neuron
Network of European Funding for Neuroscience Research

Scientific Workshop

~ Mental illness and neural dysfunction ~

Paris (France) - May 4-5th, 2009

Report by

Delphine PROU

Foreword by

Alexis BRICE

ERA-NET NEURON

Funded by the European Commission

SIXTH FRAMEWORK PROGRAMME

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The Workshop was introduced by a word from the NEURON Coordinator Dr. Marlies Dorlöchter in order to explain the ERA-Net NEURON Scheme and the scope of the Workshop.

This Workshop is part of Work Package 4
Thematic input for programme of the NEURON project,
Work Package Leaders are Inserm and CNRS.

Published in 2009

Foreword

This workshop is the third of a series devoted to narrow down frontiers, roadblocks and future perspectives in Neurosciences. The objective this time was to give some light to advances and needs for research on mental illnesses having the highest social and economic impact, and to identify remaining hurdles in this field. The concern about research in psychiatric disorders is very high given that these conditions have a huge and underestimated burden on society. The difficulties are numerous due to the complexity of the organisation of the nervous system and its fine tuning, the limitations of current classifications psychiatric disorders and of the corresponding animal models but also to the variability of neuropsychological manifestations and certainly psychobiology between individuals. In this workshop four major psychiatric disorders were explored by eight specialists and the outcome of each presentation should help visualize the challenges that the scientific community has to face and will have to overcome.

Dr Goodwin gave a comprehensive overview of bipolar disorder and the burden that these conditions pose on society. He addressed the difficulty to define boundaries between bipolar disorder and major depression, and raised the important challenge of getting early diagnosis and providing early treatment to patients.

Dr Vieta interestingly focused on the many hurdles that people with bipolar disorder have to face and the low percentage of functional recovery measured after treatment. Epidemiological data have helped identifying several quantifiable neurobiological abnormalities linked to bipolar disorder and suggested that this condition may involve a neurodegenerative-like component explaining part of the neuropsychological manifestations.

Dr Meyer-Lindenberg meticulously discussed genes found to be linked to schizophrenia and involved in the prefrontal cortex and the hippocampus functioning, brain areas showed to have abnormal activation in the disease. Environmental risk factors were also addressed and the importance of investigating the relationship between genes and environment in schizophrenia were stressed.

Dr Bourgeron convincingly demonstrated the importance in Autism Spectrum Disorder of a few genes involved in synaptic function, emphasizing the need to put lots of effort on understanding the function of the molecules identified by genetic studies particularly through the generation and characterization of appropriate animal models. The implication of the circadian rhythm and the role of melatonin in ASD were also well documented.

Dr Arango illustrated nicely the structural changes happening in the grey matter of schizophrenia patients based on the analysis of various epidemiological studies. The small volume of certain brain structures may be explained by a neurodevelopmental impairment but also probably by a progressive loss of tissue.

Dr Bebbington gave an interesting lecture on the principles supporting epidemiology, the limitations to keep in mind and guidelines to follow. Interestingly, worldwide, several large epidemiological studies on mental illnesses have been launched over the years and one conclusion is that it is necessary to carry out secondary analysis to get the full advantage of medical surveys. The impact of performing epidemiological studies in different populations (e.g. at the European level) was underlined.

Dr Deroche-Gamonet provided a well-articulated presentation on new insights on the physiopathology of drug addiction transition. A new concept has emerged postulating that addiction could be less the result of drug-induced alterations than the inability to counteract these drug-induced alterations.

Dr Kuipers elaborated on the hurdles of psychosis and models of the condition, and stressed the central role of appraisal and reasoning biases in the diseases. Emotional pathways such as anxiety and depression relate to particular symptoms and effects of stressful environments have been demonstrated.

This workshop, combined with the previous ones in Vienna, Geneva and Warsaw, gave a large overview of the recent advances and the remaining roadblocks in the field of neuroscience and related diseases. It will surely contribute to define the needs for research and its funding in neurodegenerative and mental illnesses.

Alexis Brice, Inserm

Mental illness and neural dysfunction :

Guy Goodwin
University of Oxford, Oxford, England

TITLE: *Bipolar disorder: neurobiology, challenge of early detection and treatment*

Bipolar disorder currently occupies an ambiguous position in health research priorities. On the one hand, it appears sometimes to be the unwanted twin of schizophrenia, a much better known disorder. Research funding for bipolar disorder has certainly run consistently at unaccountably low levels vis-a-vis schizophrenia, despite comparable estimates of societal burden of disease. On the other hand, the high prevalence of bipolar disorder in patients who present with major depression has been largely unrecognized. An enormous demand for both medical and social resources is attributed to the societal burden of major depression, but the fact that bipolar disorder is a major part of the depression story is not widely understood. The ambiguous status of bipolar disorder is also observed clinically: it is well recognized that diagnosis is often missed for between 4 to 8 years from the time people actually present symptoms. It is then important to strengthen the importance of the challenges to gain earlier detection and offer earlier treatment.

What is our map of mood disorders in the 21st century? There are four broad categories with reasonably defined boundaries. 1- Bipolar I is the most serious and the least common, and is defined by mania, often psychotic. Historically, it is where the concept of bipolar disorder started and it was named initially manic depression. 2- Bipolar II is defined by major depression primarily but patients also have a history of hypomania (defined as elevation of mood that lasts at least 4 days but is not necessarily dysfunctional). 3- The third group named Bipolar Not Otherwise Specified (NOS) is less well defined and is characterized minor mood elevation usually plus major depression. 4- Finally, the fourth group is the group of people who experience depression only.

The frequency of Bipolar I is about 1% of the population, as it is for Bipolar II. Bipolar NOS is in fact as common as the two others taken together. When bipolar disorder is defined as in DSM-IV, the spectrum extends the total to 4-5% of the population but, depending on definitions of mood elevation, the number of patients who may be described as part of a bipolar spectrum may be much larger. Thus, the problem of mood elevation within mental disorders is common, but has a rare extreme manifestation (mania) and a common less severe expression which, when clinically identified, usually accompanies major depression. The common factor is actually depression, which poses the major long-term burden for virtually all patients with bipolar disorder. But the obvious question remains “Where does bipolar depression stop and unipolar depression start?" The answer lies in our definition and understanding of hypomania.

Hypomania is defined by a list of symptoms that people experience: activation/agitation, decreased sleep, pressured speech, flight of ideas/racing thoughts, distractibility. The DSM-IV requires that people have to experience it for 4 days and that these symptoms (3/4 symptoms of these 7 symptoms) should be observable without impaired function. It is possible to loosen that definition to fewer symptoms and shorter duration. In a Swiss cohort, the effects of adopting criteria for 3 of these 7 symptoms, duration for more than 1 day (Zurich strict criteria) or even more liberally, 2 of these 7 symptoms, duration for more than 1 day (Zurich broad criteria) had a major impact in term of frequency of bipolar diagnosis. Taking the definition established by the DSM-IV, the ratio bipolar disorder versus major depression is 1/10. If the definition of hypomania is by the Zurich strict criteria then the population of Bipolar I and II reach 5% of the people presenting depression. If we adopt the Zurich broad criteria, up to 50% of the population that present with major depression give some kind of bipolarity in their history. This aspect of diagnosis is important to know because it has consequences in term of treatment.

The boundary between Bipolar I and Bipolar II is pretty clear and non-controversial but the one between Bipolar II and unipolar is less well defined because such a broad spectrum exists. Clinically, it matters because:

1- Should a history of hypomania influence the treatment of major depression?
2- Where should this boundary be defined? Maybe it should be based not on an arbitrary diagnostic formula, but on data relevant to treatment efficacy at different points along the spectrum.

3- Finally, most of the genetic studies of major depression have neglected bipolarity indeed, have been blind to the bipolar spectrum.

For all common diseases, the challenge is to identify what the risk factors are and what the moderating factors are. For major depression, very clear predictors of risk have been identified from genetically controlled studies: family history, temperament (the way people are, the intensity of worry) and early abuse or neglect. The next step - to get depression itself- depends on moderating factors - life events, physical illness which is a very important life stress, and drug and alcohol consumption. For broadly defined bipolar disorder, the risk factors are the same but note that the more severe forms of bipolar disorder (especially bipolar I) are more strongly genetic than unipolar major depression. Life events, physical illness, drug and alcohol consumption are also probably moderating factors but another important factor may relate to the experience of elevated mood. Manic symptoms, although less well studied, appear to be an early risk factor and a possible way into depression and bipolarity.

Knowing how and when bipolar disorder starts is a key point. These illnesses pose a big burden on health services because they start young. Interviews of cohorts of young people have identified appearance of mood disorders from the age of 10 years old and at the earlier teenage stage, the mood disorder is more likely to evolve into bipolar than unipolar disorder.
We have adopted the policy recently of recruiting from our student population. At the age of 19 years old, 20% of students screened for bipolar disorder have experienced manic symptoms. Among them, a smaller subgroup already have Bipolar II or Bipolar NOS, so 2 to 4% of all students that entered university do so with this mood disorder, almost all undiagnosed.

These findings illustrate that prospective studies are needed to clarify the neurobiology underlying this clinical challenge in a number of key areas:

- How neurocognitive mechanisms predispose to personal vulnerability
- How Life events translate their impact via stress biology
- How substance misuse/drug effects contribute to the risk of greater illness severity
- How sleep disturbance, which we don't enough about, can act as a cause of mood disorder

Mood disorder has understandable antecedents: it is not a mystery. Systems neurobiology offers us the chance to understand how cognitive mechanism moderate risk in vulnerable versus resilient individuals, exposed to similar stresses. Individual differences are likely to be expressed at behavioural, neuronal and ultimately molecular levels. We cannot know in advance which technology will be the most promising for scientific advance, but we should start at the level of cognitive neuroscience.

Hitherto, mood disorder has too often been conceptualised as beginning with a severe mood episode. While patients then certainly need appropriate treatment, it should not limit our scientific ambition. The preventative aspects are very important to consider because the consequences of not treating people early are numerous and disastrous. There is a risk for further episodes and a need for long-term medical treatment. Impaired cognition appears to develop as a scar effect with time. Symptom chronicity and cognitive impairment lead to the high rate of underemployment and dependence which pose such a major burden on society.

In conclusion, the challenge is to develop acceptable methods reliably to identify at risk populations and offer appropriate advice, education or treatment. An understanding of the neurocognitive mechanisms moderating the impact of life events and other provoking mechanisms may be critical both to more accurate identification and to the development of translational models of the disease. Translational models of mood disorder should inform both drug and psychological treatments in the future.

Eduard Vieta
Clinical Institute of Neuroscience, Barcelona , Spain

TITLE: *Neurocognition and functional outcome in bipolar disorder*

Bipolar disorder is one of the most severe, and yet treatable, mental disorders. It has been ranked as the 6th cause of disability by the World Health Organization and its early age of onset and associated stigma contribute to the many hurdles that those who have this condition have to face as regards to their psychosocial adjustment. Disability comes along for a long period of time and last almost all their life.

Mental conditions as any other conditions can be studied from several perspectives, working from genes to neurons, trying to identify causes of vulnerability and to reveal connectivity abnormalities, then to brain showing functional abnormalities and patient, characterizing changes in emotions and behaviour, and finally to analyse impacts on society. Our program is therefore based on three objectives: linking neurobiology, clinical and epidemiologic studies, and therapeutics development.

As an example of collaboration involving 14 countries over Europe, 530 investigators and more than 3500 patients, the EMBLEM study focusing on disability associated with bipolar disorder revealed that only 11% of the patients did not experience impairment related to their work or occupational activities, showing how serious this condition is from this perspective.

Yet, we can provide treatments to our patients, we have drugs and psychotherapists. But it is important to mention that one study focusing on first episode patients with bipolar disorder showed that after 6 months of treatment, 84% of the patients were able to recover from a syndromal perspective but only 30% have recovered functionally, meaning that only 30% were able to go back to their occupational activities. After 2 years, the improvement in terms of clinical perspectives is almost 100% but only 38% were able to go back to their previous status. There is therefore an important discrepancy here and there are few potential reasons to explain that phenomenon.

Across several domains of functioning, occupation is one of the most important criteria but autonomy and cognition are also impaired for these patients and they experience financial issues and interpersonal issues. There are plenty of factors that can explain why bipolar patients have functional disability: genetic factors, neurobiological factors, cognitive factors, clinical factors, treatment-related factors and social factors. From the research perspective and treatment perspective, the genetic, neurobiological and cognitive factors are the best potential targets for intervention.

As a matter of fact, we found a specific mutation in two genes, LIS1 and PAFR, related to neurodevelopment. Patients who carry this mutation have worse cognitive performances. They might represent a subgroup of patients with bipolar disorder who are closer to schizophrenia in the sense that they have problems in neurodevelopment. From the cognitive perspective, there is between 30% and 50% of bipolar patients experiencing significant social disability that may be linked to persistent cognitive impairment as measured by the tools that we have so far.

The types of cognitive problems that we see in bipolar patients are different from the ones that can be evidenced in Alzheimer's disease. They don't forget things or have trouble doing tasks that they could do in the past but they have difficulties in terms of processing speed and attention. We have demonstrated that, even if they don't present any symptoms, we can see patients either manic, depressed or even euthymic (meaning in remission) already presenting cognitive impairment such as learning and verbal memory impairment when compared to controls.

There is very interesting work that has been replicated by several groups now. People have shown that there is a difference in schizophrenia and bipolar disorder that is very important in term of neurodevelopment. It is a study where all the children were assessed at a certain age and were followed until their 20's when some of the them developed schizophrenia and some developed bipolar disorder. As compared to children who didn't present any symptoms, the ones who were diagnosed to have schizophrenia, when they were 7 years old had already impairment in motor development, receptive language and IQ. Something seems already present and might be linked to development. There are so many overlapping characteristics between schizophrenia and bipolar disorder that you would expect the same results for bipolar children. On the contrary, for bipolar patients who didn't have signs of mental disorder and develop mania later on, when they were 7 years old, they were actually smarter when compared not only to those who developed schizophrenia, but also to controls. Some of the patients were actually very bright students; they had very early motor development and were very easy to understand and to speak at an early age. So there is something different here from schizophrenia and it is interesting to note that this doesn't point out a problem in neurodevelopment but seems more related to a process reminiscent of neurodegeneration in some sense. Hence, our hypothesis is that there is a small subgroup of patients with bipolar disorder whose condition is driven by specific mutations in genes related to neurodevelopment, and who would be close to the phenotype known as

schizophrenia, and a larger subgroup in whom neurocognitive deficits would come out as a result of repetitive episodes and loss of connectivity.

The potential explanation for this is that there is actually a correlation between the number of episodes when the illness develops and some changes in the brain. One thing that happens is that with every episode there is an increase in cortisol and other cortisol related hormones levels. There are also changes in neurotrophins (implicated in neurogenesis, neuronal survival and maturation..) levels. For instance, there is an important decrease in BDNF levels in patients compared to controls. It is especially pronounced for manic patients compared to depressed patients and euthymic patients, the least affected by the phenomenon. And we can see some compensatory mechanism with an increase in the levels of GDNF.

And, this also correlates with changes in neuroimaging. We can see some grey matter loss in some areas of the brain that are related to the number of episodes and to the level of cognitive impairment, and some hippocampus atrophy. This set of events has been summarized by us and some colleagues under the name of the cycle of allostatic load in bipolar disorder. Every episode decreases BDNF levels and creates oxidative stress. This later leads to some DNA damage and carries systemic changes, even metabolic changes. We know that this can then lead to neural atrophy and cognitive impairment, the results of these successive events being for the patient a low functioning and some degree of disability plus a lack of insight. This is a vicious cycle and the only way to overcome this negative cycle is by using mood stabilizers as drug therapy but also psychoeducation and cognitive remediation.

As mentioned earlier we found that bipolar patients have memory defects, attention problems and the more impaired patients are the ones that are impaired from an occupational perspective. Clearly, there is a relationship between all these findings from the laboratory perspective and from the neuropsychological observations and certainly, the cognitive impairment is a predictor factor for social impairment. There is a way to overcome this and this is why I think research is needed to try to find treatments that address these topics. The majority of treatments that have been used in psychiatry have been focused on neurotransmitters. But today I think we have to try to target development of therapies based on these biological events that seem similar to some kind of neurodegenative process as evidenced by a big loss of connectivity at one point during the course of the illness.

Current and future research should focus on identifying all the relevant mediators of neuropsychological impairment and potential therapies that might reverse or at least prevent this process, including pharmacotherapy and psychological interventions such as cognitive remediation and psychoeducation. If we really want research to be truly translational and to have a real impact on patient's lives, it will be crucial to demonstrate that future treatment developments have not only some action on psychiatric symptoms but also on the functional outcome of the disease.

Andreas Meyer-Lindenberg
Central Institute of Mental Health, Mannheim, Germany

TITLE: *Neurogenetic mechanisms of Schizophrenia*

We urgently need new therapies in this area of psychiatry. In schizophrenia, we know that the heritability is about 80%, meaning that the answers lie in the genes if we know how to decipher them. We know also that there are shared environmental factors for the development of schizophrenia which account for about 20% of the risk. As has become increasingly clear, figuring out the relation between genes and environment is one of the main challenges. Our research approach has been to relate these risk factors, not to the categorical phenotype of having or not having schizophrenia, but to the brain mechanisms that mediate risk.

A good way to start is to look for characteristics in the brain that are abnormal in schizophrenia and that are heritable. A well-known difference between patients and controls is that the prefrontal cortex is thinner in patients. A key point is that patients with a thinner cortex have relatives with a thinner cortex meaning that this change is heritable. Similarly, when we turn to brain function, when we activate this region using a working memory task, we reliably find abnormal activation in the prefrontal cortex and this is also very nicely heritable. Also, the hippocampus is relevant for schizophrenia and for memory function. We found that the prefrontal-hippocampal circuitry also matters in schizophrenia: qualitative abnormalities can be uncovered when the interaction between hippocampus and prefrontal cortex is measured during working memory.

While many neurotransmitter and circuit abnormalities underlie these structural-functional findings in prefrontal cortex, one important aspect is that the prefrontal function of the brain and the sub-cortical dopaminergic activity are very much related, a circuitry that is very important to understand psychiatric disorders in general. Dopamine is made in the brainstem and released into the striatum and prefrontal cortex. Dopamine is critical to regulate the functional state of the prefrontal cortex and is deregulated in schizophrenia. We know that the prefrontal cortex regulates the amount of dopamine that is released suggesting the prescence of a feedback circuitry. We actually found some evidence that this feedback exists when we measured striatal dopamine synthesis and prefrontal cortex function, and showed that prefrontal dysfunction is coupled to striatal dopamine disinhibition in patients with schizophrenia.

We know increasing numbers of genetic variants related to schizophrenia. They are not causing the disease in the sense that when an individual has a mutation in one of these genes, s/he invariably gets schizophrenia. Rather, these variants increase, usually slightly, the risk for the disease. These genes act on various circuits of the brain and don't map one on one on a given complex phenotype such as schizophrenia, so we have a very complicated network to deal with. We decided to look at the link between prefrontal cortex, midbrain and striatum.

The first gene, known for quite a while and studied extensively, is the COMT (Catechol-O-Methyl Transferase) which encodes an enzyme that degrades catecholamines such as dopamine. That gene carries a common variant colloquially called the Val-Met variant which affects the amount of extracellular dopamine present in the prefrontal cortex. An individual that carries the Val allele has a lot less dopamine specifically in the prefrontal cortex than the one that carries the Met allele (about 50 to 70% less). This has functional consequences as can be seen on a working memory test. The carriers of the Met allele perform considerably better than the Val carriers. In addition to this cognitive effect, having the Val allele slightly increases the risk for schizophrenia.

Knowing that, we actually develop therapies targeted to prefrontal cortex function depending on the genotype of a patient. For example, tolcapone is a drug that inhibits COMT and is used by neurologists in Parkinson's disease. If we give tolcapone to a patient with a Val/Val phenotype, the increase of dopamine in the prefrontal cortex translates into improved cognitive function. An increase of dopamine by the same amount when tolcapone is given to a Met/Met patient leads to deteriorated function (due to the "inverted-u" curve linking extracellular dopamine and prefrontal function). So, here, we have a targeted precognitive therapy in schizophrenia that can only work as a personalised medicine. If we would give tolcapone indiscriminately to all of the schizophrenia patients, half would get better and half worse. But if we understand the system and we treat the patients whose genotype shows they can profit, we have a potentially effective therapy.

The KCNH2 gene is a gene that was picked up in a screen of transcripts that are abnormally regulated in schizophrenic brain. It encodes for a potassium channel. We found a variant of this channel, isoform 3.1, only expressed in primates and only in the brain. This variant is likely the one that confers risk for schizophrenia. This isoform encodes a deficient channel that lacks a deactivating potassium current and this has dramatic consequences on the way hippocampal neurons, expressing this variant, fire. Both in structure and in function, we can also detect a clear signature of this risk variant in the hippocampus, a brain area that we have already mentioned to be important for episodic memory and schizophrenia risk.

People are looking for genes implicated in schizophrenia across the whole genome by associated studies but the question is "What do we do once we have these genetic variants?" Clearly, what makes people sick is not

only one of theses genes. What makes people sick is that they have several, maybe 10 to 20 risk variants, so we have to understand what happens in the brain when people have several of these variants. An example showing epistasis is given by a study on COMT and GRM3, a metabotropic glutamate receptor. We know that dopamine and glutamate are important regulators of the prefrontal cortex function. When asking the question "Where in the brain do these 2 risk factors for schizophrenia show an epistatic interaction?", we found a true interaction in the prefrontal cortex as a signature of the interaction of these two neurotransmitter systems. As many know, these findings have therapeutic implications. LY2140023, which is a partial agonist of GRM2/3, when tested against the atypical antipsychotic olanzapine, proved an effective antipsychotic action that had no dopaminergic side effects such as prolactine increase, akathisia, etc..It is currently in phase-3 trials. If confirmed, this is the first mechanistically innovative antipsychotic that we have had in close to fifty years, with a mechanism of action predicted by genetic approaches.

There are established environmental risk factors for schizophrenia like urbanicity, which increases risk by 2-3 fold. Social status is clearly important. Migration also increases the risk quite dramatically. Altogether these factors are not as important as all the genes taken together, but individually, each environmental factor has a much higher impact on disease risk than any individual frequent genetic variant that we know of. Social status is highly relevant for physical and mental health and is critical for survival in primates. It is present throughout the animal kingdom and it interacts with genetic risks. We were interested in understanding how the human brain processes social hierarchy. We found that social superiors, but not inferiors, are reflected in an extensive allocation of brain responses when tested in an implicit artificial hierarchy. Furthermore, looking at the activation of the amygdala in unstable hierarchies only (which carry increased disease risk), we could predict how important it is for people to be in a hierarchically superior position. If this position is very important for the person, the amygdala activation is higher and if a person does not care about his social status we have pretty much no activation of this area. The fact that the amygdala shows an activation in that form of emotional processing, known to be a risk factor for schizophrenia, makes us think that this brain area is probably one that should be looked at for the interaction of gene variants and environmental risk.

We have tried to give a brief overview of how to use data on genetic and environmental risk to try and understand the systems that they act on and thereby understand the neural architecture of schizophrenia risk in order to find new treatments.

Thomas Bourgeron
Institute Curie, Paris, France

TITLE: *Synaptic and clock genes in autism spectrum disorder*

Autism spectrum disorder is a neurological disorder defined by a lack of social interaction and problems of language; sometimes individuals present no language at all and sometimes the development of language is delayed. There is also restrictive pattern of interest and stereotypies.

In 1944, Hans Asperger described the Asperger syndrome which is also defined by a lack of social interaction, the presence of stereotypies but with an absence of clinical problems of language. This syndrome affects more men than women, the ratio being 8 men for 1 woman.

The prevalence of autism spectrum disorder is highly debated and in the USA, Canada and England it is estimated at 1 in over 156. Studies in California showed a huge expected increase in the number of cases 10 years from now. In fact, this increase can be largely explained by the broader diagnostic criteria that are currently used. When taking the criteria from the typical Kanner's diagnosis of autism, the prevalence is still 1 child in over 1000 and when using the broader criteria of autism spectrum disorder, the numbers increase to I child in over 150-160.

Autism is an extremely variable disorder, some people call it a disorder, some others call it a condition. Nevertheless, there is a wide range of manifestations and the Autism Spectrum Quotient has been designed to enable scoring of individuals with autism. This test is similar to an IQ test but dedicated to autism symptoms. The severity of the diagnosis depends on the score. There is some overlap, likely a normal distribution, between controls and people with autism. There are some categories, but it is more likely a continuum.

A lot of work has been done to study genes responsible for vulnerability to autism spectrum disorder. Our projects are focused on neuronal signalling and circadian clocks. Neurons are connected to each other by the presence of synapses and the period from 0 to 3 years old of age is critical for the establishment of these interactions. We have made lots of progress in understanding the functioning of synapses and we know more and more about the proteins that are implicated at the pre and post-synaptic sites. Some of these proteins have been found to be associated with autism.

We first identified mutations in a protein family called the neuroligins, which are cell adhesion molecules present at the post-synaptic site of the synapse. We also found mutations in another protein named SHANK3, which is a scaffolding protein located at glutamatergic synapses. The first mutation was found on the neuroligin gene with a very classical approach. When we looked at the X chromosome to try to identify differences that could explain the prevalence difference between men and women, we could find a deletion in the neuroligin-4 gene in several patients with autism spectrum disorder. We also identified a stop mutation in one family. The mother carries this stop mutation and transmitted it to one son that has typical autism and started to speak at 11 years old, to another son who was diagnosed with Asperger syndrome and did not transmit it to a third son, neurotypique. We also found a point mutation (R451C) on the neuroligin-3 gene in a similar family with one child with autism and his brother with Asperger syndrome. The work on the neuroligin-4 has been replicated by several groups now and it seems that when there is a stop mutation in this gene in a male genome, something deleterious happens to the brain and leads to mental retardation, autism, pervasive developmental disorder (PDD) or Asperger syndrome as in our case. The second mutated gene that we identified is SHANK3. One family was interesting because it seemed like only one single mutation in SHANK3 is enough to lead to an autism diagnosis with almost no speech. This gene dosage was interestingly illustrated by another family. One girl has one copy of SHANK3 missing and she has almost no speech, knowing around 5 words. On the contrary, her brother, who was diagnosed with a typical Asperger syndrome, has an additional copy of the gene so 3 copies and started to speak before the normal age and has a very rich vocabulary. It seems that one copy of the gene leads to a typical autism diagnosis and 3 copies of the same gene generate an Asperger syndrome diagnosis. And, finally, the third gene implicated in autism spectrum disorder that we identified is the neurexin gene.

Even if for each molecule identified to be implicated in autistic symptoms, there is only a limited number of individuals, it indicates that there are nevertheless few pathways that seem to be linked to autism. And, one important question is "What are their function?"

In vitro it has been shown that the mutation R451C in the neuroligin-3 gene leads to a defect in synaptogenesis. The same is true for the neuroligin-4 stop mutation. For Shank, it looks like the post-synaptic clusters of shank-3 at the post-synaptic site are abnormal. We have done studies in vivo and we developed knock-out mice for the neuroligin-4 gene. These mice are similar to controls except that they are defective in terms of social interaction. When we recorded the sound that they make and analysed the frequency, we observed a clear decrease in their vocalization. At day 2 to day 6, there is almost no defect but when tested later on during development, this characteristic seems really impaired. It's not their ability to produce vocalization that is abnormal, it is their ability to use it. This is a very interesting discovery and we need to investigate the possible mechanisms leading to this phenotype.

During the past few years, the development of the Snip array technology has led to a technological revolution and has tremendously helped the discovery of new genes related to autism. Using this method, we could study more than 256 patients and found duplication in the neuroligin-4 gene, the shank-3 gene (that we already knew) but we were able to identified mutations also in other genes. In the last years, the number of mutations has been considerably enriched in the autism population. Finding all of these copy number variants (CNV) is not easy, but we could identify a combination of CNVs related to autistic symptoms. The challenge is now to understand what is really the meaning of these mutations.

Another axis of our research is focused on the circadian rhythm and the role of melatonin. Several publications have shown that patients with autism had low levels of melatonin. When we looked at our cohorts, we surprisingly saw very low levels of melatonin related to autism. We also found alterations of the ASMT gene coding for the last enzyme of the melatonin synthesis pathway. In several families, we could clearly show that the deficit in melatonin is not a consequence of autism since the deficiency is already present in one of the parents.

Pr. Segawa showed that the sleep of people diagnosed with autism has a very specific pattern. Since 2006, there have been many studies showing the benefit of supplementing patients with melatonin. During the largest genetic study conducted in United Kingdom including 170 patients, very interesting CNVs have been identified relating to the melatonin pathway.

In conclusion, I would like to use a quote from Theodosius Dobzhansky who said "It is incorrect to think of an organism's genotype as determining its phenotype, it is correct to think of the genotype as determining the "reaction norm" of the phenotype" and emphasize that, in autism, we have to find for each individual the best environment.

Celso Arango Lopez
Hospital General Universitario Gregorio Maranon, CIBERSAM, Madrid, Spain

TITLE: *Schizophrenia, a neurodegenerative disorder?*

Neuropsychiatric disorders account for most of the DALYs (Disability Adjusted Life Years) taking into account all medical disorders and, among the diseases that cause life years lived with disability, schizophrenia represents 2,6 % of the total.

People with schizophrenia have an increased risk of mortality as compared to the general population. They die sooner, 15% of them commit suicide and there is a high rate of co-morbid physical illness. Even if more research has been conducted during the last years, it has not changed these numbers and actually the situation is getting worse and worse. The chances of dying from schizophrenia have increased by 2-fold between1970 to 1990.

A hundred years ago, bipolar disorder was differentiated from schizophrenia based on the longitudinal course of the disease. People with schizophrenia would have a very degenerating clinical course and would finally eventually end up with having dementia early in life. This proves not to be the case, at least for a vast majority of patients with schizophrenia. We know that when patients experience their first cognitive symptoms, at that time already they present from a biological perspective a decrease in the volume of the grey matter and that happens during brain maturation.

So, what are these progressive brain changes?

Between the first episode of schizophrenia to five years later, after the age of 7 years old, a significant decrease of the grey matter is observed compared to healthy controls. A study showed that for schizophrenia patients the progressive brain tissue decrease was 0.5% per year, compared to controls who have a 0.2% decrease, and that the phenomenon is more pronounced in the frontal and temporal areas.

Another study demonstrated that brain tissue decreases and lateral ventricle volume increases, up to 20 years after the first symptoms of delusions and hallucinations. It is interesting to note that the more pronounced progressive brain changes are associated with patients that have poor outcome, more negative symptoms and decline in neuropsychological performance, these conditions pointing to a more severe prognosis.

The whole brain and cerebral grey matter volumes decrease excessively in patients compared to their siblings and controls. It looks as if some of this grey matter loss is not only genetically mediated and that it does not appear in relatives. Also, there is an association between longer duration of psychosis, larger gray matter volume decrease and larger ventricular volume increase after 5 years of follow-up. Some studies, now replicated from different groups, have shown that treatment with some of the second-generation psychotics may reduce the amount of grey matter that is lost through the 2 first years of treatment, although these findings are controversial.

But brain changes not only take place after patients become psychotic, some brain changes already take place before patient have the first manifestations of the disease in the form of positive symptoms.

A large study involving 40 patients and 100 controls showed that patients not only had decreased grey matter volume but they also had more cerebrospinal fluid (CSF). This is important information because the cranium doesn't grow unless the brain pushes it and in theory we should not find any "gap" in between the cranium and the brain. So, there is a phenomenon happening here, maybe similar to a neurodegenerative event. Otherwise, it is not normal during development to see this excess of CSF volume. This 15% increase of CSF volume observed cannot be explained just by a lower maturation of the grey matter but probably by a loss of this tissue at some point in time.

So, what happens in a brain that is still developing?

For numbers of years, we have been following up children and adolescents presenting their first episode of psychosis, or both schizophrenia and bipolar disorder. This is important because we know that psychotic disorders account for 5% of mental disorders in adolescence and for 20% of the inpatients in adolescent psychiatric units. We know also that about 25% of the patients with schizophrenia had their onset before 18 years of age. That strengthens the importance of early detection and early intervention for prognosis.

In a multicenter study conducted across Spain, we showed that progressive loss of cortical grey matter volume and increase in ventricular volume are present during adolescence in patients with childhood-onset schizophrenia (COS). These progressive changes are also present in non-schizophrenia early-onset psychosis, meaning that it is not specific to schizophrenia. When patients were followed for one year and diagnosis was made after this period of time (25 schizophrenia patients, 20 bipolar patients and 25 with others psychosis), it was possible to identify a grey matter deficit in the left middle frontal gyrus that is specific for schizophrenia. It was also shown that schizophrenia patients have a lower level of N-acetyl aspartate (NAA), which is a marker of neuronal integrity, in the left-dorso-lateral prefrontal cortex.

We conducted a large two-year longitudinal study involving 61 patients presenting their first episode of psychosis for less than 6 months, to exclude unspecific brain changes, and 71 healthy controls, across 6 different hospitals in Spain. The goal was to assess clinical characteristics, prognostic factors, diagnosis specificities of findings and pathophysiological changes in the brain through an integrative and translational approach. The patients and controls were scanned by anatomical brain MRI at baseline and 2 years later, after they became psychotic. At baseline, the main duration of illness was 2 months and we did not expect brain changes to occur during that time. The rate of grey matter volume loss in the left frontal area within the 2 years follow-up was higher in patients than in controls. Considering the CSF volume, we saw the opposite. The patients end up with larger volume of CSF, with no significant differences between male and female. The same happened in other areas like the left parietal grey matter and on the contrary there were no changes in CSF volume in the left temporal grey matter. Why do these changes take place? It could be some inflammatory processes going on or it could be some oxidative stress. We had the fortune to measure some stress markers in this study. Both for schizophrenia patients and bipolar patients, the total antioxidant status is significantly lower than in controls and they present higher levels of lipid hydroperoxides, which is a marker of oxidative stress. When we looked at the correlation between these markers and the volume of grey matter, looking at the lateral ventricle, we found that the higher the levels of stress markers are, the higher the lost of tissue is.

So, to conclude, all these results suggest that most patients with a first episode psychoses have structural changes, some of them being difficult to explain only with a neurodevelopmental theory, and that some of those changes (frontal lobe mainly) are progressive.

For the future, the questions that we should focus on should be:

- What causes the progressive brain changes?
- Can the excessive loss of gray matter be prevented?
- Would that in turn translate into better prognosis?

Paul Bebbington
University College London,, United Kingdom

TITLE: *Epidemiology of mental illnesses*

Epidemiology is essentially a medical discipline, as it is based on the idea of disease, of cases of disease, of case definition, and of case finding. Epidemiology has several different purposes.

- Identification of syndromes
- Refining the clinical picture of disorders
- Community health
- Individual risks
- Analytical and experimental epidemiology
- Operational analyses of health services
- Historical epidemiology

The principles of epidemiology also underpin the methods used to conduct clinical trials. It is not commonly remembered or acknowledged that the precepts of epidemiology form the basis of clinical trial methodology.

Epidemiology enables society to assess the health of communities by making comparisons between them, and this can alert authorities to problems in particular communities. It is obviously of use to establish individual risks for getting a disorder, and again epidemiology is the basis of such calculation. It is important to know how health services are functioning, and epidemiological surveys permit us to access this kind of information. Finally historical epidemiology allows an evaluation of the change in the burden of disease when a population changes over time.

The key concept in epidemiology is that of a case. A case is represented by someone who suffers from a disease. In order to identify cases, case definitions are required. Case definitions are based on disease constructs, and carry the assumption that it is useful to arrange the clinical material in particular ways. This involves the definition of syndromes. Syndromes are heuristic categories that allow us to speculate about possible causes and treatments. The specification of a syndrome requires considerable intellectual effort, and there is of course no guarantee that our arrangement of clinical phenomena into a syndrome is meaningful. We can only find this out by attempting to validate the syndrome empirically, another task for epidemiology. Sometimes our choice of syndrome is a failure, in that the syndrome turns out not to be useful. In other words, the chosen definition has proved not to be adequate for the task. There is an increasing awareness that this may be the case with schizophrenia. There is a complexity about schizophrenia which may not be encapsulated by our current definition of cases. Having defined a case, we are in a position to find cases within populations. Case finding depends on applying the case definition to individuals to see if they match it.

Another key activity in epidemiology is sampling strategy, that is deciding how to find a sample that may be taken as representative of the population of interest. This always involves an inevitable trade off between cost and generalisability. The sample needs to be representative of the chosen population, but the size and spread of the sample will be limited by cost constraints.

Diagnosis in psychiatry is particularly difficult. This has resulted in a compensatory attention to operationalisation and standardisation. We operationalise the definition of a case, and this then becomes the basis of the procedure by which we identify cases. Once we have obtained a description of the relevant clinical features seen in the individual, operationalisation enables us to standardise the process of case recognition with theoretically perfect accuracy, using a computer programme if we wish.

The problem is that it is always possible to operationalise a definition, but some of the precision involved in this process is arbitrary. This means we can never be sure that the operationalisation criteria encapsulate the concept of the syndrome adequately and effectively. Operationalisation inherently requires precision, and the level of precision is quite likely to exceed what we know about the validation of the syndrome. Operationalisation allows us to be highly reliable in identifying cases, but at the same time the cases may not represent the underlying concept of the syndrome. Thus there is a trade off between reliability and validity. The more precise we get in our operationalised definitions, the more opportunity we have to miss the point, and the operationalisation may therefore not be valid. We achieve a reliable procedure but we lose validity.

In psychiatry, case definitions were first operationalised in the United States, in the 1980 revision of the Diagnostic and Statistical Manual (DSM-III). Similar operationalisation in the International Classification of Disease arrived in 1992 with publication of ICD-10.

On the basis of operationalised definitions, instruments were created and designed to identify cases in surveys. The instruments currently used are of two types:

- Fully structured questionnaires: the way in which questions are delivered is completely fixed. The advantage of this is that administering the questionnaire does not require high levels of skill, and means that the interviewers can be relatively cheap. However there is no flexibility and the interviewer is not able to pursue suggestive responses by the participant. Examples of this type of instrument include CIDI (Composite International Diagnostic Interview) and CIS-R(Clinical Interview Schedule – Revised).

- Semi-structured interviews have a degree of flexibility within a set of constraints. This means that the interviewer can pursue leads in a way that is not possible with a fully structured instrument. The disadvantage is that the interviewer requires good clinical judgement, and therefore has to have clinical training, which tends to render them more expensive. An example of this type of instrument is SCAN (Schedules for Clinical Assessment in Neuropsychiatry).

These instruments have been the basis of large psychiatric surveys. The implementation of large epidemiological psychiatric surveys has become almost an industry. Such surveys originated in the 1980s in the Epidemiologic Catchment Areas surveys. These were based on the development of a completely structured instrument which was the precursor to the CIDI. These surveys involved interviewing almost twenty thousand people in five different locations in the United States. Two US National Co-morbidity Surveys followed. In the the 1990s there were also British and Australian National Surveys involving around ten thousand people each.

There have now been three British National Surveys for Psychiatric Morbidity, carried out in 1993, 2000, and 2007. These use virtually identical methods of evaluation, allowing comparison across the years. The surveys had two phases, the first based on the CIS-R (for common mental disorders) and the second on SCAN (for psychosis). The repetition of the surveys was intended to detect changes in the population, for example, in the prevalence of major depressive disorder. The programme also included sub-surveys on homeless populations, institutionalised people and prisoner populations. As part of the programme, there have also been surveys on children and adolescents.

There has been a tendency for survey projects to increase in size. Thus ESEMeD involved six European countries and twenty-one thousand people. It was based on CIDI, and investigated risk factors, disability, quality of life, use of services, and drug use.

The WHO World Mental Health (WMH) survey initiative was started in 1998, and has involved 154,000 thousand people in twenty eight countries. It mainly comprises national surveys, and all are based on the CIDI. However it is not clear if the CID in each country generates equivalent results. For example, the prevalence of major depressive disorders ranges from 1.1% (Nigeria) and 9.7% (USA). Do we really believe that there is a nine fold difference in the rate of depressive disorders in these two countries? Do these differences in prevalence actually indicate differences in the impact of the social conditions in these countries, or do they represent differences in the way the questionnaire was used? It is difficult to be sure, and this represents a major limitation in this type of study.

If we want to use medical surveys to the full, we have to ask what are they really for. Increasing the number of countries in the WMH survey may be relevant to individual countries, but whether it is relevant to the world as a whole is difficult to tell. Just counting disorders is not useful, and is actually an under-exploitation of the data sets. Thus it is important to carry out secondary analyses. The risk in any kind of scientific venture, which involves large amounts of data, whether in neuroscience or in social psychiatry, is that it is possible to acquire much more data than can actually be used. People are typically funded for obtaining the data, they are not adequately funded for analysing them. Ideally, grant giving bodies need to set up funding systems whereby the data can be analysed adequately. In the British surveys, for example, there is a writing group that takes responsibility for driving forward analyses of particular aspects of the survey. This results in a rich utilisation of the data.

I will provide two examples from the British Survey of Psychiatric Morbidity of creative secondary analyses. The first concerns the evolution of the use of anxiolytics and antidepressants between 1993 and 2000. In the female population there was a small increase in the use of anxiolytics but a large increase in the use of antidepressants. Just over 6% of women with neurotic disorder were being given antidepressants in 1993, the figure rising to over 17% by 2000. There is a comensurate increase in men, from just over 4% to over 14%. In men, but not in women, there was also an appreciable increase in the use of anxiolytics.

Thus there were major changes in the way people could be identified as having a neurotic disorder were being treated. Interestingly this did not produce a change in the prevalence of the depression itself. This is because antidepressants are not actually that effective. It takes the treatment of around seven people to

produce one additional recovery (the *number needed to treat*). While it is a good sign that people are being given appropriate treatment, this cannot necessarily be expected to produce differences in prevalence.

Another example of a secondary analysis from the British National Surveys concerns whether people have experienced sexual abuse. The data demonstrates a very large increase in suicidal ideation and suicidal attempts in people who have been sexually abused. Women are more likely to be sexually abused than men, thus an appreciable proportion, over a quarter, of suicidality in women could be attributed to their experience of sexual abuse. This clearly has large public health and clinical implications.

In conclusion, how can epidemiology assist in the neuroscientific endeavour?

Epidemiology is a powerful tool, and epidemiological surveys are capable of generating enormous amounts of information that contribute to neuroscience.

- It is important in designing such surveys that they are guided by current ideas of aetiology and treatment, so that these can be tested.
- We have to remember that samples and controls should be representative. We have to keep in mind always to ask how representative our samples are.
- We should consider inserting neurocognitive elements, for instance neurocognitive tests, in population surveys. It would be particularly useful to include neurocognitive tests in longitudinal surveys, where they can be very useful in term of prediction.
- We should always consider collecting genetic material in surveys. While this should be planned in relation to specific intentions, it also has value in terms of as-yet-unknown future developments.
- It is useful to collect data that serves the study of continua that may underlie categorically defined psychiatric disorders (this also means we can examine genetic material in terms of quantitative trait loci).

Véronique Deroche-Gamonet
Neurocentre Magendie, Bordeaux, France

TITLE: *Questions about addictions that can or should be addressed by experimental research*
Experimental research on drug addiction: a turning point

Drug use can be part of the recreational activities of a normal subject. When drug use becomes the main activity at the expense of the others, one can suspect the development of an addiction. Central to the physiopathology of drug addiction is the question of the causes of transition from occasional use to addiction.

Research on drug addiction started 50 years ago and, based on this, therapies have been developed that help people deal with their disease. Most of these therapies, however, are only substitutive. For cocaine addiction in particular, there is even no substitutive treatment, while cocaine use tripled in Europe between 1995 and 2005 becoming the most used drug after cannabis. This apparent failure could rely on inappropriate strategies of experimental research. Over the last 10 years, indeed, opinions have evolved on What should you be studied, How it should be studied, and The specific questions that should be answered, to investigate the causes of transition to addiction.

What should be studied?

Addiction was initially seen as a result of changes in drug effects and nowadays it is being seen as a result of changes in drug use. Absence of control over drug use and drug seeking is the phenotype that should be studied and not only drug use or even excessive drug use.

How it should be studied?

Previously, two main theories were opposed. The drug centered theory is grounded on the clinical observation that transition to addiction only occurs after prolonged drug use. This theory postulates that prolonged drug use produces biological alterations that are phenotypically translated into tolerance, sensitization, withdrawal and conditioning, i.e. psychopharmacological adaptations that would be responsible for addiction. The individual centered theory is grounded on the clinical observation that not all drug users develop an addiction. This theory postulates that the biological characteristics of the drug user constitute the critical factor. Some individuals are resistant to addiction while others, due to a pathological response to drugs, are vulnerable.

Recent data allowed us to offer a unified theory to addiction. Transition to addiction would not only result from repeated drug use or from a particular vulnerable phenotype, but from the interaction of both. Only vulnerable subjects, due to a particular biological phenotype, would develop an addiction but only after repeated drug use. Drug addiction should therefore be studied by taking drug - individual interactions into account.

The specific questions that should be answered?

Recent data revealed that addiction is in fact a two-step process: The first step is the one that brings some occasional users to develop and maintain a sustained drug intake over a prolonged period of time. This drug intake-prone phenotype sets the conditions for the second step to occur, i.e. it sets the conditions for some of the regular users, the addiction-prone ones, to be revealed and develop addiction. In this context, for each step, two issues are of interest: phenotypes predicting, and biological factors determining vulnerability to shift to the next step.

The first specific question to answer then is the one of factors that predict and determine the vulnerability to shift from occasional use to regular use. Concerning this first phase, some answers have already been obtained. Phenotypes associated with the vulnerability to develop a sustained drug use such as stress sensitivity, anxiety or impulsivity have been identified. Biological mechanisms, in particular for those underlying stress-related vulnerability, have been characterized and a pathophysiological pathway has been identified that involves interactions between glucocorticoid hormones and the meso-accumbens dopaminergic transmission.

The second specific question to answer is the one of factors that predict and determine the transition from regular use to addiction. This question, which is also the true central question to the physiopathology of addiction, needs some prerequisites. Indeed, are we simply able to study the shift from regular use to addiction? Do we have a model to study the loss of control over drug use and drug seeking? Spontaneous intake of drugs is a behaviour largely conserved along phylogeny and we measure it in experimental

conditions for more than 40 years using intravenous self-administration in animals. However, drug use is not addiction. Over the last 10 years, three to four research teams investigated whether addiction could be observed in rodents. Our team was one of those. We developed the first multisymptomatic model of addiction. We were able to identify rats showing difficulties to limit drug seeking, showing a high motivation for the drug and maintaining drug use despite negative consequences. Importantly, this addiction-like behaviour fulfils the characteristics of human addiction. i.e. it develops progressively, it is associated with a high vulnerability to relapse and is observed only in 15-20% of users.

Models of addiction are new and research on the psychobiological basis of the shift from regular use to addiction is really starting now. Some insights have been found on factors predicting transition from regular use to addiction. In naive animals, a form of impulsivity predicts the development of addiction. Early binge cocaine taking also predict vulnerability to cocaine addiction. After 20 to 30 days of cocaine use, addiction is not developed yet but future addicts already show a particular pattern of use. They take the amount of drug than the others but they take it faster. Concerning the biological basis of transition to addiction, no data have been published so far, but the first available data will revolutionize our common perception. Indeed, addiction could be less the result of drug-induced alterations (as thought during the last 40 years) than the inability to counteract these drug-induced alterations. Indeed, non-addict users would be able to counteract early drug-induced neurobiological changes while addicts would not. Measuring gene expression of 14000 genes using Affymetrix gene chips, we showed that specific cocaine-induced alterations in gene expression were higher in users than in addicts. Measuring NMDA-dependent long-term depression (LTD) in the nucleus accumbens, a form of synaptic plasticity that is lost after 18 days of cocaine use, we showed that users recover it after 80 days of cocaine use, while addicts do not.

In conclusion, research on the physiopathology of drug addiction is at a turning point. First, pertinent animal models of addiction are now available that will allow identifying factors underlying transition to addiction. Second, we still know little about the psychobiology of transition to addiction, but the first available data will revolutionize our common perception. Addiction could be less the result of drug-induced alterations than the inability to counteract these drug-induced alterations. Now that we know what should be studied, how it should be studied, the specific questions that should be answered and that it seems that we are able to do so, we should be able to find the causes of transition to addiction with adequate resources.

Elizabeth Kuipers

King's College London, United Kingdom

TITLE: *Evidence based psychological interventions for psychosis: individual cognitive behavioural therapy and family intervention*

The diagnosis of psychosis is associated with poverty and reduced work opportunities. Stigma and social exclusion are common. Most people remain unemployed, many have never worked and there is also a higher rate of physical ill health and increased mortality. If people have schizophrenia, they are called elderly at 50 years old because they are more likely to die 15 years earlier than the rest of the population. 30% will attempt suicide and 5% will do so. Around 5% of homicides in UK are committed by people with this diagnosis. This is a disease that has high societal costs of care and the lifetime risk is 1 in 100 and 2 in 100 if bipolar disorder is included. The first line of treatment is medication with new antipsychotic drugs but up to 40% of people have limited response to these.
Since Jasper (1912), delusions and hallucinations of psychosis are seen as different from other disorders such as neuroses. They are seen as "un understandable" disease process which have been associated with cognitive deficits (although 25% do not show these). (In this presentation, 'cognitive' refers to thinking, not to cognitive deficits such as poor attention or memory).. Diagnosis in schizophrenia depends on the presence of positive symptoms, not just deficits. The emotional processes associated with these diagnoses have not been generally considered, and this is part of what the new psychological models discuss.

New cognitive models of psychosis were proposed in the late 1980's:
- CBT (Cognitive Behavioural Therapy) for psychosis developed
- Empirical studies and early RCTs (Randomised Control Trials)

The cognitive models of psychosis posit that vulnerable individuals make appraisals of oneself and the social world that lead to recurrence and persistence of positive symptoms of psychosis. More recently, models specified that cognitive, social and emotional processes might contribute to these appraisals, a key point of the process. Basically, a cognitive model of the positive symptoms of psychosis stipulates that bio-psycho-social vulnerability is triggered by stressful events, which can then cause unusual experiences. These can be misinterpreted, and appraised as worrying, and it is this that leads to symptoms. The particular appraisal of what is going on contributes both to the appearance and persistence of positive symptoms.

We focused our research particularly on how does such psychiatric process work and what we might do about it.
Our recent research evidence shows that:
- The symptoms and phenomena associated with psychosis are a continuum and exist in the whole population as well.
- The importance of appraisals and reasoning biases
- Social adversity such as isolation and social exclusion, trauma, adverse environments, like high expressed emotion (EE) in carers and life events, is an important factor
- Negative beliefs about yourself, negative emotions and anxiety are key points too

The Continuum Hypothesis is supported by large-scale epidemiological studies (Nemesis and Bristish National Household Survey). Psychotic thoughts and experiences are observed in the general population as well as clinical populations. They are associated with the same risk factors as a clinical disorder (substance dependence, gender, victimisation, stressful events, urbanicity, neurotic symptoms and IQ.) We even found more recently that up to 40% of the population have paranoid ideas associated with anomalies, anxiety, worry, perceptual and cognitive inflexibility. The presence of symptoms alone is then not enough to diagnose somebody. It is the other things going on that will be determinant.

There is also now the question about the role of emotion. It was never thought that emotion could be involved because the question was never asked. But there is evidence for a wide overlap between psychosis and emotional problems. 40% of patients have clinical levels of depression and low self esteem, 30% fit the criteria for previous trauma, 20% have panic disorder, 25% have evidence of obsessive compulsive disorder, 50% have a co morbid personality disorder and high bed use. So, now we know that emotion and emotional deregulation are keys in the development of psychosis. We know that positive symptoms are associated with schemas, extreme negative evaluation of self and others, but also criticism in carers. It was also shown that existing depression contributes to later development of delusions in people with pre-existing anomalies of experience.
The role of appraisal is true in psychosis and as it is in many physical diseases such as heart attack. The illness appraisal is actually a key determinant; the way people understand what is happening to them when they get a physical illness determines how they take treatment and change the way they deal with it. We have

also shown illness appraisals can be found in psychosis. Similarly, it has been showed that safety behaviours such as avoidance (found in neurotic disorders) exist in psychosis, and help to maintain delusional ideas.

Regarding the reasoning biases, it has been demonstrated that in the general population many people hold ideas with conviction that are not supported by evidence (ghosts, telepathy, aliens, astrology). Once a view is held with conviction, people are less likely to consider alternatives impartially. Attributional biases also exist with persecutory delusions. Additionally, people with psychosis have a tendency to jump to conclusions (JTC), and use less evidence to make a decision. In a study involving 100 patients, it was found that 50% of sample had JTC and that JTC contributes to delusional conviction. Whereas affective pathways link to delusional distress. JTC is present in people with delusion and in patients in recovery from delusions. JTC is related to belief inflexibility, and an inability to generate alternatives. In conclusion, JTC is a phenotype of vulnerability factor in psychosis. In a cross sectional study using structural equation modelling and latent variables, across a number of samples (173 patients with depression, positive psychotic symptoms or related diagnosis) it was demonstrated that both cognitive and emotion related processes are involved in paranoid delusions. There are of course other cognitive processes that contribute to psychosis. People with psychosis may have self-monitoring problems that may lead to hallucinations or delusions of control. Disruption to "sense of self" and poor use of contextual information disrupts ability to process ongoing experiences. Kapur has discussed how stress can increase dopamine levels and "salience" of stimuli. And, it is well established that cognitive difficulties in attention and working memory happens for about 50% of patients even at the first episode.

There is a lot of research going on into the effects of stressful environments in psychosis. For instance, there is a high risk of schizophrenia associated with living in an urban area. It was found that social isolation is associated with reduced insight and cannabis use can increase the risk for schizophrenia by 3 fold. Social adversity increases the risk of psychosis for ethnic minority populations. We have known for a long time that negative or intrusive family settings relate to later relapse in psychosis. High levels of expressed emotion in carers, particularly criticism, predicted anxiety in patients with a recent relapse of psychosis. Patient perceived criticism relates to expressed emotion in carers (important role of appraisal of difficult social interaction). All these data confirm our view that family intervention (FI) needs to work through an affective route, by calming down aversive environments. High rates of trauma and social adversity also occur before onset of psychosis, particularly associated with sexual abuse and bullying at school. It has been demonstrated that there is a link between intrusiveness of life events, persecutory delusion and hallucinations in patients with first episode.

Thus, there is a whole range of factors that seem to be impacting on people which are then, we think, both making symptoms develop and maintain their persistence.

As a conclusion, in psychosis we have some evidence for our model: non clinical groups confirm that there is a continuum of experiences, that there is a central role of appraisal and reasoning biases, that emotional pathways such as anxiety and depression relate to particular symptoms and that there is an influence of adversity in clinical groups.

Various treatments have been developed in term of talking to patients in a different way about their symptoms, about their stress, about what they understand about their problems and there are moderate effects suggesting that these methods are helpful.

In summary,

- using Cognitive Behavioural Therapy (CBT) there is some evidence that depression and persistent symptoms can be improved, particularly if there is social support
- Family intervention (FI) reduces relapse.
- CBT and FI are both recommended by the original (2002) and updated (2009) NICE Guidelines for schizophrenia in UK

My suggestion for the future is that theoretical ideas supported by experimental evidence can inform the development of CBT and FI psychosis. The answer is not just about giving treatment drugs or performing randomized trial because we do not necessarily know what is working for whom nor what dimensions of symptoms should be targeted. Understanding mediators of change to develop specific and more targeted treatment is likely to be most productive.

Annex I, List of Experts

3rd Workshop - May 4-5th, 2009- Paris
ERA-Net NEURON
Experts

1. **Prof. Dr. Celso Arango Lopez, Spain**
   carango@hggm.es

2. **Prof. Dr. Paul Bebbington, United Kingdom**
   rejupbe@ucl.ac.uk

3. **Prof. Dr. Thomas Bourgeron, France**
   thomasb@pasteur.fr

4. **Prof. Dr. Véronique Deroche-Gamonet , France**
   veronique.deroche@inserm.fr

5. **Prof. Dr. Guy Goodwin, Unted Kingdom**
   Guy.Goodwin@psych.ox.ac.uk

6. **Prof. Dr. Elizabeth Kuipers, United Kingdom**
   Elizabeth.Kuipers@iop.kcl.ac.uk

7. **Prof. Dr. Andreas Meyer Lindenberg, Germany**
   a.meyer-lindenberg@zi-mannheim.de

8. **Prof. Dr. Eduard Vieta, Spain**
   EVIETA@clinic.ub.es

Annex II, Scientific Advisory Board

NEURON Scientific Advisory Board

1. **Prof. Luca Battistini,** Italy
   l.battistini@hsantalucia.it

2. **Prof. Rafael Maldonado,** Spain
   rafael.maldonado@upf.edu

3. **Prof. Shlomo Rotshenker,** Israel
   rotsh@md.huji.ac.il

4. **Prof. Dr. Ana-Maria Zagrean,** Romania
   azagrean@gmail.com

Annex III, List of participants

NEURON Meeting Participants

1. **Julio Barbas**, Ministry of Education and Science (MEC), Spain
   julio.barbas@mec.es

2. **Giorgio Stefano Battaglia**, Neurological Institute Carlo Besta, Italy
   battaglia@istituto-besta.it

3. **Brita Beije**, Swedish Research Council, Sweden
   brita.beije@vr.se

4. **Howard Bergman**, Fonds de la recherche en santé du Québec, Quebec
   hbergman@frsq.gouv.qc.ca

5. **Bernard Bioulac**, Centre National de la Recherche Scientifique, France
   bernard.bioulac@cnrs-dir.fr

6. **Véronique Briquet-Laugier**, Agence Nationale de la Recherche, France
   Veronique.BRIQUET-LAUGIER@agencerecherche.fr

7. **Alexis Brice**, INSERM, France
   brice@upmc.fr

8. **Rafael De Andrés-Medina**, Fund for Health Research, Instituto de Salud Carlos III
   rdam@isciii.es

9. **Marlies Dorlöchter**, DLR Projektträger des BMBF, Germany
   marlies.dorloechter@dlr.de

10. **Dominique Douguet,** Ministère de la santé et des sports, France
    Dominique.DOUGUET@sante.gouv.fr

11. **Carlo Duprel,** Fonds National de la Recherche, Luxembourg
    carlo.duprel@fnr.lu

12. **Astrid Eberhart,** Canadian Institutes of Health Research, Canada
    Astrid.Eberhart@cihr-irsc.gc.ca

13. **Iris Fortmann,** FWF - der Wissenschaftsfonds, Austria
    Iris.Fortmann@fwf.ac.at

14. **Rainer Girgenrath**, DLR Projektträger des BMBF, Germany
    rainer.girgenrath@dlr.de

15. **Marianne Kordel-Bödigheimer**, DLR Projektträger des BMBF, Germany
    marianne.kordel@dlr.de

16. **Joanna Latimer**, Medical Research Council, United Kingdom
    joanna.latimer@headoffice.mrc.ac.uk

17. **Benny Leshem,** Israeli Ministry of Health, Israel
    benny.leshem@moh.health.gov.il

18. **Michèle Longuet,** Ministère de l'Enseignement Supérieur et de la Recherche, France
michele.longuet@recherche.gouv.fr

19. **Etienne Magnien,** European Commission, Bruxelles
Etienne.Magnien@ec.europa.eu

20. **Herbert Mayer**, FWF - der Wissenschaftsfonds, Austria
herbert.mayer@fwf.ac.at

21. **Delphine Prou**, INSERM CNRS, France
Delphine.prou@cnrs-dir.fr

22. **Rémi Quirion**, Douglas Mental Health University Institute, Canada
remi.quirion@douglas.mcgill.ca

23. **Erkki Raulo**, University of Helsinki, Finland
erkki.raulo@helsinki.fi

24. **Anne Laure Rey**, INSERM CNRS, France
anne-laure.rey@cnrs-dir.fr

25. **Jukka Reivinen**, Academy of Finland , Finland
jukka.reivinen@aka.fi

26. **Mika Tirronen**, Academy of Finland , Finland
mika.tirronen@aka.fi

27. **Birgit Wetterauer**, Bundesministerium für Bildung und Forschung, BMBF, Germany
Birgit.Wetterauer@bmbf.bund.de