illness. In this regard, a new method has been developed to investigate a potential marker of neurogenesis in vivo in humans by magnetic resonance spectroscopy (MRS). Manganas and colleagues[16] have detected a prominent peak at the frequency of 1.28 parts per million (ppm) unknown in brain tissue by analyzing neural progenitor cells in animals. These known and new techniques seem well-suited for repeated intra-individual measurements, which is desirable for monitoring the course of a disease process and interventional approaches. While neurogenesis most likely might not be involved in the pathogenesis of depression, stimulating neuroplasticity may be one of the mechanisms contributing to recovery.

The above considerations suggest that new studies are necessary to convey the separate bits of evidence regarding major depressive disorder. Of more interest, such studies must be addressed to the very onset of the illness, given the likelihood of recurrence of MDD and even worse, a probable evolution to chronicity. It is likely that an early start of treatment with antidepressants and psychotherapy may prevent neuroplastic changes that, in turn, worsen the clinical course.

FIDEs: a new approach to study the neuropsychobiology of MDD

Neuronal plasticity may have a critical role in the pathophysiology of MDD. A variety of genetic, endocrine and environmental factors involved in the development of MDD exert a high influence in neuroplasticity/neurogenesis processes, which in turn might be crucial in recovery from episodes and prognostic of the illness. Assessing all these factors at the very beginning (during the first episode) allow an early characterization of the illness, shed light on the interrelation of these factors, and how they intervene in the course and the clinical outcome. It is expectable that dysfunction of neuronal plasticity might contribute to the pathogenesis of depressive disorder, so as that patients with a MDD will show structural differences compared to healthy control subjects even in the first stages; such differences will be associated with neuroplasticity/neurogenesis-related factors (high levels of cortisol, decreased brain-derived neurotrophic factors, decreased 1.28 ppm spectral peak as a MRS neural progenitor cell biomarker in the hippocampus) and cell endangerment markers (telomere length and telomerase activity). These neuroanatomical and neurochemical factors might account for the clinical course of the disorder, i.e., more pronounced structural abnormalities and neuroplasticity/neurogenesis-related factors will be associated with worse clinical outcomes. In addition, some psychological and environmental factors (neurotic traits, poorer psychosocial status and longer duration of untreated episode) might interfere in such neuroanatomical and neurobiochemical changes, as well as in clinical and cognitive outcomes. Finally, genetic vulnerability determined by polymorphisms of BDNF and

5-HT genes (Val66Met, and SLC6A4 and STin2, respectively) might modulate neuroanatomical abnormalities, neuroplasticity and cell endangerment-related factors.

With this neuropsychobiological approach we pretend to adapt the model of first episodes of psychosis to MDD, taking into consideration the notion of neuroplasticity. It does not mean that depression is a neurodevelopmental disorder as psychosis, but a condition which exerts important changes in the brain and its inner processes that seem to be reverted in some cases by treatment.

In this regard we believe that carrying out a project where the patients will be detected, diagnosed and treated at the very beginning of the illness will help on the one hand to determine what clinical, social or psychological variables might be related to antidepressant response, and on the other hand, this approach will reduce the costs of no treating the depressive episode as soon as possible[2,6].

First depressive episodes have started to gain momentum in psychiatric research. In this regard our group has published two preliminary articles on this issue. The results are promising but new designs are needed to disentangle the pathophysiology and subsequent neuropsychobiological consequences of the disorder.

Our group

The Mental Health Research Team of the *Hospital de la Santa Creu i Sant Pau* is a consolidated group composed by 13 researchers (8 PhDs and 5 post-graduates) with a wide experience in coordinated works in psychiatric disorders, and which currently is integrated in the CIBERSAM (CIBER of Mental Health, Spanish Ministry of Health, *Instituto de Salud Carlos III*). The team is formed by clinicians (psychiatrists, psychologists and clinical neurophysiologists) with remarkable experience in clinical practice and research, and by basic-oriented researchers (clinical pharmacologists, pharmacists and neuroimaging) who develop and evaluate neuropsychopharmacology studies.

The main research lines are related to patients with mood disorders, psychoses and personality disorders. Studies in patients resistant to pharmacological treatment, and studies about factors predictors of therapeutic response to antidepressants, mood stabilizers, typical and atypical antipsychotics are remarkable. Since 2001, our team has combined basic, clinical and epidemiological research, focusing its research lines in next topics:

i) Psychotic Disorders: Studies about environmental, biological and genetic factors in psychosis; studies of efficacy and effectiveness of antipsychotic drug; neuroimaging studies of psychotic first episodes; and collaborative studies in the treatment of negative symptoms of schizophrenia and in neuroimaging of auditory hallucinations in schizophrenia; ii) Personality Disorders: clinical trials of the usefulness of combined treatments in patients with Borderline Personality Disorder (BPD), and validation of diagnostic instruments; genetic and neuroimaging studies in BPD; iii) Mental Health Therapeutics: Efficacy-resistance of treatments and systematic reviews; iv) Affective Disorders: Identification and evaluation of new therapeutic targets in depression; implementation of new therapeutic programmes, evaluation and social aspects of depression; collaborative line in pharmacologic and psychological research in treat-

ment-resistant major depressive disorder (MDD); assessment of psychological intervention in prevention of relapses in recurrent MDD patients; v) Neuropsychopharmacology: Clinical trials in early phases of therapeutic development (phase I and IIa); evaluation of transcultural drugs; use of mathematical models in pharmacology; vi) Specific Psychological approaches to mental disorders treatment: Clinical research in treatment-resistant and recurrent MDD; usefulness of psychological treatments in patients with Borderline Personality Disorder (BPD) and validation of diagnostic instruments; validation of event-related potentials and EEG as potentially tool to monitor treatment effects in specific phobias.

The fact that the lines of research described above include the main topics of the CIBERSAM, demonstrates that the group is consolidated in research, and has leader capacity and national and international projection. The integration of clinical and more basic-oriented research facilitates the translational interpretation of the results, and provides great chances of collaboration.

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THE "RAMON Y CAJAL HOSPITAL-FUNDACION JIMENEZ DIAZ" RESEARCH GROUP: FILLING THE GAP IN MENTAL DISORDERS

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The "Ramon y Cajal Hospital-Fundacion Jimenez Diaz" research group: Filling the gap in mental disorders

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ABSTRACT – The "Ramon y Cajal Hospital-Fundacion Jimenez Diaz" group started its research projects ten years ago with the aim of becoming a leading research group within the field

of Psychiatry. It belongs to the CIBERSAM, a mental disorders network created in Spain within a national medical research enterprise (RETICS). The research interest of the group covers a broad area. Some of the most intensive fields of study are: metabolism of psychopharmacological drugs, phenomenological and clinical aspects of impulsive and compulsive behaviors, genetic and molecular bases of mental disorders, epidemiology and evaluation of health care provision process. Looking to the future our aim is to integrate psychopathology, genetics and environment through the use of the newest and more powerful data analysis techniques.

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Introduction

Recently, there is common agreement that Spain is gaining importance in the field of research. Far enough from satisfied, the research community is devoted to continuing these efforts for Spain to be a leading researching country in the next few years. The "Ramon y Cajal Hospital-Fundacion Jimenez Diaz" (RC-FJD) research group is a good exponent of the Spanish medical and research development. The RD-FJD group is one of the 17 groups of the Mental Disorders Network (REM-TAP), which was created within the RETICS enterprise (RETICS RD06/0011). REM-TAP has been presently transformed in CIBERSAM. The study areas of our group are basically the same that are listed as the "descriptors" of the Mental Health CIBER.

Following Cloninger's impulsivity spectrum schema[1], we initially focused our research in obsessive-compulsive disorder as a paradigm of impulse control on one side, and impulsive behaviors on the other. Impulsivity has been explored since from several perspectives. Our group has pioneered the study of pathological gambling, a disorder which due to its high prevalence and impact on the family system entails considerable social relevance[2]. Also suicidal behavior and obsessive-compulsive disorder have been largely investigated and we are experienced in multicenter studies devoted to clarify the cultural components of these behaviors[3].

In recent years, we have progressively included several other research areas, thus covering a wide range of investigations from epidemiology to genes, including psychopathological and clinical topics (e.g.: side effects of antipsychotics, medical diseases in psychiatric inpatients). Indeed, the exploration of the genetic underpinnings of psychiatric disorders has been the endeavor of our group since the very beginning. During the past 12 years we have carried out several association studies with functional polymorphisms. Currently, we have developed the capacity for patient recruitment and our gene bank includes samples from more than 2,000 patients, 300 of them diagnosed with schizophrenia. We are already projecting network studies to replicate our results. To date, the study of functional polymorphisms has provided some of the most interesting findings of our group, especially in the fields of affective disorders, schizophrenia, and impulse control disorders. Our effort has already given place to several publications and research grants.

Review

The RD-FJD group has carried out research in 6 out of the 10 descriptors for the Mental Health CIBERSAM. We have selected the descriptors in which we are currently performing intensive research.

Psychotic disorders: Epidemiology, clinical characteristics and treatment. The metabolism of psychopharmacological drugs is a field of the utmost importance because it could contribute to the establishment of "personalized medicine" in Psychiatry. The future uses of specifically directed treatments could greatly limit adverse effects and enhance its efficacy. We have studied the activity and genetic variants of several enzymes of the citochrome family, which metabolize antipsychotic drugs and therefore affect their therapeutic activity[4,5]. Our aim is to make individualized prescription possible, with the type of drug and dosage required, and minimizing the risk of side effects and subtherapeutic doses.

We have also been interested in suicide behavior within the field of psychosis. We have found that patients with schizophrenia have suicide attempts that are more lethal, less impulsive and less related to life events than other psychiatric patients[6].

Affective disorders: Epidemiology, diagnosis, and treatment. Our group has taken part in many clinical trials, and the principal investigator (PI) has participated in the design and coordination of some of them. We have also developed methods to evaluate the adequacy of treatment in patients with depression[7,8], and we have assessed the impact of treatment adequacy on suicidal behavior[9]. The field of bipolar affective disorders is of great interest for our group. The PI was the founder of REBIPMA (Research Network for Bipolar Disorder in Madrid) and of the Bipolar Disorders Research Section of the Spanish Psychiatry and Mental Health Foundation.

Epidemiology and clinical characteristics of behavioral and emotional disorders. One of our main lines of work is related to the phenomenological and clinical aspects of impulsive (suicide, pathological gambling) and compulsive (obsessive-compulsive disorder) behaviors. We have studied this area from clinical[10,11], epidemiological[12], endocrine[13], biochemical[14,15], personality[16], and genetic[2,17-19] standpoints. Of particular relevance was the demonstration of a functional polymorphism in the serotonin transporter gene being associated with pathological gambling and suicidal behavior[18]. Pathological gambling was associated as well with a polymorphism in the monoaminoxidase enzyme[2]. Furthermore, we have carried out several association studies with functional polymorphisms within the field of drug abuse and dependence[20]. We are prepared to launch multicenter studies in collaboration with other European countries in order to replicate our previous findings in larger samples. At this time, we are also engaged in the research of new tools to better identify vulnerability and grant adequate treatment to suicidal patients. Deficiencies of actual means of diagnosis, based on clinical factors, are reflected in the fact that up to 25% of patients committing suicide had visited a mental health facility[21].

Psychotic disorders: Genetic, cellular and molecular bases. During the past 10 years we have carried out several association studies with functional polymorphisms[22, 23] within the field of schizophrenia. More recently, an opened target is the role of polymorphic variants of genes involved in polyamine metabolism in psychosis[24].

Affective disorders: Molecular, genetic and pharmacological bases. During the past 12 years we have carried out several association studies with functional polymorphisms with the collaboration of the Department of Molecular Genetics of the Universidad Autonoma de Madrid[2,17]. These studies have focused on affective disorders and particularly on bipolar disorder, and they have generated a sample bank of about 600 patients with affective disorders. Our publications in the 90s on polymorphic variations associated with bipolar affective disorder[25,26] were the first of their kind within this line of research.

Early detection, adherence and treatment response, and evaluation of health care provision processes. During last years our group has established a close collaboration with a team from Carlos III University to develop and apply machine-learning techniques to database analyses[27]. These techniques bring hope to the field of mental disorders, in which research designs and patient assessment measures are very complex. We have already used these techniques to investigate clinical decision-making criteria[27]. These techniques could be very useful to other researchers within the network who may want to evaluate health provision processes.

Our knowledge on database analysis together with our previous work on population-based morbidity might prove especially useful in the near future. The analysis of Cumulative Case Registries in our Catchment Area has allowed us to evaluate health care provision processes considering active patients and historical data[28]. We have also performed a pilot study on the temporal consistency of psychiatric diagnoses in adults, including the registries of one single area within the province of Madrid. The relevant results on schizophrenia and bipolar disorder obtained have already been published[28,29]. Currently, data from other healthcare areas and from the Regional Mental Health Office of Madrid (remaining areas) are being added to the original database. The psychiatric cases registry covers a population of 950.000 inhabitants. Using this growing database, we are currently developing a study on the course and pathways of psychiatric disorders in public mental health facilities within the province of Madrid.

Conclusions

The "Ramon y Cajal Hospital-Fundación Jiménez Díaz" research group has become a noteworthy research group within the field of Psychiatry in Europe. Initial projects were focused on impulsivity, and our group has pioneered the study of pathological gambling, while performing intensive research on suicidal behavior and obsessive-compulsive disorder. In recent years, we have progressively included several other research areas. Some of the most interesting findings of our group were obtained from the study of functional polymorphisms, especially in the fields of affective disorders, schizophrenia, and impulse control disorders. Recent access to large datasets has permitted the group to amplify its interest to epidemiological studies and evaluation of health care provision processes. To apply the modern data analysis techniques (data mining, machine-learning) on an integrated database containing environmental, genetic and psychopathological information is our future goal.

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Table I
Main publications and research topics since 2000

Main research topics	Journals
Pathological gambling	
DNA polymorphic markers at MAO-A and MAO-B genes	Mol Psychiatry (2000)
Psychiatric comorbidity	Am J Psychiatry (2001)
Gender differences	J Clin Psychiatry (2003)
Suicidal behavior	
Intrauterine effects	Lancet (2004)
Epidemiology in the USA	Mol Psychiatry (2008)
Issues for DSM-V	Am J Psychiatry (2008)
Gender-specific association of serotonin transporter gene	Neuropsychopharmacology (2002)
Relationship between impulsivity and lethality of suicide attempts	J Clin Psychiatry (2001)
Differences in aggression between New York and Madrid	J Clin Psychiatry (2006)
Association with low serum cholesterol	J Clin Psychiatry (2008)
Menstrual cycle and suicide attempts	Acta Psychiatr Scand (1998); Psychosom Med (2000; 2003); Eur Arch Psychiatry Clin Neurosci (2003; 2004)
Suicide attempts and impulsivity	Eur Arch Psychiatry Clin Neurosci (2005)
Severity of personality disorders and suicide attempt	Acta Psychiatr Scand (2009)
Genetics	
SAT-1 -1415T/C polymorphism and susceptibility to schizophrenia	Prog Neuropsychopharmacol Biol Psychiatry (2009)
Positive association between SAT-1 -1415T/C polymorphism and anxiety	Am J Med Genet (2008)
BDNF and NTRK2 genes: haplotypes against obsessive-compulsive disorder	Biol Psychiatry (2007)
Mood changes after delivery: serotonin transporter gene	Br J Psychiatry (2008)
Compulsivity and impulsivity in females: The serotonin transporter promoter polymorphism	Prog Neuropsychopharmacol Biol Psychiatry (2005)
New susceptibility genes for psychiatric disorders by association analysis of SNPs in 306 genes	Am J Med Genet (2008)
Epidemiology and management	
Diagnostic stability of mental disorders in clinical practice	Br J Psychiatry (2007)
Patterns of mental health service utilization	Eur Arch Psychiatry Clin Neurosci (2008)
Hospitalization after a suicide attempt	J Clin Psychiatry (2006)
Diagnostic stability and evolution of bipolar disorder	Acta Psychiatr Scand (2007)
Cultural values, sources of guidance, and their relevance to managerial behavior - A 47-nation study	J Cross Cult Psychol (2002)
Data mining	
Weighted least squares training of support vector classifiers leading to compact and adaptive schemes	IEEE Transactions On Neural Networks (2001)
Support vector method for robust ARMA system identification	IEEE Transactions On Signal Processing (2004)
Psychopharmacology	
QTc interval related to CYP2D6 and CYP2C9 genotypes and plasma concentration of thioridazine and risperidone	J Psychopharmacol (2002; 2004)
Risperidone and 9-hydroxy-risperidone plasma concentrations and CYP2D6 activity	Pharmacopsychiatry (2002)
Mesoridazine/thioridazine on CYP2D6 activity	Ther Drug Monit (2000; 2001)
CYP2C9 genotypes and diclofenac metabolism	Eur J Clin Pharmacol (2003)
Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype	Eur J Clin Pharmacol (2003)
Olanzapine in first-episode schizophrenia: a naturalistic study	Prog Neuropsychopharmacol Biol Psychiatry

J. Sanjuán, E.J. Aguilar and J.C. González

AUDITORY HALLUCINATIONS: A CLINICAL, GENETIC AND NEUROIMAGING APPROACH

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Auditory hallucinations: A clinical, genetic and neuroimaging approach

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ABSTRACT – Auditory hallucinations (AH) are characteristic symptoms in psychotic patients. We present here our main line of research focused on AH. We have followed an integrative approach including clinical, genetic and neuroimaging data. First, in the clinical approach, we validated the Spanish version of Psychotic Symptoms Rating Scales (PSYRATS) and identified clinical variables relevant to the persistence of AH. Second, as part of a molecular genetics approach, we studied several polymorphisms of genes particularly related to language and neurodevelopment (FOXP2, HAR1, ASPM), as well as others linked to emotional regulation and neurotransmission (HTT, CCK-AR). Third, we have performed several MRI studies in a select group of patients with persistent AH. We found enhanced activation of limbic and frontal brain areas in response to emotional words in these patients. Using voxel-based morphometry, we observed significant gray matter decreases in different brain areas that were directly related to the intensity of AH. Moreover, a new method was used to analyse areas of coincidence between gray matter loss and functional activation; large overlapping clusters were detected. We further supplemented our MRI data with a spectroscopic study of metabolic abnormalities in the thalamus. Finally, we integrate all these clinical, genetic and neuroimaging findings into a comprehensive etiopathogenic model in order to explain the neurobiological bases of AH.

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Introduction

Auditory hallucinations (AH) are some of the most relevant symptoms for diagnosis of psychosis. In the last twenty years, two different approaches have been used in order to understand these perceptual abnormalities. First, the psychosocial-cognitive approach deals with AH as a common human phenomenon in the normal population. The hypothesis is that differences between normal and pathological hallucinations are quantitative rather that qualitative. This model proposes psychotherapeutic techniques based on cognitive models that pay special attention to the emotional reactions to hallucinations. The second line of research is based on the medical-neurobiological approach, which dictates that the hearing of voices should always be considered a pathological phenomenon. This model mainly relies on data from functional neuroimaging and provides new information about abnormal activation of specific neural networks, particularly in language areas, during hallucinations. Neurobiological findings have been used as the basis for biological treatments with antipsychotics and transcranial magnetic stimulation (TMS)[1]. However, there is little cross-talk between the cognitive and neurobiological approaches, and neither investigates the genetic vulnerability to AH[2].

The principal aim of our research group is to analyze AH in psychosis with a multidisciplinary approach that integrates phenomenological, genetic, and neuroimaging data. To the best of our knowledge, we are the only group simultaneously using all these methodologies for the study of AH.

Phenomenology of AH

Before searching for biological markers of a psychopathological disorder, it is compulsory, in our opinion, to carefully examine the phenomenological characteristics of the symptoms. Surprisingly, no scales for AH were available in Spanish when we started our studies. Thus, after reviewing 12 English scales for AH, we translated and adapted the Psychotic Symptoms Rating Scale (PSYRATS)[3,4]. PSYRATS is an 11-item scale for which each item is scored from one to five. The Spanish version showed high reliability and concurrent validity. It should be remembered that although AH can appear with other mental disorders and even in normal populations, it remains the hallmark of psychosis and especially of schizophrenia-spectrum disorders. There are three main characteristics in the phenomenology of AH in psychosis: 1) mainly human voices; 2) identification of the origin of the voices as an "alien"; and 3) induction of an intense emotional response. Two additional main findings arose from our clinical studies. First, we found that pleasurable hallucinations could be detected in a substantial proportion of patients[5]. Second, we also described clinical variables relevant to the persistence of AH[6]. More recently, we have described the different types of hallucinators among psychotic patients[7].

The genetics of AH

In addition to several collaborative studies on the genetics of schizophrenia[8,9], we have been focused since 2004 on the molecular genetics of AH in psychotic patients.

We assume that not all individuals have the same vulnerability to AH. Some individuals have an inherent capacity to experience hallucinations and are thus hallucination-prone[1]. Surprisingly, most genetic studies of hallucinations have been done in neurological patients,

mainly those with Parkinson's and Alzheimer's disease. Few studies have focused on the genetics of AH in psychosis[1,2]. According to our data regarding the clinical phenomenology of AH, there are three likely neurobiological pathways for genetic vulnerability. First, general vulnerability to hallucinations may exist independently of the sensory modality and could be related to several polymorphisms such as that of the CCK-A receptor gene in Alzheimer's and Parkinson's patients, as well as in psychotic patients[2,10,11]. Second, in almost all conditions in which hallucinations occur, visual hallucinations predominate. The exception is schizophrenia, in which AH, particularly voices, predominate[12]. Finally, the voices usually have a disturbing content that induces an intense emotional response[1].

Thus, apart from a general vulnerability to hallucinations, two different pathways emerge. The first is a vulnerability to language disorders that could increase the probability of hearing voices. This vulnerability could be due to changes in the *FOXP2* gene, among others[13,14]. *FOXP2* is the first gene to be linked to a language disorder, and is associated with functional and structural abnormalities in the temporal lobe[15]. We have also studied other genes (ASPM, HAR1A) that have been implicated in neurodevelopment, but with more contradictory results[16,17]. The second potential pathway involves a vulnerability to abnormal emotional response. This emotional dysfunction has a crucial role in schizophrenia, as shown in previous studies that have linked AH with negative emotional states and behaviors such as suicidal behavior[18,19]. This emotional response is partially regulated by serotonergic neurotransmission. We have investigated whether the functional promoter polymorphism of *SLC6A4*, 5-HTTLPR, is associated with AH in psychotic patients. Our data suggest that patients carrying the *s* allele show an increased emotional response to AH[20].

Neuroimaging of AH

Functional

Functional (fMRI, PET, and SPECT) studies have demonstrated a relationship of AH to abnormal activation of cerebral areas involved in normal processing of auditory stimuli, especially in areas implicated in verbal self-monitoring.

We designed an auditory emotional paradigm to elicit emotional states experienced by patients with schizophrenia when suffering from AH[21]. This paradigm was applied to evaluate cerebral activation using fMRI in 11 patients with schizophrenia and persistent hallucinations when compared to 10 healthy subjects. In contrast to many studies on the emotional response of such patients, we observed enhanced activation of limbic and frontal brain areas in our group of persistent hallucinatory patients[22].

Structural

Different techniques (VBM and ROI) have been used to correlate volumetric changes and AH in patients with schizophrenia[23,24]. Although several brain areas are likely involved, the superior temporal gyrus (STG) has been proposed as a crucial region for the pathogenesis of AH by several studies that an ROI approach. Interestingly, a significant decrease of grey matter in the left superior temporal lobe and left orbitofrontal cortex was shown in patients with schizophrenia who had attempted suicide when compared to those who had not[25].

We performed a VBM study on a highly homogeneous group of persistent hallucinatory patients, comprised of 18 patients with schizophrenia and 19 healthy control subjects[23]. The results showed a significant de-

crease of grey matter (GM) in the insula (bilateral), STG (bilateral), and amygdala (left) in patients as compared to controls. The PSYRATS variable was negatively correlated with GM values in the left inferior frontal gyrus and right postcentral gyrus.

Coincidence study: A new approach to fuse structural and functional techniques

In order to integrate functional and structural data we performed a study to determine whether fMRI abnormalities associated with listening to emotional words (aimed at reproducing AH) colocalized with focal brain volume decreases in 21 male schizophrenic patients with chronic hallucinations[26]. Large coinciding clusters of fMRI abnormalities and volume decreases were found in the left and right middle temporal and superior temporal gyri.

Spectroscopy

Several studies have found neurochemical abnormalities in thalamic nuclei in schizophrenia patients, but no metabolic spectroscopy studies have been performed that specifically focused on AH. In a recent study, we found that patients with schizophrenia had significantly lower bilateral NAA/Cho ratios when compared with healthy subjects. There was also a significantly lower NAA/Cho ratio in the right thalamus in patients with auditory hallucinations as compared to patients without auditory hallucinations and control subjects[27].

An integrative model

Integration of all these data leads us to propose an etiopathogenic model of AH in psychosis[2,24] (Figure 1). We present here our model with slight modifications. We dif-

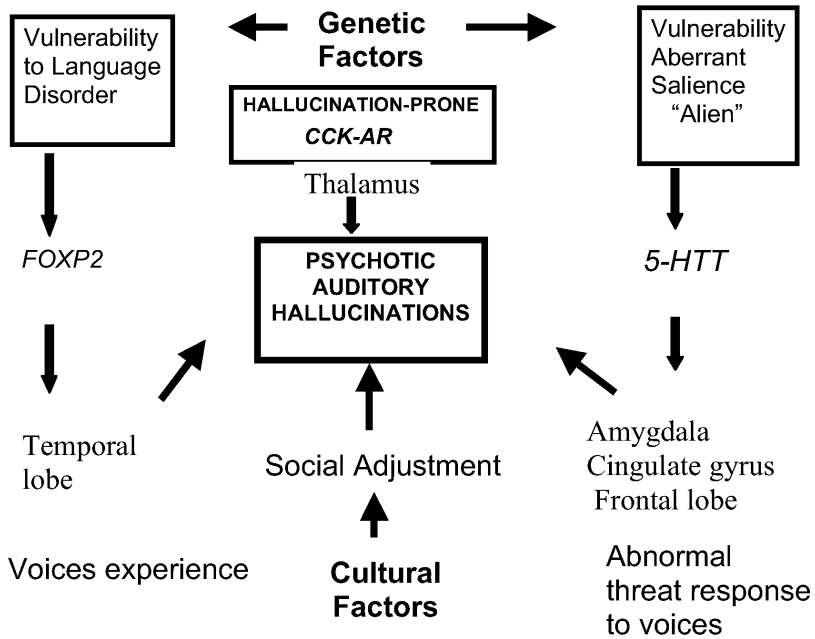

Figure 1.

ferentiate between three etiopathogenic pathways for AH in psychosis. The first is a general vulnerability to hallucinations in any perceptual modality. This general vulnerability could be related to genes (CCK-AR and others) that modulate all perceptual input through the thalamus-cortical loop (A). Such a thalamic abnormality is consistent with our spectroscopic findings[27]. The second pathway involves vulnerability to language disorders that could increase the probability of hearing voices. This vulnerability could be the result of changes in the *FOXP2* gene, among others[14,16]. This pathway is associated with functional and structural abnormalities in the temporal lobe (B). The third pathway involves vulnerability to abnormal emotional responses partially regulated by genes related to serotonergic neurotransmission. This pathway is related to abnormal activation of the limbic and frontal brain areas. Finally, cultural aspects can influence the spoken content of voices and the social adjustment.

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LOOKING AGAIN, AND HARDER, FOR A LINK BETWEEN MOLECULES AND SEVERE MENTAL DISORDERS: A TRANSLATIONAL AND INTEGRATED MULTI-DISCIPLINARY APPROACH

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Looking again, and harder, for a link between molecules and severe mental disorders: A translational and integrated multi-disciplinary approach

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SPAIN

ABSTRACT – The last decade has witnessed a growing interest to evaluate the aetiology of schizophrenia and bipolar disorders through a genetic, molecular and cellular analysis, as well as to assess the influence of epigenetic factors in the phenotypic presentation of these severe disorders. We have used the following methods: We analysed six lines of research: The Valencia Follow-Up Study of Schizophrenia and Bipolar I Disorders, The Neurocognitive Endophenotype (Endophenocognitype) Study, The Negative Comorbidity Study, Experimental Embryology, Neurogenetics, and Clinical Genetics. We have described a translational and integrated multi-disciplinary approach to set a framework aimed to identify molecular mechanisms and valid endophenotypes for schizophrenia and bipolar

disorders. Conclusions: The University of Valencia and the Alicante Neuroscience Institute (UVANI) - CIBERSAM node is a specialized resource providing basic topics, clinical care, education and research in the area of severe mental disorders.

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General Overview

In 2007, the University of Valencia and the Alicante Neuroscience Institute (UVANI) research team joined the Spanish Network on Mental Disorders (Red de Enfermedades Mentales: Trastornos Afectivos y Psicóticos, REMTAP), which involves 17 expert centres in Spain working on shared objectives, measurements, and outcome. The network successfully achieved most of its initial objectives and as a result of this has been upgraded by the Spanish Ministry of Science and Innovation as the CIBERSAM (Centro de Investigación BioMédica en Red de Salud Mental), which is a network with a long-term funding and commitment.

The UVANI CIBERSAM node integrates expertise in developmental and molecular biology (ANI), as well as human genetics and psychiatric clinic care of patients (UV). This node is composed of two research groups:

1. The University of Valencia (UV) branch lead by Prof. Tabarés-Seisdedos, an expert in the study of psychosis. The other senior members are four researchers specialized in psychiatry (Prof. Balanzá-Martínez, Dr. Salazar, Dr. Selva and Prof. Gómez-Beneyto) and two psychologists specialized in neuropsychology (Prof. Fuentes and Dr. Correa). Members are involved in clinical practice at different community mental health centres in the area of Valencia. During the last decade, this branch has focused on the comparative study of severe psychiatric disorders, namely the research lines have focused on psychopathological, neuroimaging, neurophysiological, neurocognitive, therapeutic, and prognostic facets schizophrenia and bipolar disorders, and has become a team of reference and also has made some pioneer research in this field.

2. The group of Experimental Neurobiology of Cerebral Cortex (ENC) at the Alicante Neuroscience Institute-ANI (Miguel Hernández University) branch lead by Prof. Martínez. This is an international team of reference in the biology of development as well as in the genetics of the forebrain. This group is made up of professionals with an extensive experience in processes closely related to cerebral regionalisation and its cellular consequences (Dr. Escámez, Prof. Echevarría, Dr. Bahamondes and Prof. Geijo-Barrientos). Its work, in collaboration with other national and international groups, is focused in the analysis of molecular and cellular mechanisms underlying the development of cerebral regions in the neural tube and the effects derived from alterations in these initial processes of regionalisation. The ENC group has actively investigated the molecular mechanisms that regulate telencephalon regionalisation, and the development of the functional areas of the cerebral cortex.

Accordingly, the analysis of corticogenesis alterations and its implications in brain development is one of the main objectives of

ENC, since modifications in process involving in cerebral cortex development (neuronal migration, connectivity and cortical sinaptogenesis) cause structural and functional alterations that set off serious diseases, as lissencephaly and cortical dysplasia, and could increase the risk of suffering severe mental diseases (including schizophrenia and bipolar disorders) . The ENC group participates in many national and international projects as EUROEXPRESS (A European consortium to generate a WEB-based gene expression atlas by in situ hybridization), and is a group belong to CONSOLIDER.

Main Research Lines

The following is a summary of the main research lines to date:

1. The Valencia Follow-Up Study of Schizophrenia and Bipolar I Disorders

To our knowledge, this research line is the first to use a follow-up design to examine simultaneously the level of neuropsychological abnormality in the clinically unaffected first-degree relatives of individuals with schizophrenia and bipolar disorder type I at baseline and years later compared with healthy subjects. This longitudinal perspective is used to establish how neurocognitive impairments affect patients' daily life and functional outcome in schizophrenia as compared to bipolar disorder. Specifically, we found that a global index of cognition was more predictive of functional outcome than clinical factors in both schizophrenia and BD. In addition, improvements in neurocognitive status predicted changes in functional outcome, but only in bipolar subjects[1-6].

We also use this novel strategy to identify potential neurocognitive endophenotypes (endophenocognitypes). Family studies are relevant to leave apart the potential confounding effects which factors such as subsyndromal symptoms, comorbidities, medication side-effects, and neurotoxicity due to disease progress, can exert on cognition. Moreover, follow-up studies allow discern the trajectories of cognitive functions over the illness course, which is a relevant in clinically relevant terms, such as functional outcome. Surprisingly, no previous research had used a combination of both approaches to identify putative, suitable neurocognitive endophenotypes in schizophrenia and bipolar disorder.

We are currently implementing several research lines conjointly with the Bipolar Disorders Program at the Hospital Clínic in Barcelona, lead by Prof. Eduard Vieta. Ongoing randomized clinical trial with three arms to assess the clinical, cognitive, and functional efficacy of two psychological therapies in BD. Currently, we do not have data on rehabilitation programs in bipolar patients. We are interested on the application of an intervention program specifically developed to reduce cognitive impairment and improve psychosocial functioning to determine its usefulness and implementation in clinical practice. A randomized clinical trial ad-hoc with 2 arms will be conducted in order to assess the efficacy of a psychological intervention focused on neurocognitive and functional issues, addressed to patients (PI0890416: Comparative efficacy of two psychosocial strategies of intervention (neurocognitive vs psychoeducative) as add-on therapy versus treatment as usual in bipolar disorder).

We have also contributed to the use of neuropsychological evaluation in patients as well as in their unaffected first-degree relatives. In addition, our experience in conduct-

ing follow-up studies of cognition is a contribution to ongoing CIBERSAM projects (PI081024: Phenotype-genotype and environmental interaction. Application of a predictive model in first psychotic episodes).

2. The Neurocognitive Endophenotype (Endophenocognitype) Study

The Endophenocognitype Study is a 5-year longitudinal study that involves the assessment of cognitive functioning in patients with severe disorders (schizophrenia and bipolar I disorder) as well as in their unaffected first-degree relatives. Traditional cognitive performances (memory, attention, verbal fluency, general intelligence, executive and motor functions) are assessed from a neurobiological point of view[7-19]. The main objectives of this line of research are:

– Identification of candidate endophenocognitypes in schizophrenia and bipolar disorder through the neuropsychological assessment of patients and relatives.

– Analyze the cellular and molecular mechanisms that underlie the relationship between migratory and synaptogenic alterations as predisposing (vulnerability) factors for the development of schizophrenia and bipolar disorder.

Our experimental hypotheses are: a) LIS1, TP53, SMG6, PAFR, NRG1 and FGF17 genes, which may be altered in psychotic patients, participate in neurodevelopment of mammals, mainly in cerebral cortex development. Their mutations cause alterations in neuronal migration and, consequently, in cortical connectivity and sinaptogenesis; b) these genetic variations are associated with prefrontal dysfunction and/or reduced memory function (temporal lobe); c) and thereby increase the risk for schizophrenia or/and bipolar disorder; and d) the neurocognitive and functional intervention will improve the cognitive functioning of schizophrenic and/or bipolar patients and other areas of psychosocial functioning as compared to the group with treatment as usual. Concretely we have demonstrated that genetic alterations in the Lissencephaly Critical Region (LCR; locus 17p13.3) could be related with predisposition to psychosis (schizophrenia and bipolar disorders), and influence on frontal executive functioning. In addition, the results of this research line have been awarded with two International prizes - the International Review on Bipolar Disorders (IRBD) and the Aristotle's Research awards.

3. The Negative Comorbidity Study

This is the analysis of the biological connections between disorders that at first glance are considered to be distinct. Explanations for the excess of comorbid somatic illnesses among patients with severe mental disorders usually include several clinical and social factors, like patients' lifestyle, but this epidemiological fact may also be partly explained by specific biological overlaps at the genetic and molecular level[20,21].

Interestingly, this lower-than-expected probability of occurrence of diseases ("negative or inverse" comorbidity) in the psychiatric or medical fields has received less attention. Although schizophrenia is consistently associated with tobacco smoking, subjects with schizophrenia and their relatives have been recently found to show a significantly lower risk of respiratory and prostate cancers compared with the general population. A similar finding is the reduced occurrence of rheumatoid arthritis in people with schizophrenia. The genetic predisposition toward schizophrenia might confer genetically re-

duced susceptibility to lung and prostate cancer. Hence, comorbidity represents a significant opportunity to understand the biological connections among disorders. Moreover, epidemiological data suggests that the negative comorbidity may be a valuable model for investigating common or related pathways or processes and testing new therapies

We are currently working with experts from the University of California in San Francisco (Prof. John Rubenstein and Dr. Joan Climent) in order to understand the biological pathways linking severe psychiatric disorders and cancer.

4. Experimental Embryology

Through embryonic manipulations we want to study the molecular and cellular factors that rule the regionalization, proliferation, differentiation and cellular migrations processes in the Central Nervous System. The interspecific transplants between quail and chicken embryos as well as the in vitro culture of mammal's embryos are examples of experimental methods that allow us to experimentally manipulate wild-type and genetically manipulated animals[22-24].

5. Neurogenetics

We study the expression patterns of important genes in the structural organization of the brain through embryonic development. The experimental manipulations (*in ovo* electroporation and microelectroporation) and the mutagenesis by homologous recombination allow us to complete the study of functional role of these genes. We also analyze genes involved in human genetics disorders; we have a specific research line in several pathologic processes: multiple sclerosis, Down syndrome, Lissencephaly/Heterotopy and psychosis[25-27].

6. Clinical Genetics

Integrated in our research in cortical migration disorder and function of *Lis1* gene, we realize clinical genetic studies. They allow us to diagnostic mutations in referred clinical cases in different hospitals of our country[28-30]. Nowadays we are working in the study of LCR, PAFR and FGF17 genes expression pattern during neurodevelopment in wild type and mutant (Lis1/sLis1 and Fgf17 +/- and -/- animals) mice trough electrophysiological, behavioural and functional analysis. Also, we analyze changes produced by inactivation of these genes to know their role in the molecular interactions underlying schizophrenia and bipolar disorder pathophysiology analysing the mechanisms that they could control. To determine which alterations are provoked by these genes mutations during neurodevelopment, we inject RNA interfering both in mouse brain slices in vivo, to analyze organotypic cultures, as intrauterine female mice pregnant for embryos analysis. In this way, we will study the morphological, functional and molecular changes in transfected cells (detected by GFP reporter labelling) that take place during embryonic development in these animals and/or organotypic cultures. So, we could demonstrate the implication of Lis1, p53, Smg6, Pafr, Pafah1b3 and Fgf17 genes in the cellular mechanisms that could be involved in the pathophysiology of severe mental diseases.

On the other hand, we analyze LCR, PAFR and FGF17 genes compared expression in human post-morten brains (controls and patients) in medial, dorsolateral and suprorbitary prefrontal cortical areas and carry out the genetic and molecular study of patients and their relatives to check the im-

pact of these mutations in the schizophrenia and bipolar disorder.

Conclusions

In sum, the UVANI CIBERSAM node is a specialized resource providing basic topics, clinical care, education and research in the area of severe mental disorders. Over the last decade, it has become one of the leading institutions in health care and particularly research focused on schizophrenia, bipolar and migration illness in Europe, with over 50 high-impact publications and an outstanding number of grants and awards. The UVANI node has also taken the lead of the schizophrenia and bipolar disorder research project within the CIBERSAM. The UVANI team is multidisciplinary, involving psychiatrists, clinical psychologists, molecular and cellular biologists, residents, and technicians.

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RECENT FINDINGS ON CLINICAL AND BIOLOGICAL BASES FROM THE LONGITUDINAL INTERVENTION PROGRAM OF FIRST-EPISODE NON-AFFECTIVE PSYCHOSIS (PAFIP) OF CANTABRIA

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Recent findings on clinical and biological bases from the longitudinal intervention program of first-episode non-affective psychosis (PAFIP) of Cantabria

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ABSTRACT – This article summarises recent findings from the first-episode psychosis program of Cantabria (PAFIP). The program was implemented in 2001 and offers an integrated clinical service with a well structure research program. The high participation rates and the characteristics of this study population represent a unique opportunity for research on schizophrenia. Findings regarding efficacy and tolerability of antipsychotic treatment, structural neuroimaging and the influence of genetic variations on specific phenotypes are discussed.

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Introduction

Within the last decades, the investigation of first-episode schizophrenia has attracted much interest. Studies with first-episode drug-naïve individuals represent the exclusive opportunity to provide intensive phase-specific multi-component care and to explore the implication of biological variables in the pathophysiological mechanisms and outcome of the illness while avoiding several confounding variables.

Taking this into consideration the Psychiatric Research Unit of Cantabria (*A World Health Organization Collaborating Centre)* of the Department of Psychiatry of the University Hospital "Marqués de Valdecilla", initiated in 1989 a prospective follow-up of all First Episodes of Psychosis occurring in the Autonomous Region of Cantabria[1,2]. Based on the experience acquired with that project our Department established in 2001 a phase-specific clinical intervention program, with a research protocol included, to provide intensive an multi-component long term care for all first-episode of psychosis occurring in our community (*The PAFIP Clinical/research Program*). The Mental Health Services of Cantabria provided funding for implementing the program. None pharmaceutical company supplied any financial support to it. Referrals to the PAFIP came from the inpatient unit, emergency unit, and outpatient mental health units. As the Department of Psychiatry is the only institution providing in patient an emergency care for mental disorders in Cantabria, and runs the majority of the Community Mental Health Centers, and taking also into consideration that the PAFIP Program constitutes the only alternative form of mental health care for first episodes psychosis, we could defend that the population included constitutes a epidemiological representation of the first episode psychosis occurring in the entire region of Cantabria. Accordingly the patients included in the PAFIP Program reached an age-corrected (15-50) incidence rate for schizophrenia spectrum disorder of 1.38 per 10,000[3], a figure which is equivalent to the one reported in most epidemiological studies.

As stated, in addition to the long term clinical interventions, several clinical, cognitive, genetic, neuroimaging investigations have been conducted based on the PAFIP research protocol. The objective have been to investigate relevant clinical and biological information regarding neural mechanisms implicated in the illness. In this paper we intend to contribute to a better understanding of the different main areas which are still open in the field of psychosis, by discussing some of the findings drawn from the PAFIP. Thus, we will focus on the most recent literature from our group investigating the effectiveness (clinical and cognitive) and safety (metabolic side effects) of different antipsychotics, the brain morphology, and the impact of genetic variations in clinical and biological aspects of the illness.

Antipsychotic Treatments Effectiveness

In a randomized clinical trial, we have investigated the effectiveness, tolerability, and safety of SGAs (olanzapine mean modal dose = 15.3 mg/d, risperidone mean modal dose = 4 mg/d) and FGAs (haloperidol mean modal dose = 5.4 mg/d) in the acute treatment of individuals with a first-episode of nonaffective psychosis[4]. No advantages of any of the three treatments as determined by mean change between scores at baseline and 6 weeks on the Brief Psychiatric Rating Scale, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Neg-

ative Symptoms, and the Clinical Global Impression Scale. The percentage of study participants responding by week 6 (≥ 40% Brief Psychiatric Rating Scale total improvement from baseline) was 57.1% for haloperidol, 52.5% for risperidone, and 63.6% for olanzapine; no significant differences were found among the groups. Moreover, the mean time to response was similar in the three treatment groups (haloperidol 4.32 weeks [SD = 0.24], risperidone 4.85 weeks [SD = 0.21], and olanzapine 4.36 weeks [SD = 0.23]), with no differences between groups. Similar improvements in negative symptoms as measured by total Scale for the Assessment of Negative Symptoms score were found in the three treatment groups. As expected, the percentage of patients with treatment-emergent parkinsonism (a total score > 3 on the Simpson-Angus Rating Scale at any postbaseline visit, given a total score of > 3 at baseline) was statistically greater in the haloperidol group (46.4%) compared with olanzapine (5.5%) and risperidone (24.6%). We also observed that 47% of olanzapine-treated patients experienced a significant increase in body weight (≥ 4 kg), compared with 23% in the risperidone-treated group and 9% in the haloperidol-treated group.

We also aimed to investigate the neurocognitive effectiveness of haloperidol, risperidone and olanzapine in first-episode of schizophrenia-spectrum disorders[5]. In this study 104 patients randomized to haloperidol (N = 35), olanzapine (N = 30) or risperidone (N = 39) who completed clinical and cognitive evaluations at baseline, 6 months and 1 year were included in the final analysis. We also included a group of 37 healthy individuals who were also longitudinally assessed. Interestingly, and consistent with precious literature, the three treatment groups showed a significant improvement in cognitive scores after 1 year without a differential cognitive effectiveness between the three antipsychotics. Moreover, Haloperidol, olanzapine and risperidone were equally effective in treating cognitive deficits of psychosis. The magnitude of cognitive changes was similar in the three treatment groups and controls, although a greater improvement in Finger Tapping, Trail Making Test B and Rey Complex Figure Test was found in the treatment groups. Therefore, we concluded that effect of practice clearly contributes to cognitive score improvements after treatment with antipsychotics. We did not demonstrate that clinical changes, use of concomitant medications and the emergence of motor side effects might account significantly for cognitive changes over time.

The impact of antipsychotic treatment in drug-naive patients

Patients with schizophrenia are at greater risk for obesity, hypertension, hyperglycaemia, diabetes and dyslipidaemia than general population. These factors, associated with a less healthy lifestyle and higher rates of smoking, make these patients more vulnerable to suffering a cardiovascular disease (CVD). Despite the growing number of studies on the subject remains unclear if it is the genetic risk, the unhealthy lifestyle or the antipsychotic treatment which is the factor that confers higher rates of morbidity and mortality secondary to CVD.

Several findings should be highlighted from our research on first-episode drug-naive population: 1) body mass index, glucose and lipid parameters before antipsychotic exposure were comparable to general population[6]; 2) weight gain is the most frequent side effect induced by antipsychotic treatment: 77.1% of our patients gained more than 7% of their initial

weight[7]; 3) the magnitude of weight gain (mean = 10.5 kg after one year of treatment) was higher than reported in previous studies based on chronic populations[7]; 4) after the first year of treatment we have observed an increase in insulin-resistance index and a worsening lipid profile—but no clinically relevant illnesses including diabetes mellitus or dyslipidemias that require pharmacological treatment were detected[8]; 5) changes in glucose and lipid parameters were correlated with weight gain: those patients who experienced a higher weight increase also showed a significantly greater increase in insulin plasma levels, insulin resistance index, triglyceride levels and a significant decrease in HDL-cholesterol levels[6]; 6) at long term, no significant differences in weight gain or metabolic parameters between first generation antipsychotics (haloperidol) and second generation (olanzapine, risperidone) were found[7-9]; 7) patients did not experience a significant increase in body weight after the first year of treatment (article in prep.)

In conclusion, antipsychotic treatment contributes substantially to increase the cardiometabolic risk in patients with schizophrenia. Drug-naïve patients are a specially vulnerable population with a critical period during the first twelve months of exposure to antipsychotic drugs. Specific interventions on modifiable risk factors like weight gain[10] at these early phases could be useful to prevent metabolic syndrome induced by antipsychotics.

Structural volumetric studies

Extensive evidence exists for structural brain abnormalities in schizophrenia and many brain regions have been implicated in the neural basis of schizophrenia (see Shenton *et al.*[11], for detailed review).

Striatal dysfunctions have been traditionally implicated in the neural mechanisms of schizophrenia[12]. However, structural imaging investigations have failed to drawn consistent results regarding the presence of caudate nucleus volume differences in first episode schizophrenia. Our group explored the caudate nucleus volumes in previously untreated first episode patients with non-affective psychosis (N = 76) and healthy comparison subjects (N = 45). No evidence of significant differences in caudate nucleus volume in a large representative sample of minimally treated patients with a first-episode non-affective psychosis was found. Beside this lack of volumetric abnormalities, delays in receiving antipsychotic treatment and the severity of initial positive symptomatology were significantly associated with reduced caudate nucleus volume. Unexpectedly, caudate nucleus volume reduction was not associated to worse clinical and cognitive outcomes.

In another imaging research study, our group aimed to explore the presence of thalamic volume differences in patients with schizophrenia[13]. In that study thalamic volumes in right-handed minimally treated first episode patients with non-affective psychosis (N = 61) relative to those of right-handed healthy comparison subjects (N = 40) were measured. Interestingly, thalamic volumetric differences between patients with non-affective psychosis and healthy controls were already present at early phases of the illness. Our finding of a reduction (mean = 12.47cc; SD = 1.43) in thalamic volume in minimally treated patients with a first-episode non-affective psychosis is consistent with the results of other studies exploring thalamic morphometry in early course as well as chronic schizophrenia. An earlier

age of onset, a poorer executive functioning and more severe negative symptoms at intake were associated with a larger thalamic volume. The lack of a clear significant relationship between thalamic volume and attentional and verbal learning cognitive functioning was somewhat surprising, due to the well established association between both variables described in lesion and functional imaging studies.

Genetics studies

The basic objective of our genetic studies in the firs-episode of schizophrenia sample has been to examine whether genetic variations in candidate genes for schizophrenia might be associated with specific phenotypes, including clinical presentation, cognition, structural brain abnormalities, and treatment response.

Regarding the Catechol-*O*-methyltransferase (COMT) gene *Val158Met* functional polymorphism, which is known to mediate dopamine availability in the prefrontal cortex, we have reported that first-episode patients with the *Val/Val* genotype show, compared to *Met* allele carriers, an earlier age of onset and more severe negative symptoms[14]. On the other hand, *Met* allele carriers presented, compared to *Val/Val* patients and healthy controls, enlarged lateral ventricles[15]. Finally, in our sample of patients, this polymorphism did not influence cognitive performance as assessed by an extensive neuropsychological battery[16].

We have also examined whether variations in the interleukin-1-receptor antagonist gene (IL-1RN) were associated with risk for psychosis, response to antipsychotic treatment, or brain structure as measured by MRI. We found that the genotype in a variable number of tandem repeats (VNTR) polymorphism was not associated with increased risk for a nonaffective psychosis or structural brain measures[17], but predicted negative symptom improvement during antipsychotic treatment[18]. We also found an association between a 44 base pair insertion/deletion functional polymorphims in the promoter region of the serotonin transporter gene (5-HTT-LPR) and early response to antipsychotic treatment[19].

Our group has recently focused in the study of genes involved in brain development. One of these genes, Neuregulin 1 (NRG1), is according to linkage, association studies, and its function in the CNS, a clear candidate gene for schizophrenia. Although no single causative allele within this gene has yet been identified conferring risk to schizophrenia, one of the SNPs included in the original Icelandic at-risk haplotype, SNP8NRG243177 (rs6994992) has been associated with brain structure and function, and working memory performnce. We examined whether this SNP was associated with brain structure in a sample of 95 first-episode psychosis patients[20]. We found that patients carrying the *T* allele, which is the one that has previously been associated with cognitive and structural brain abnormalities, had a 31% increase in lateral ventricles volume compared to *C/C* homozygotes ($p = 0.007$).

In light of this finding we are now examining the role of other neurodevelopment-related genes on the brain structure abnormalities of first-episode schizophrenia patients. Other lines of genetic research in our group include DNA sequencing using next-generation sequencing techniques, and gene expression analysis using prospectively colected RNA samples which will allow the study of changes associated with antipsychotic treatment.

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PROGRESS IN RESEARCH AT THE CIBERSAM'S AFFECTIVE DISORDERS PROGRAMME OF THE UNIVERSITY OF BARCELONA HOSPITAL CLINIC

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Progress in research at the CIBERSAM's Affective disorders programme of the University of Barcelona Hospital Clinic

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SPAIN

ABSTRACT – The affective disorders programme at the University of Barcelona Hospital Clinic involves two separate subgroups according to their research target: the Unipolar Depression subgroup and the Barcelona Bipolar Disorders Programme. Both are part of the Spanish "*Centro de Investigación Biomédica En Red en Salud Mental*" (CIBERSAM), which is a Virtual Center of Network Research in Mental Health and Psychiatry, which has gathered the best research groups in Psychiatry and related disciplines in Spain. The Clinic-Affective Disorders research group has focused on the neurobiology (genetics, biomarkers, neuropsychology, neuroimaging), epidemiology (clinical subtypes, comorbidity, psychometric assessment, functionality), and treatment of bipolar and unipolar affective disorders (including pharmacological, biophysical, and psychosocial strategies). It has an outstanding and long tradition of collaborative research with national and international groups, and publishes over 60 original articles per year based on research findings, many of which have had significant impact on clinical practice.

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The CIBERSAM and the precedents

The birth, since 2008, of the Spanish "*Centro de Investigación Biomédica En Red en Salud Mental*" (CIBERSAM), which is a Virtual Center of Network Research in Mental Health and Psychiatry, was a cornerstone in the history of Spanish research in mental disorders. The CIBERSAM has enhanced quite substantially the productivity

of the best research groups in Psychiatry and related disciplines, most of which had already been funded in 2007 by the Instituto de Salud Carlos III through the Red de trastornos afectivos y psicóticos (REM-TAP) and a few other networks on neurologic diseases, child psychosis, epidemiology, genetics, and consultation psychiatry. In the past, psychiatry research in Spain was very much dependent on individual action from specific research groups, which would look for funding from the Spanish *Fondo de Investigación Sanitaria* (FIS), foreign institutions (such as the Stanley Foundation), and the pharmaceutical industry. This fact, combined with the dearth of actual investment, had a negative impact on the strategy of the groups that were struggling to do high-quality research on a long-term basis. The CIBERSAM was born as a new era in Mental Health research in Spain, providing unprecedented long-term funding to the best research groups and enhancing translational, collaborative research across the country. Moreover, all the process was made under the highest transparency, fair competition, and peer-review.

The affective disorders programme at the University of Barcelona Hospital Clinic which I have the honour to coordinate involves two separate subgroups according to their research target: the Unipolar Depression subgroup and the Barcelona Bipolar Disorders Programme.

The Unipolar Depression Subgroup

This subgroup is leaded by Cristóbal Gastó, Chair of Psychiatry at the University of Barcelona, and includes Jordi Blanch, Teodor Marcos, Víctor Navarro, and recently Rocío Martín-Santos. They have been extremely succesful in investigating genetic polymorphisms and their relationship to therapeutic response[1], the role of serotonergic receptors in depression and its treatment[2], the specific issues related to depression in the elderly[3], and cognition[4]. The group is involved in several CIBERSAM-funded multicenter projects, such as the DEPRES study, and collaborates on a long-term basis with other CIBERSAM groups such as the one leaded by Lourdes Fañanás.

The Bipolar Disorder Subgroup

This subgroup involves most members of the Barcelona Bipolar Disorder Programme at the University of Barcelona Hospital Clinic (BDP). The BDP integrates clinical care, education, research and management devoted to provide excellence in care and knowledge on bipolar disorder, and it belongs to 3 institutions: the Hospital Clinic, the University of Barcelona, and the *Institut d'Investigació Biomédica August Pi i Sunyer*, (IDIBAPS).

The functional unit that provides clinical care to patients with bipolar disorder is the Bipolar Disorder Unit at the Hospital Clinic, which delivers specialized care to bipolar patients attending the hospital regardless of their condition as in-or out-patients. Bipolar outpatients may come for specialized secondary care (Mental Health Center) or for tertiary care as reference center for particularly difficult-to-treat cases. I am the director of the Programme and I coordinate a large multidisciplinary team, which involves excellent mental health professionals and researchers such as Antoni Benabarre, Mar Bonnín, Francesc Colom, Mercè Comes, Núria Cruz, Claire Daban, Carolina Franco, José Manuel Goikolea, Anabel Martínez-Arán, Isabella Pacchiarotti, María Reinares, Adriane Rosa, José Sánchez-Moreno, Carla Torrent,

and Marc Valentí. Several professionals collaborate with the team, including young investigators, fellows and residents, such as Piero Castro, Andrea Murru, Lorenzo Mazzarini, Alessandra Nívoli and Ekaterina Popova, among other.

The BDP research has focused on the neurobiology (genetics, biomarkers, neuropsychology, neuroimaging), epidemiology (clinical subtypes, comorbidity, psychometric assessment, functionality), and treatment of bipolar illness (including pharmacological, biophysical, and psychosocial strategies). It has an outstanding and long tradition of collaborative research with national and international groups, departing from the premise that true science has no geographical or cultural borders, and that little can be done separately. The CIBERSAM has provided further impulse to collaborative projects, yielding a growing number of multi-authored scientific publications involving two or even more groups within the CIBERSAM and beyond. Special mention is deserved for the long-standing collaboration with the CIBERSAM's Valencia-Alicante group (leaded by Rafael Tabarés), Vitoria (Ana González-Pinto), Madrid (José Luís Ayuso), Sant Joan de Déu (Josep María Haro), and several more that are currently ongoing.

Some of the most relevant BDP output in 2008, just after one year since the start of the CIBERSAM, include, in the neurobiological arena: the development of a model of allostatic load for bipolar disorder[5], the replication of genetic findings involving specific mutations in bipolar disorder and schizophrenia[6], cross-sectional[7-9] and longitudinal[10-12] neurocognitive studies indicating long-term persistence of cognitive deficits, even during remission, and innovation in brain neuroimaging quantification techniques[13]. In the area of epidemiology, our group has developed strategies to improve the screening and early detection of bipolar disorder in depressed patients, the assessment of subclinical symptoms[15] and depression subtypes[16], and comorbidity[17-18]; furthermore, we have conducted studies on psychosocial adjustment and functional outcome[19] and innovative proposals related to the forthcoming classifications of mental disorders, such as the DSM-V[20-22]. Innovation has been further fostered through the development, adaptation, and validation of several psychometric tools aimed at diagnostic screening[23], neuropsychological assessment[24], severity rating[25], and evaluation of comorbidity[26]. Our group has been particularly active in the publication of international consensus documents for the diagnosis, cognitive assessment, follow-up and treatment of people with bipolar disorder[27-33]. Finally, in 2008 our group has made important contributions to the progress in the treatment of bipolar disorder[34-41], including a better knowledge of the efficacy and safety profile of traditional therapies such as lithium[42], and modern strategies such as the use of long-acting injectable risperidone in difficult-to-treat and poorly adherent patients[43]. Several pivotal randomized clinical trials were conducted and published this year, allowing the registration of new indications for drugs as aripiprazole[44], quetiapine[45,46], and ziprasidone[47], and several more, not necessarily sponsored by the pharmaceutical industry, provided relevant input on the potential role of oxcarbazepine[48] and amisulpride[49]; a third group of trials has yielded substantial information on treatment response in specific clinical subgroups[50-51]. The BDP priorizes research upcoming from the clinical arena, and although basic and translational research are seen as crucial, and methodology is given the greatest attention, observational studies are considered highly valuable as well[52-56]. Such studies lack the rigour of placebo-controlled, randomized trials, but they have greater external validity and ecological value. One of them is the European study called EMBLEM. The contribution of

the BDP to bipolar therapeutics is not limited to pharmacological treatment, but actually involves a great deal of psychotherapy research, including the empirical testing of innovative approaches such as group psychoeducation, (with the first report on psychoeducation for bipolar II disorder)[57], family psychoeducation[58], and biophysical treatments, such as vagus nerve stimulation[59] and the traditional electroconvulsive therapy[60]. Our group has also made relevant contributions to research methodology[61,62].

Ongoing and future projects

The main output from the Affective Disorders Program at the University of Barcelona Hospital Clinic after the birth of the CIBERSAM has been summarized in the preceding pages, but there is evidently a great deal of ongoing research that may yield further publications, patents and innovation within the forthcoming years. Some of those involve a large, multicenter study on first-episode psychosis (including affective psychoses), the clinical trial on treatment-resistant unipolar depression named DEPRES, a large, innovative, multicenter trial involving 10 groups from the CIBERSAM on the efficacy of cognitive rehabilitation in bipolar disorder, a translational study on molecular biomarkers in collaboration with the Vitoria group, and several psychometric projects on the validity of the Functioning Assessment Short Test (FAST) subscales and the predictive validity for weight gain of the Barcelona Bipolar Eating Disorder Scale (BEDS). Among the non-collaborative projects, there is one on individual neurocognitive rehabilitation (funded by the *Fondo de Investigación Sanitaria* with Anabel Martínez-Arán as principal investigator), another one on biomarkers for treatment response to psychoeducation, leaded by Francesc Colom, a third one on genetic polymorphisms and lithium response by Antoni Benabarre, and another one on long-term efficacy of electroconvulsive therapy, by José Manuel Goikolea, among other. The recent finalization of a large FIS project, linked to the European study named MHADIE, in cooperation with the group from the Hospital de La Princesa in Madrid, may produce a large number of publications in the nearest future. Moreover, international collaboration may be substantially fostered by means of the ENBREC project, of which I am the principal investigator in Spain. The ENBREC (European Network of Bipolar Expert Centres) is a 7th-Framework-European-Programme funded project that aims at developing networks of networks for bipolar disorder research in Europe. The ENBREC project has also received funding and support from the European College of Neuropsychopharmacology (ECNP).

Conclusions

The Affective Disorders Program at the University of Barcelona Hospital Clinic is one of the most active and productive teams of the CIBERSAM and conducts high-quality research in the fields of unipolar depression and bipolar disorder with a strong collaborative, multidisciplinary, translational, and innovative emphasis. During the short period of a year since the birth of the CIBERSAM it has been already able to generate over 60 high-impact publications and over 1 million Euro additional funding. This is a tangible and unequivocal proof of the success of the CIBERSAM and of the quality and productivity of Spanish Psychiatry when enough funding and resources are provided. In the near future, the CIBERSAM may expand its

research activity and networking over Europe through networks of networks, fostering its capacity to develop further large, multisite collaborative international projects for a better use of research resources beyond local policies, as proven by the ENBREC project in the specific case of bipolar disorder. Hopefully this will be a foundational item in the agenda of decision-makers on European and international research on Mental Health.

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