from neurobiology to nosology
desde la neurobiología a la nosología
of mental disorders
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FROM NEUROBIOLOGY TO NOSOLOGY OF MENTAL DISORDERS

Pages

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The classification of mental disorders: trends and challenges

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The World Health Organization (WHO) and the American Psychiatric Association (APA) have begun their work on the revision of their classifications of mental disorders. The WHO classification is part of the classification of all diseases (the ICD) that will be revised for the eleventh time and submitted to the nearly 200 governments who are members of the WHO for approval. The latter (the DSM) is a classification developed by a national professional organization (the APA) that will be approved by the governing bodies of the association. The work on the revisions should be completed by 2012 so that the revisions can be released for use in 2013.

It is expected that the government of the United States of America will do the necessary to ensure that the diagnostic categories contained in the DSM are coupled with the numbers of the categories of the ICD and that the categories of the DSM can be translated into the ICD: this however is a process that takes a long time and will not prevent the APA from publishing the 5th Revision of its classification and introducing it into research, practice and education. Even when that is done certain differences between the two classifications are likely to remain in existence. This was the case with the 9th Revision of the ICD (ICD-9) and the third revision of the Diagnostic and Statistical Manual of the APA (DSM-3) and to a much lesser extent with the ICD10 and the DSM 4. The differences were not in the names of the disorders that are grouped into the categories of the classifications – they concern some of the criteria used to define conditions and in the indications about (and diagnostic terms) that should not be included in a category (the exclusion terms). Some of the differences are banal, others more important: both occur when the evidence is insufficient and the criteria are based on the consensus among the makers of the classifications. Thus, for example the duration of an illness before the diagnosis of schizophrenia can be made is 3 months in the ICD and 6 months in the DSM: there is however no evidence that would contradict a decision to agree that the syndrome of schizophrenia should last 4.5 months before the diagnosis is made.

The makers of the classification will face a variety of dilemmas and problems on their way to the new revisions of the classification. The first of these is that none of the conditions included in the classification of mental disorders satisfies the nosological criteria for being considered as a disease (a clear definition of causes, pathogenesis, clinical picture, reaction to treatment and outcome) The ICD has decided to label the syndromes that are included in the chapter dealing with mental health problems "disorders", a vague term that could include diseases as well as less well defined conditions. The definition of disorders relies on symptoms although the DSM classification until now required that a syndrome be accompanied by disability and by distress in order to be considered as being above the threshold for the establishment of a diagnosis to be counted in for epidemiological investigations or allow the reimbursement of the cost of a therapeutic intervention.

The ICD classification explicitly recommends that a diagnosis (and thus assignment into an ICD category) be based on symptoms, not on the presence of distress or on a deficiency of function; there are of course exceptions to this rule – thus, the diagnosis of dementia has to be made on the basis of the presence of cognitive symptoms and a failure of performance in personal roles, such as self care.

Reliance on symptoms, however does not guarantee that the diagnoses describe nosological entities. The same clinical picture can be the consequence of different pathological processes and vice versa – the same pathological process might result in different symptoms. In practice, psychiatrists usually make their decisions about initiating treatment of severity of their patients' distress rather than on the full satisfaction of all criteria for a diagnosis. The treatment of conditions which cause significant distress but do not satisfy all criteria of the classification ("sub threshold"

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disorders) causes a variety of ethical and practical problems for which there is no easy solution

A similar problem arises in relation to the use of psychotropic medications. At present medications are approved for use in the treatment of particular disorders rather than for their action on a particular symptom (e.g. delusional thinking). In practice, psychiatrists are usually focusing on the treatment of symptoms which may lead them to "off-label" use of psychotropic drugs. How to resolve this issue is not yet clear.

There are also numerous other challenges that the makers of the classifications will have to face. They will have to decide who will be the main users of the classification: if the classification is too complex it is unlikely that it will be properly used. The World Health Organization attempted to deal with this problem by producing three parallel versions of the classification of mental disorders contained in the 10th revision of the ICD. The first version was intended for use in research; it contained a precise definition of the disorders that were to be grouped in the same category and thus allowed the composition of symptomatologically homogenous groups of patients for research. A second version was intended for use by the practicing psychiatrists. The criteria for assignment of a diagnosis to a category were less rigid: thus in defining schizophrenia the guidelines stated that the disorder "usually starts before the age of 45..." (the version for research did not allow the diagnosis of schizophrenia in an individual whose disorder started after the age of 45 years) A third version of the classification was intended for use by the general practitioner and medical specialists who were not exposed to postgraduate training in psychiatry. This version had only 22 categories and each of these was accompanied by a description of the typical symptoms for the condition as well as with instruction about action that the doctor should take. The choice of the 22 categories relied on the frequency of the diagnosis seen in non-psychiatric practice and on the need to apply a particular treatment. There are obviously advantages and disadvantages in producing several versions of the classification: thus, for example, different versions of the classification can never be fully translatable into each other and their usefulness may remain limited to interventions that are relevant to the group that uses that version of the classification; on the other hand, however the acceptability of the classification and the probability of its correct use is greatly enhanced. The makers of the classification will have to decide which of the two paths – one classification for all users or different versions of the classification for different users - to follow and the decision which they will reach will have to be based on practical, political and economical considerations rather than on science alone.

The makers of the classification will also have to decide how they will combine an assessment of the impairment and disability with syndromes; how to deal with dimensions of the mental illness that intersect the categories of the classification; how to make it possible to continually update the classification (without major revisions of the classification as a whole) when new evidence becomes available; and how to create an information flow that will ensure that the classification is introduced into research, education and service without delays and used as a common language in the health system and in scientific endeavours.

Numerous other challenges and dilemmas that will have to be faced could be listed: the above examples are meant to illustrate them. If they are to be resolved in a useful way they will have to be debated by the many stakeholders who will experience the effects of the new classification. The mechanisms that have to be put in place to arrive at a consensus about questions that cannot be answered by scientific evidence are complex and it is to be hoped that they can be constructed in time and constructed in a manner that will allow the production of a revision of the classification that will be based on evidence and experience, that will fit the tasks of service and research, serve usefully in the education of health personnel and be communicable to all the partners who have to be involved in resolving the mental health problems in a society.

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The Limits of Depression: Normal Sadness or Mental Disorder?

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The response to what the limits of depression are, and the question on normal and pathological sadness have to be answered at two levels: 1) what concerns a particular person visiting a psychiatrists and 2) what are the public health consequences of setting the limits.

It is necessary to raise the problem of particular persons because of the questions of deciding when to treat or not to treat, of avoiding the risks of medicalizing sufferings, of dealing with health as if it were a consumer's good and of preventing cosmetic psychopharmacology. Moreover, an unsuitable treatment may interfere with normal psychological processes, leading to severe or chronic pathologies in the future due to badly elaborate losses. The possibility to create dependency to drugs, to the health system or even to the own physician has also to be taken into account.

At the public health level, the possible artifact of the high incidence and prevalence figures of depression has to be taken into account. There great and unexpalines differences throughout the world and there is also sensation of failure of psychiatry from a public health point of view since the incidence and prevalence of mental disorders rises steadily. So, the prevalence of mayor depressive episodes oscillates between more than 3,500/100,000 inhabitants and year for the women of WHO region of the Americas, to less than 1,500 for the men of the Western Pacific region.[1] In primary health care the differences are even greater: around 30% of consultations in Santiago de Chile on the one hand and less than 3% in Nagasaki.[2]

It may be possible that this has to do with the fact that most depressive disorders are not seen by a specialist but also because of an abuse of the diagnosis, due to the importance of the market for psychiatric drugs, since these are used for not therapeutically clear indications.[3]

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On the other hand it has to be taken into account that when dealing with largely prevalent disorders, the important thing is to find out why there are individuals that do not suffer them instead of investigating its causes.

Present classification systems in psychiatry can give way to confusion if it is not taken into account that a classification is not a treaty of psychopathology, able to define what illnesses are, and when diagnostic criteria are confused with symptoms and symptoms with illnesses. For instance, it is possible that two patients that show the same symptoms (e.g. depressive mood during most of the day and most of days; marked reduction of their ability to show interest or enjoy of all or almost all activities most time of the day and most of days; significant weight loss; insomnia and psychomotor inhibition) get the diagnosis of mayor depressive episode or of bereavement depending on the albescence or not the loss of a beloved person.

Main diagnostic criteria are depressive mood and anhedonia (marked reduction of one's ability to show interest or enjoy of all or almost all activities). Therefore, the challenges are to define what mood is, to define what a depressive mood is, to define what anhedonia is, to establish the relationship between depressive mood and anhedonia and of both of them with the rest of the diagnostic criteria.

The proposal that is outlined in this text aims to overcome the dichotomy normal-abnormal and raise the question if mood has any adaptative value, and if this includes "negative" states of the mood like depressive mood. The challenge is even more important in the less severe cases in which the difference between normal sadness and depression may not be clear, not as in those where sadness has become malicious, very intense and is out of control.

It is a question of following, for example, the model of the sickle cell anemia. Is it "normal"?. The response is that it depends on having an adaptative value in countries with high incidence of malaria. We can also ask ourselves if

bipolarity of some creative persons is a gift or a price they have to pay or for what are pain and anxiety good for.

Research difficulties in this field come from the fact that feelings are everything what in psychic life is not prone to be objectified, they are subjective and therefore difficult, may be impossible, to be investigated. They are object to literature, alien to science.

The philosopher Max Scheler defined feelings as states of the I. They are the answer to questions like: How are you? He applied Husserl's phenomenological method to the study of sentimental life coming to the conclusion that they have a cognitive function. So as knowledge allows accessing the world of essences, emotional feeling is the door to achieve immediate access to the world of values.

Experience and emotional behavior are so varied and so omnipresent in human beings and in animals that they must play an important role for the survival of the individual. The philosopher Sartre[4] considers that emotion is a replacement behavior (according to the *Ersatzpsychologie*) that appears when a objectively guided behavior is not possible. Given the impossibility to face a too rational World, the affected person establishes a new relationship with the World in which an aparently non adaptative reaction makes sense. Affective reactions have a significance that is not rational, it is symbolic and magical.

The concept of depressive mood characterized by the different quality of sadness appears with Kraepelin and disappears with DSM-III-r. The different quality has been considered as a lack of subjective response (blunting, affect anesthesia), as behavioral (inhibition), as an alteration of vitality (vital sadness, K. Schneider[5]) associated to the presence of somatic symptoms and to a lack of motivation.

Ramos Brieva et al.[6] In a series of studies carried out during more than twenty years, came to define pathological sadness as being weary, internal, uncontrolled, permanent, lasting, durable, desperate, unexplainable, coward and strange. These traits can be grouped into two factors: the different quality (strange, coward, unexplainable, desperate, uncontrollable and durable) and the link to body experience and feelings (internal, permanent, weary and lasting).

Sentimental life is multifaceted and five aspects have to be differentiated: 1) affective experience; 2) cause; 3) vegetative correlate; 4) verbal and physical expression and 5) request of help. Each one of them has its adaptative value.

Sadness has positive functions: it increases the ability to confront adaptative challenges when the effort to achieve an important goal may give way to dangers, losses, harms or be a useless effort,[7] it communicates a need for help, it shows and makes the person cease in front of a hierarchical conflict by inhibiting aggression in front of rivals and superiors, it promotes the removal of compromises for unreachable goals, modulates interventions and lead to recover lost bonds.

Stress factors are important in initial episodes in which the persons' ability to adapt is accumulated and exceeded unless other protective factors get involved, among them resilience.

Neurobiology of depression resembles hibernation, which is a state of drowsiness in which determined physiological and biochemical activities are suppressed and energetic consumption is scrolled down to a minimum, which is a strategy to survive under extreme environmental conditions.

The expressive demonstration of emotions and the articulation of the need for help attract empathy and needed support in a situation of stress.

Summarizing, to take into account the possible adaptative value of feelings of depression and of sadness may help to take into consideration states of the mood as being "normal" or as being pathological and help to take the appropriate clinical decisions.

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Temperament Research: The Emerging Clinical and Cultural Relevance of an Ancient Concept

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We examine terminological aspects of the concepts of temperament, personality, and personality disorders, new instruments for measuring temperament, as well as prospective studies on the role of temperament in suicidality and artistic creativity. In doing so, we refer to our own research in developing a new temperament scale (TEMPS), which addresses ethologically-based positive traits of temperament relatively overlooked by other instruments. We consider therapeutic—both pharmacologic and social–implications, as well as recent genetic vistas.

The ancient venerable concept of temperament has made a recent come-back in clinical psychiatry and psychology research.[1-5] This brief overview highlights major current developments which we believe represent a veritable renaissance in the field of temperament.[6]

Since Darwin's pioneering studies on emotional expression in animals,[7] ethologists and psychologists have studied emotional behavior across species, particularly mammals such as dogs[8] and among infrahuman primates.[9] The experimental paradigms have involved separation studies from mothers and peers, as well as observational studies on "dominant" and "submissive" behavior in rodents.[10] It has also been observed that individual animals may display tendencies or traits to exhibit certain emotional behaviors more often and more consistently.[11-15] The term "temperament" is used for such traits, and has been used in breeding "desirable" characteristics[16] in such species as horses[17], among others. These developments underscore the hereditary underpinnings of temperament.[18,19]

In humans temperament has a distinguished legacy going back to Hippocratic times, and the formulation of the four temperaments –sanguine, melancholic, choleric and phlegmatic-- by the Greco-Roman physician Galen. In modern times, Kretschmer's work in its descriptive and conceptual rigor is the classic reference in this field.[20]

TERMINOLOGY, CONCEPTS AND MEASUREMENT

Whereas "temperament" refers to largely the innate component of individuality, "character" has come to connote the developmental anlagé of the individual, presumably with stronger psychological determinants. "Personality" is the interactive sum of both, and "personality disorder" refers to the abnormal facets of personality. Table 1 highlights the major conceptual and operational attributes of temperament.[1, 6]

A brief historical narrative will be useful to orient the reader to the major developments in this field. Kretschmer[20] distinguished cyclothymic and schizothymic tendencies as the foundations from which the endogenous psychoses, manic-depressive and schizophrenic, arose. In his description of "psychopathic personalities," Kurt Schneider[21] took a fundamentally different position; in his view such abnormal personalities as the "depressive," "hyperthymic" or "labile" were to be considered sui generis, i.e. not necessarily precursors of depressive, manic, or hysterical disorders. While he appeared reluctant to commit himself to an etiological causative paradigm, he provided a thorough characterization of at least a dozen abnormal personality prototypes that have largely stood the test of time. Eysenck's work,[22] building on Jung's imaginative descriptions of psychological types,[23] evolved into one of the dominant theoretical yet pragmatic psychological testing instruments on neuroticism and extraversion. Clonlinger,[5] whose work is in part rooted in animal research, despite his somewhat complex theoretical paradigm, succeeded in popularizing harm-avoidant and novelty- seeking patterns. The five-factor model of Costa and McCrae[24] is a succinct, though oversimplified description of the essentials of human personality that, nonetheless, can in practice be administered in a self-rating format.

While the foregoing personality constructs derive from science-based evidence, the Axis II (personality disorder)

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Table 1 Definitional Characteristics of Temperament

- Hard-wired: The biological or constitutional core of the personality
- Reactivity, variability, and intensity of emotional dispositions
- Can be associated with desirable outcomes such as adaptation and achievement
- Or it could be the precursor of a state mental disorder
- Distinguished from personality disorder, which refer to rigidly stereotyped interpersonal patterns with relatively little adaptive resilience

Table 2 Self-Rated Cyclothymic Temperament

- I get sudden shifts in mood and energy
- My mood often changes for no reason
- I constantly switch between being lively and sluggish
- I feel all emotions intensely
- I am the kind of person who can be sad and happy at the same time
- I often have a strong urge to do outrageous things
- I am the kind of person who falls in and out of love easily

chapter of the American Psychiatric Association's Diagnostic Manual, even in its latest published edition of DSM-IV-TR[25] is largely based on psychodynamic and clinical considerations. Exceptions include the schizotypal (based on Meehl's[26] work and the schizophrenia spectrum[27]) and the avoidant (based in part on Kretschmer's[20] and Millon's[28] sensitive type, as well as biological[29] and behavioral[30] paradigms of anxious-phobic behavior).

Whether DSM-V (in progress) will succeed in providing a synthesis of the foregoing rich classic and modern formulations of temperament, personality, and personality disorders remains to be seen.

TEMPERAMENT EVALUATION OF MEMPHIS, PISA, PARIS, AND SAN DIEGO (TEMPS)

The authors' research, based primarily on Kraepelin's,[31] Ketschmer's,[20] and Kurt Schneider's[21] conceptual frame, initially began as a frustration with the DSM concept of personality disorders which emphasized what is pathological about an individual, i.e. "sadistic," "anti-social," "paranoid," "borderline," and "dependent." Our dissatisfaction led to an exploration of traits which define "positive" attributes, such as sensitivity to the suffering of others, altruism, leadership, and creativity to enrich the fabric of personality.[32] This was first published as a semi-structural instrument that could be administered in an interview format (TEMPS-I);[33] it subsumed the classic three temperaments of sanguine (hyperthymic), melancholic (depressive) and choleric (irritable) types to which was added the labile (Cyclothymic).

With the addition of yet another temperament, the anxious type, we developed an auto-questionnaire version (TEMPS-A) with 110 items.[34] In the current version, TEMPS-A consists of the depressive, cyclothymic, irritable, hyperthymic, and anxious temperaments in self-rated "yes/no" format. It has been translated and/or validated in at least 25 languages, representing distinct cultures, e.g. USA (Memphis and San Diego), France (Paris, Bordeaux, Marseille, and Besancon), Italy (Pisa, Rome, and Cagliari), Spain (Barcelona), Argentina (Buenos Aires), Portugal (Lisbon), Brazil (Sao Paulo), Hungary (Budapest), Denmark (Copenhagen), Lebanon (Beirut), Egypt (Cairo), Tunis, China (Hong Kong), Japan (Tokyo), South Korea (Seoul), Turkey (Izmir, Istanbul), Armenia (Yerevan), Russia (Moscow), and others.

There are at least two prospective psychometric validation studies, one with the TEMPS-I,[35] and the other with TEMPS-A.[34] In yet another prospective validation from a clinical perspective is the French study of cyclothymic adolescents:[35] it showed such a high outcome of suicide attempts that the protocol had to be modified to attend to this clinical-prognostic issue. This finding is in line with other research[37, 38] implicating cyclothymic traits –predisposing to increased cycling-- as a major substrate of suicidality.

As reviewed elsewhere in greater depth,[39] in most cultures women are over-represented among the cyclothymic; an exception is Hungary, where men are over-represented among the cyclothymic. This raises the provocative hypothesis that the historically higher rates of suicide in Hungary might partially reside in this epidemiologic "peculiarity." It is beyond the scope of this brief review to do justice to the complex

Table 3 | **Psychosocial Interventions for Individuals with Cyclothymic Temperament**

- Professions with liberal working hours
- Reside in artists' and intellectuals' quarters
- Availability of clinician at times of crisis and scandal
- Not pre-judge them by mundane norms of society
- Limit setting on outrageous behavior
- Marriage to rich much-older spouse
- Counseling for significant others

subject of suicide, a behavior with multi-faceted etiology. Further exploration of this topic can be found in yet another collaborative effort with Professor Rihmer.[40]

All in all, three research papers[37, 41, 42] deriving from the longitudinal prospective follow-up study of the National Institute of Mental Health (Bethesda, USA) have shown that mood lability, and associated energy-activity and, to some extent, daydreaming represent the predictive triad of the recurrence of mood episodes switching from unipolar to bipolar II, and suicidal behavior including completed suicides. Thus, unique temperamental traits along cyclothymic lines emerge as the most powerful traits that shape the course and prognosis of affective disorders. Clinicians should be better acquainted with the cyclothymic temperament (see table II), as well as psychosocial preventive approaches in mitigating its impact (see table III).

FAMILIAL- GENETIC STUDIES

Given that the patterns of cycles of mania-depression-interval versus depression-mania-interval are governed by genetic factors,[43] it is relevant that Lithium Carbonate is more efficacious in the first pattern,[44] suggesting that pharmacogenetic factors govern the prognosis of manic-depressive illness. This is hardly surprising. What is surprising is the fact that, of the multitude of courses of bipolar disorder and its subtypes, no reference in the DSM and ICD manuals to the pioneering research by Koukopoulos and collaborators at the Lucio Bini Center[45] about the profound therapeutic implications of the sequence of depression and mania, and that by Grof et al. [46] on course and response to lithium.

Without going deeply into the intricacies of pharmacogenetics, it is relevant to point out that when clinicians treat trait psychiatric syndromes such as dysthymia, medications can exert far reaching influences on social functioning. For instance, in a large clinical study conducted in private practice over a two decade period,[47] we found that fluoxetine was associated with an overall robust and sustained response in 76% (in addition to preventing subsequent major depressive episodes and suicidality). The positive impact of fluoxetine was most observed among women, many of whom were able to walk out of dependent-abusive relationships for the first time in their lives; even hyperthymic switches occurred, though in a minority of 12%, mostly among those with bipolar family history. The most protypic response among the dysthymic responders consisted of coping with "daily hassles" without being overwhelmed. Agitation occurred in 11% and was associated with failure to respond to fluoxetine. In another long-term study [48] of case series of women referred to our mood clinic with a diagnosis of "borderline personality," after treatment with lamotrigine, many patients achieved complete sustained resolution of their labile emotionality, impulsive sexual and suicidal behavior, as well as related interpersonal and maladaptive social behavior. Such clinical findings suggest that it is extremely important to conduct long-term studies with existing psychopharmacological agents in order to fully appreciate their benefits and short-comings. Pharmacogenetics represents a promising future application of research in the field of temperament.

Such biological markers of serotonin and dopamine function as lowered platelet MAO have been examined in sensation seeking bullfighters[49] and pathological gamblers[50] , testifying to the ingenuity of psychobiologic methodology that can be brought to bear to understand human behavior in all of its intense emotional moments. It would have been relevant to measure these and other markers among spectator audience as well.

The most fascinating of all complex activities of the human mind is artistic creativity, which curiously is on the basis of research data reviewed elsewhere, correlated with cyclothymic tendencies.[51] Provocatively, this is the same temperament which appears relevant to suicidal behavior.[36-39] Whether future physiologic investigations would shed light on such higher mental function is at the edge of human knowledge,[52] a challenge to the investigative genius of researchers who can bridge art and science or art and the brain.

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Gene Environmental - Interaction in Psychiatry: lessons from an Evolutionary Approach

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One hundred fifty years ago Charles Darwin wrote: *"In the distant future I see open fields for far more important researches. Psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation. Light will be thrown on the origin of man and his history"*.[1]

At what extent this prophecy has been carried out? Three of the most relevant thinkers in the History of psychology and psychiatry, Sigmund Freud father of psychoanalysis, Emil Kraepelin, father of the clinical psychiatry and John B. Watson father of behaviorism, developed very different theories to understand normal and abnormal behavior of humans beings. Nevertheless, they had at least one thing in common: all of them ignored Darwin's evolutionary ideas.[2]

On the other hand, one of the greatest biologist of the XX century T. Dobzhansky said *"Nothing in Biology makes sense except in the light of Evolution"*.[3] What about the so called Biological Psychiatry?

Key words:
Gene - Environmental Interaction, Depression, Infant Temperament, Darwin, Genetics, Evolutionary Psychiatry

GENE –ENVIRONMENTAL INTERACTION AND PSYCHIATRY

The main idea of natural selection is that genetic variants carried by individuals who reproduce more than others (are better adapted to their environments) tend to increase in frequency over generations. Therefore, evolutionary theory is mainly focused on gene-environment interactions.

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On the other hand, the general medical model explains that both genetic and environmental factors contribute to the development of complex diseases. Thus, gene–environment (G x E) interaction is a very important topic in human genetics and there are great expectations for potential applications in medicine.[4]

In the last years there has been extensive efforts to catalogue human genetic variation and correlate it with phenotypic differences. Central to the field of psychiatric genetics is the search for "vulnerability genes". Following the general medical model, it is assumed that there are genetic and environmental risks and protective factors in the etiology of any complex disease. The main idea supported by this model is the existence of "good" and "bad" polymorphisms.

In Psychiatry, the author who introduced the most relevant studies of gene-environmental interaction in Psychiatry was A. Caspi. The first study was published in 2002 This study was focused on anti-social behavior in relation with maltreat children and *MAO* gene interactions.[5] The second study, one year later, focused on depression related with serotonin transporter gene (*5-HTT*) and life events interactions.[6] Finally, the third study was published in 2005, trying to explain psychosis as a result of cannabis abuse in interaction with *COMT* gene variants[7]. Here we are going to consider only the second and most cited study (more than 1900 citations), the issue about *5-HTT* gene-environment interaction.

GENE ENVIRONMENTAL INTERACTION IN DEPRESSION

There are at least three reasons to focus in this gene. First, serotonin transporter protein is the key for the regulation of the serotoninergic system. Second, there is a very well studied polymorphism in the promoter region of this gene. This polymorphism has two variants: a short allele implicating lower functional activity (ss) and a long allele (ll) implicating high functional activity. Finally, many animal and human

studies have shown that this polymorphism is very important in the modulation of the emotional response to environmental stress. Before Caspi's study, we had numerous genetic association studies with this gene in relation with many psychiatric disorders. Taken together, the result of these studies were controversial. The relevance of the work of Caspi and colleagues was that they found significant results of the short allele (ss) of this polymorphism "only in interaction with life events". In the last paragraph they justified the lack of conclusive results in previous studies: *"We speculate that some multifactorial disorders, instead of resulting from variations in many genes of small effect, may result from variations in fewer genes whose effects are conditional on exposure to environmental risks."*[6]

However, the main question I would like to discuss is the idea supported by the medical model of "good" and "bad" polymorphisms in common variant genotypes. According to Caspi's result, if you are part of the 20% of people with the "ss" variant you have the "bad" allele, so if you have a number of stressful life events you are more likely to suffer depression or anxiety. What is the evidence for this?.[7]

Since 2003, several studies have tried to replicate Caspi's results about the interactions between the short allele and life events as a risk for depression. Unfortunately, once again, results were not conclusive. In a meta-analysis concerning this issue, the conclusion was that there is no evidence proving that serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression.[8]

Trying to solve some of the methodological problems, we made a longitudinal study of postpartum depression on 1804 Spanish women. The advantage of postpartum depression is the homogeneity of the sample, the unmistakable life event (delivery) and the brief time gap between this life event and the clinical evaluation. In order to assess the postpartum mood, we made three clinical evaluations: right after delivery, at 8 weeks and at 32 weeks.[9] Contrary to Caspi's results, we found a higher risk for depression in women with high expression serotonin transporter genotype (long allele). Previous experimental studies inducing tryptophan depletion found more significant mood changes in people with the long allele.[10] As postpartum is a natural experiment of acute tryptophan depletion, our explanation was that postpartum depression could have a specific genetic pathway vulnerability to depression due to gene-hormone interaction.

GENE ENVIRONMENTAL INTERACTION ON INFANT TEMPERAMENT

Therefore, one explanation for the lack of conclusive results of psychiatric genetic association studies could be the influence of environmental factors. Another possible way to solve this problem is to look at temperament of preschool children. It is expected that variability in infants' behavior might have less environmental influence.[11]

New mothers often ask "why is my baby so irritable; is it because of my anxiety or am I anxious because my child was born irritable?" Many studies have demonstrated that the mother's emotional state and rearing behaviors are closely related to the infant's temperament. More recently, genetic association studies have focused on infant temperament. Several studies have focused in how the infant's 5-HTTLPR genotype may modulate mother–infant attachment.[11, 12.] It has also been shown that children with the "s" allele are more vulnerable to lack of social support, low maternal responsiveness, or insecure attachment. We made a prospective study of 317 newborns and their mothers.[12] Infant temperament and the mother's anxiety and confidence in care-giving were evaluated at 8 and 32 weeks after childbirth using the Mother and Baby Scale. These variables were correlated with the serotonin transporter genotypes of both the infants and their mothers. The irritability scores of infants with the "s" allele showed a linear relationship with their mothers' anxiety of care giving at 8 and 32 weeks, while the irritability of infants carrying the "ll" genotype was independent of their mothers' anxiety.[12] So, the main result of this study is that long allele is a protective factor about infant irritability if the mother has anxiety about rearing. Our results are consistent with previous studies that used different methodologies.[11, 12] Our results are also consistent with previous animal studies. Monkeys with the short allele on the 5-HTTLPR polymorphism show behavioral developmental difficulties only if they have a lack of supportive mother-infant relationships.[13]

CONCLUSIONS

Taking into account the evolutionary theory, it is worth asking: what is the evolutionary meaning of this serotonin transporter gene polymorphism? Years ago, P. Lesch and colleagues found that this variant of the serotonin transporter gene is only present in hominids.[14] The presence of the 5-HTTLPR in humans and simians but not in prosimian primates and other mammals raises some interesting questions: why are anxiety-related personality traits so common in humans? What is the function of anxiety-related personality traits? Is there a relationship between functional 5-HTT expression, anxiety, and the complexity of socialization in humans and primates?

Whatever are the answers to these questions, our results suggested that, contrary to the classical medical model, there are no 'bad' or 'good' genotypes in relation to common variant genotypes. In depression, the "ll" genotype might be a risk factor for depression in women under tryptophan depletion after delivery, but in other life-time and

environmental conditions, such as mother anxiety in early childhood, it might be a protective factor.

In summary, Biological Psychiatry is not "biological" without an evolutionary framework. We need evolutionary genetics in order to understand the controversial results of gene-environment interaction studies in Psychiatry. Moreover, as recently emphasizes by Nesse and colleagues: "*evolutionary biology is not just another topic vying for inclusion in the curriculum; it is an essential foundation for a biological understanding of health and disease*".[15]

Glossary

- **Natural Selection:** is the process by which traits become more or less common in a population due to consistent effects upon the survival or reproduction of their bearers.
- **Allele:** one of several alternative forms of a gene or DNA sequence at a specific chromosomal location.
- **Polymorphism**: different (two or more) variants (alleles) of a gene within a population, usually expressing different phenotypes.
- **Serotonin:** or 5-Hydroxytryptamine (5-HT) is a monoamine neurotransmitter, biochemically derived from tryptophan, that is primarily found in the gastrointestinal tract, platelets, and central nervous system of humans and animals. In the CNS serotonin has various functions, including the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions.
- **Postpartum depression**: a clinical mayor depression that occur in about 12% of women after delivery.
- **Temperament:** refers to those aspects of an individual's personality, that are often regarded as innate rather than learned.
- **Life events**: Any major change in person's circumstances– eg, divorce, death of spouse, loss of job, etc, that affects interpersonal relationships, work-related, leisure or recreational activities

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Biology of Neuropsychiatric Disorders

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We study neuropsychiatric disorders, using a wide range of techniques, with an ultimate goal of illuminating normal human brain function. Huntington's disease (HD) and Parkinson's disease (PD) are models which may provide methods for approaching the more complex psychiatric disorders such as schizophrenia.

HD is an autosomal dominant, progressive, fatal neurodegenerative disorder causing abnormality of movements, thoughts and emotions, with degeneration in the striatum of the basal ganglia. An expanding CAG repeat coding for polyglutamine in the huntingtin protein causes altered conformation of the protein, aggregation and the formation of intranuclear neuronal inclusions. We have suggested that the major source of cell toxicity may be an oligomeric soluble aggregate with a compact beta sheet conformation. Proteolytic processing of huntingtin and nuclear translocation of an N-terminal fragment leading to alterations of gene transcription appear to be key pathogenic events. We use biophysical and biochemical techniques, cell models, and mouse models in order to better understand these processes, and provide targets for development of rational therapeutics.

More recently we have focused on molecular pathogenesis of Parkinson's disease. We have studied alpha-synuclein, the first identified cause of genetic PD, and more recently Leucine Repeat rich Kinase 2 (LRRK2), another autosomal dominant form. We find that both alpha-synuclein and LRRK2 interact with Parkin, one of the recessive PD genes, suggesting the potential emergence of a pathogenic pathway. We have developed a very effective model for cell toxicity caused by mutant LRRK2, and have shown that kinase activity is necessary for LRRK2 cellular toxicity. This raises the hope that LRRK2 could be an excellent target for therapeutics development, analogously to the way kinases are therapeutic targets in the cancer field. We are currently studying protein interaction partners and attempting to develop transgenic mouse models.

Schizophrenia has long been believed to be a subtle disorder of neuronal development. Disrupted in Schizophrenia 1 (DISC1) was previously identified as being interrupted by a chromosomal dislocation, which strikingly segregates with schizophrenia and other major mental illness in a large pedigree in Scotland. The predicted protein product of the DISC1 translocation appears to act as a dominant negative, causing neurite outgrowth abnormalities in neurons in culture and cortical migration defects in vivo. We have preliminary data indicating that transgenic mouse models over-expressing the predicted mutant DISC1 protein product have subtle abnormalities of neurite outgrowth and behavior. Thus, the hope is that by using similar cellular and molecular techniques which have been successful in the neurodegenerative diseases, we can better understand psychiatric disorders such as schizophrenia. Ultimately, neurobiologic study of schizophrenia may help illuminate normal thought perception and emotion--and help us understand the biology of human nature itself.

Genetics and neurobiology are beginning to illuminate the biology of psychiatric diseases. Neurodegenerative diseases can provide a model, with insights into dementia, Parkinson's disease, and triplet repeat disorders including Huntington's disease. Genome-wide association studies and other genetic techniques are identifying new candidate genes for schizophrenia and bipolar disorder. Cell models, including iPS cells, and mouse models, may elucidate pathogenesis. As additional genes are identified, an iterative process of genetic and phenotypic nosological reclassification of psychiatric disorders can begin. Understanding genetic causes, and development of genetic models, will facilitate the study of the interaction of genes and environment, and the development of novel approaches to rational therapeutics.

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Schizophrenia: From Neurobiology to Nosology of Mental Disorders

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Schizophrenia, unlike most mental illness, is an exclusively human disorder. It has been said that is the risk to which man is exposed for being able to think and have verbal language.

It has taken 150 years to be recognized as a medical condition, being considered nowadays common and stable in time and space.

It is defined as a weakening and disintegration of psychic awareness. Thus, it is a complex global psychopathological disorder, which induces in the subject three conditions: distance, eccentricity and incomprehensibility.

The disease entity of schizophrenia was formed after the descriptions of Morel (who described cognitive impairment in young), Kraepelin (who coined the concept of dementia praecox) and Bleuler (who incorporated elements of the theory of mind and extended the term *schizophrenia*). In the current paradigm, it is a genetic and neurodevelopment disease, with environmental interactions, which alters the cortico-cerebellar-thalamic circuit. These alterations cause psychotic, defectual, affective and cognitive symptomatology and a progressive trend attributable to dopaminergic neurotoxicity (and possibly also to other neurotransmitters, especially glutamate).

These groups of symptoms are the language of the disease, how it expresses. But we still haven't found the nosological definition of the disease regardless of how it is expressed.

In this context, it is necessary to reformulate the concept of schizophrenia.[1] In this regard, multiple theories have emerged, such as the term schizotaxia, defined by premorbid conditions that configure the propensity to the disorder.[2] We now have increasingly more scientific evidence of the disease. Research into schizophrenia is developing in all areas, especially in first episode psychosis and meta-analysis. The first psychotic episodes are currently the focus of most of the efforts and research results.

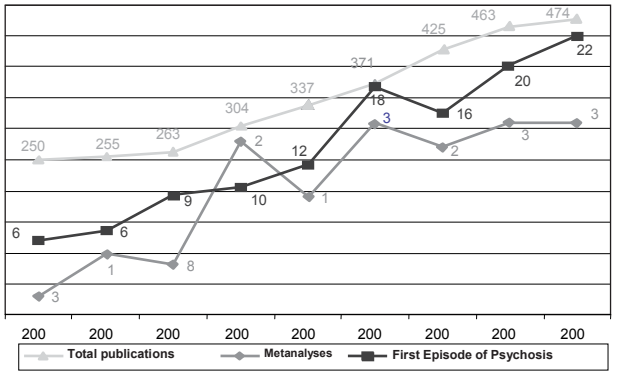

Figure 1

This core of evidence has been transferred to the clinical practice by means of evidence based medicine, but we must be aware not to fall in an evidence biased medicine, risk that has to be monitored.

Research in the eighties was concerned with laying the nosological groundwork (with the publication from of DSM-III to DSM-IV-TR),[3] sizing and characterizing the epidemiology and establishing the scientific method and statistical approaches. In the nineties, the brain decade, the areas of neurochemistry, neuropharmacology, neuropsychology and neuroimaging were developed. Finally, from 2000 to 2010 has been the decade of the genome and ambiome. Thus, schizophrenia and can be conceived as a genetic disorder of the synapse.[4] We know there are a number of genetic alterations (dysbindin, DISC1, Akt1...) that determine a level of dysfunction in neurotransmission (mainly dopaminergic), neuronal plasticity (particularly in the neurodevelopment)

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or synapse formation (including neuronal migration). These alterations cause two phenomena: dysregulation of dopaminergic transmission (which would cause the psychotic symptoms) and cellular neuropathology (responsible for cognitive deficits and other symptoms).

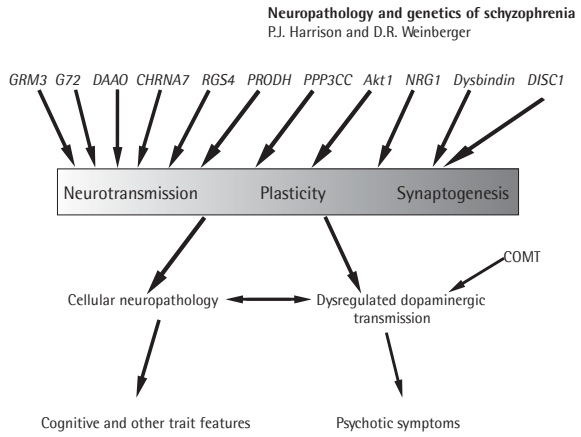

Figure 2 Adapted from Harrison PJ, Weinberger DR[4]

This conceptualization has led some authors to consider revising the term *schizophrenia*, reformulating it as a salience dysregulation syndrome, understood as distorted sensory amplification that should be evaluated with a multidimensional model.[5, 6]

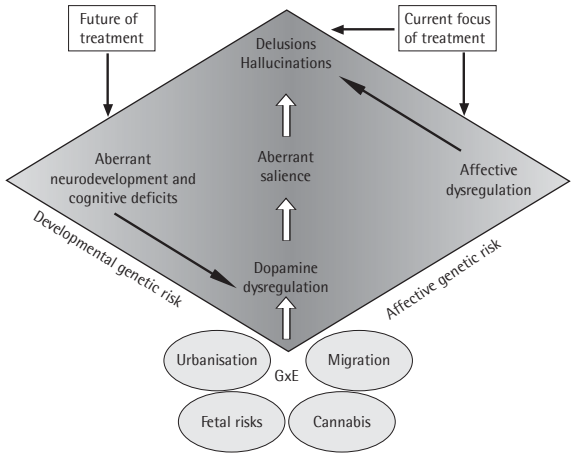

Figure 3 A model of schizophrenia and related psychotic disorders

At this time there are a number of unmet needs: only one third of patients remain without symptoms and adequate functional capacity, being the third leading cause of years lived with disability in young subjects (15-44 years). The therapeutic efficacy is limited, appearing partial responses or resistance to treatment. Maintenance therapy should be improved to reduce relapses, suicide and depression, as well as negative and cognitive symptoms. Side effects (extrapyramidal symptoms, metabolic syndrome ...) and ineffectiveness increase treatments discontinuation rates. Over the past thirty years we have experienced a set of semantic and conceptual changes: we speak of "patient with schizophrenia" and "antipsychotic drug" instead of "schizophrenic patient" and "neuroleptic drug". New concepts have been introduced such as early intervention, intensive community treatment teams, psychoeducation and cognitive-behavioral therapy in schizophrenia. The main goal of treatment has become "recovery" instead of "symptom reduction."

Another series of changes have been made in reference to care and treatment: shorter hospital stays (avoidable in some cases), the possibility of involuntary outpatient treatment, greater family involvement, changes in side effect profile (lower extrapyramidal symptoms but higher metabolic disorders) and abolition of "rest" periods without treatment.

In order to approach patients with schizophrenia to recovery, consensus of standardized criteria has been established, validated in European population.[7, 8]

For these reasons, it is essential to point out in the detection and treatment of disease early stages, which include the period before the onset of first episode psychosis and the prevention of relapse after the onset.[9] In this context, our team is coordinating a multicenter longitudinal study - funded by the Spanish Health Research Fund (Fondo de Investigaciones Sanitarias) and conducted the Biomedical Research Centre in Mental Health Network (CIBERSAM) - collecting the conceptual model of gene-environment interaction.

In this line of future, we attend to a new formulation of the concept of the disease, which suggests that schizophrenia is not only a psychotic disorder, but it is a developmental disorder with abnormalities in many brain functions, including psychosis. In this line of thinking, schizophrenia would not be a brain illness, but a systemic disease that affects other parts of the body besides the brain and where the equation psychosis = anomaly of dopamine is considered, in some ways, a historical aberration based in the fact dopamine antagonists were the first effective treatment available.[10] This model would consider the disease as a syndrome of accelerated aging, with new evidence pointing in this line as telomere shortening, increased pulse pressure, metabolic and structural changes in untreated patients.[11-13] In conclusion, the nosology of schizophrenia as a disorder of consciousness is based on a three-tiered approach. A first prephenomenological level, where there is a neuro-developmental disorder, minor symptoms and signs and

adaptive deficits. A second transphenomenological stage, which define a basic cognitive phenomenon, the loss of hierarchy in the habits of thought and behavior, and phenomena associated with derangement of the filtration (sobreinclusión) and decoding (interference responses). Finally it appear the third phenomenological level, where emerge the typical psychotic symptoms (hallucinations, delusions...) as "reaction" to the deficits caused by the basic symptoms.

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Neuromodulation and mental disorders

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INTRODUCTION

Psychiatric surgery has been one of the most controversial medical activities of the last century. Initiated by Egas Moniz and Almeida Lima, after the observation by Fulton and Jacobsen that frontal lesions made chimpanzees less aggressive, it was initially associated with severe adverse effects, specially apathy and the moria syndrome.

The initial results obtained and the description of the transorbital leucotomy, led Freeman, a neuropsychiatrist, and Watts, a neurosurgeon (who later left Freeman), to popularize this procedure through the United States in the 50s. Transorbital leucotomy was a very easy and quick procedure performed under the anesthesia obtained by an electroshock, under doubtful indications. This led to an opposite reaction by the social community which, added to the introduction of neuroleptics, led to a nearly abandon of these procedures.[1]

Meanwhile, neurosurgeons began to design operations with smaller targets, obtaing similar results and less adverse effects. The introduction of stereotactic techniques contributed to this less invasive approach. Lately, the discovery that high frequency stimulation may have similar effects than brain lesions, has led to the possibility of performing "reversible" procedures, as the stimulator can be turned off. This procedure is called deep brain stimulation (DBS). Also, programming of the stimulators with different voltages, frequencies and pulse widths, and the possibility to use combinations of four electrodes make stimulation more flexible. This has led to a renewed interest in psychiatric surgery, with the discovery of new targets and indications and the increase in the number of procedures.

The targets used in the stereotactic lesioning procedures were aimed at different points of the circuit of Papez, intented as the neural basis of emotion. Anterior capsulotomy placed a lesion at the anterior limb of the internal capsule, including pedunculus thalami anterior and the frontopontine tract, interrupting the the flow of information between the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and the thalamus and basal ganglia. Subcaudate tractotomy (innominotomy) interrupted fiber of the pedunculus thalami inferior, ansa peduncularis and amygdalofugal fibers, and also probably fibers of the anterior limb of the internal capsule. Cingulotomy interrumpted the fasciculus cinguli projections from the cingulate and frontal cortices to the hippocampus.

Initially, the targets used in psychiatric DBS were the same used in the classical lesioning procedures. Nuttin started stimulating the anterior limb of the internal capsule, trying to reproduce the lesions of the anterior capsulotomy.[2] Nuttin's group realized that better results were obtained if the target was placed more posteriorly. This target is very close to the ventral striatum (or Nucleus Accumbens), and Sturm proposed the stimulation of the shell of Nucleus Accumbens, both for OCD and depression. Other targets have been described, trying to emulate those of the lesioning procedures (for example, the stimulation at the inferior thalamic peduncle,[3] or the stimulation of the hypothalamus for aggressiveness),[4] or after considerations on psychopathology and review of other targets for other diseases (such as the limbic part of the subthalamic nucleus (STN) as a target for OCD proposed by Benabid, or the thalamic centromedian and ventral oralis targets for Tourette's syndrome proposed by Visser-Vandewalle).[5]

Lozano and Mayberg introduced the use of targets identified by functional neuroimaging.[6, 7] They were based on studies showing that the subcingulate cortex, or Brodman's area 25, was hyperactive in depressive patients and also in voluntary subjects instructed to feel sad. This area was also the first to decrease its activity when depressive patients were cured. They reasoned that inhibiting this area would ameliorate the symptoms of depression. This area has connections with hypothalamus, amígdala, periaqueductal

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gray, and the mesolimbic and mesocortical pathways, thus controlling depressive symptoms other than sadness such as anhedonia, insomnia, fatigue, eating disorders or guilt and sucidal ideations.

Key words:
Psychiatric surgery, deep brain stimulation, neuromodulation, obsessive-compulsive disease, depression

INDICATIONS

Classically, the best results were obtained in affective disorders (major depression, obsessive-compulsive disease -OCD-, anxiety), and the symptoms best controlled were those related to emotional suffering. Also, aggressive behavior and chronic pain associated with depression were indications for psychiatric surgery. Schizophrenia per se was not an indication and even psychosis was a formal contraindication when associated with affective syndromes, but aggressive behavior or schizo-affective symptoms in schizophrenics could respond to surgery. These indications are still active. Also, Tourette's syndrome has been treated with DBS.

PATIENT SELECTION

To admit a patient as a candidate for psychiatric surgery, some criteria must be met:

- The disease must be disbling. It may be either a long term evolution resistant to treatment or more acute courses with severe symptoms and suicidal risk. In any case, all reasonable non-surgical therapies must have been tried during appropriate periods. A minimal period of treatment of 1 year is a minimum, but usually patients are considered for operation after 5 years of psychiatric treatment. On the other hand, a delay to perform surgery may lead to irreversible personality changes.
- Both the psychiatrist and the neurosurgeon must be familiar with this kind of procedures and must agree in the indication. Besides, both the patient and the family must be aware of all the information related to results, complications and altertative treatments, and must give an informed consent. Free informed consent is possible from patients suffering from affective disorders, since their cognitive functions are intact. If free consent is not possible, then complete ethical and legal warranties must be met before surgery.
- Finally, an adequate postoperative psychologic and psychiatric treatment, and rehabilitation in an appropriate family and social environtment must be assured.

In most hospitals, the application of these criteria is supervised by a committee which studies all surgical candidates.

The operation is contraindicated when other brain diseases coexist, such as dementia or organic lesions, or other systemic diseases which may be aggravated by surgery.

Advanced age is not an absolute contraindication, but surgical risks are higher. On the other hand, patients under age 18 are seldom operated (except in cases of severe autoaggresivity), since their prognosis is not well stablished and the possibility of an adequate informed consent is doubtful. Personality disorders, specially antisocial or hysteric personalities, may constitute a contraindication.

THE PROCEDURE

We will describe the prodedure of implantation of DBS electrodes. The target point is calculated from neuroimaging data, mainly MR with T1 and T2 potentiated sequences. Some key structures can be seen in the images (such as the subthalamic nucleus, the internal capsule or the ventral striatum), but the taget selection is done using data from atlases and calculating the distances of those targets to reference points (such as the anterior and posterior commisures). As MR can have a spatial distortion, a CT is performed with the stereotactic frame placed (or with fiducials attached to the patient's skull in frameless techniques) and the images fused to let the MR chosen target be driven using the CT defined coordinates.

The procedure is performed under local anesthesia and intermitent sedation of the patient, since he or she must collaborate during the recording and stimulation periods of the surgery. After the placement of the appropriate burr-holes, the targets are approached using semi-microelectrodes, which record the activities of individual neurons. This recording lets an experienced neurophysiologist or neurosurgeon to know which structure is being recorded. Should the appropriate target be missed, the reconstruction of the actual trajectory based on this recognition permits to reposition a new trajectory. During the recordings, visual stimulation showing the patient pictures which may trigger his or her symptoms (such as emotionally charged pictures, or those showing his or her obsessions) is performed to determine if this modifies the neuronal activity of the target nucleus.

Once the target is reached, stimulation is performed to test for possible unwanted effects, in order to check if the electrodes are going to elicit side effects once implanted. If this does not happen, tetrapolar electrodes are placed with the distal contact located at the target point. Sometimes, an acute effect can be observed over the patient's symptoms, but the absence of it is usual and does not preclude a long term positive effect. The electrode is connected to a temporary extension cable which exits the surgical wound.

This cable is connected to an external stimulator, permitting test stimulation during the following days. Once side-effects are discarded, a permanent pulse generator is implanted subcutaneously at the abdomen or at the suclavicular space connected to a definitive cable extension also placed under the skin. This pulse generator can be later programmed through a transcutaneous electronic transceiver.

RESULTS

We will review the results in OCD, since depression is covered elsewhere in this volume[7] and DBS for other indications has still a few number of cases reported.

The most complete series is that leaded by Nuttin, whose results are evaluated by a multidisciplinar group.[2] The psychiatrist-rated Yale-Brown Obsessive Compulsive Scale (YBOCS) score was lower in the stimulation-on condition (mean, 19.8 +/- 8.0) than in the postoperative stimulator-off condition (mean, 32.3 +/- 3.9), and this stimulation-induced effect was maintained for at least 21 months after surgery. Other groups have used a similar target, with DBS electrode arrays placed bilaterally in an area spanning the ventral anterior limb of the internal capsule and adjacent ventral striatum referred to as the ventral capsule/ventral striatum.[8] A recent report[9] of the results of a prospective study using a blinded, staggered-onset design with more than 12 months of follow-up, showed 4 of 6 "responders" (defined as those with more 35% improvement in the Y-BOCS and end point Y-BOCS severity < or =16). There was no improvement during sham stimulation. Depressive symptoms and CGI improved. Interruption of stimulation led to a rapid but reversible induction of depressive symptoms in two cases. Adverse events were mild and modifiable with setting changes.

In a report from Sturm's group, DBS aimed at the shell of the nucleus accumbens for OCD was performed on the right side in four patients.[10] Mean Y-BOCS scores decreased significantly, from 32.2 (+/-4.0) at baseline to 25.4 (+/-6.7) after 12 months (p=0.012). 5 of 10 patients showed a decrease of more than 25%, considered at least a partial response (1>35%). Depression, CGI, QOL improved within 1 year. Anxiety, global symptom severity and cognitive function showed no significant changes, and DBS was well-tolerated.

A multicenter, cross-over, blinded trial was done in France[11] with 18 patients, targeting the limbic part of the subthalamic nucleus (STN) for OCD patients. Y-BOCS score was significantly lower than the score after sham stimulation (mean [+/-SD], 19+/-8 vs. 28+/-7; P=0.01), and GAF score was significantly higher (56+/-14 vs. 43+/-8, P=0.005). Neuropsychological measures, depression, and anxiety were not modified by stimulation. They recorded 15 adverse events in 11 patients overall (1 hemorrhage).

Ventromedial caudate has been used for refractory OCD and depression, but the high currents needed for capsular DBS "raised the essential issue of the exact area to be targeted".[12]

We conclude quoting the resultas of a systematic review[13] of all the cases of psychiatric surgery treated with DBS. It states the low number of cases treated, which were extremely resistant to psychiatric treatment. Overall, there was a 50% dramatic improvement. Associated adverse events were trivial in younger psychiatric patients, but often severe in older movement disorder patients. Procedures differed from study to study. It concludes that DBS is a promising technique for OCD and TRD although there is a need for series of larger number of cases, using genetic and imaging studies (MRI, fMRI, PET, and tractography).

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Deficit Schizophrenia: An Overview

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Kraepelin described "two maladies" within Dementia Praecox: a weakening of the will and the loss of unity of mental processes. Several attempts to reduce heterogeneity within schizophrenia by identifying more homogeneous subtypes of the syndrome are based on the description of the former maladie provided by Kraepelin.

The dichotomy proposed during 1980s between a schizophrenia subtype characterized by positive symptoms and one characterized by negative symptoms is an example of these attempts. The lack of diagnostic stability over time, the scarce prognostic implications, the inconsistency of the findings provided by correlational studies and the failure of investigations based on factor analysis to support the two-syndrome model were soon recognized as limitations of the proposed dichotomy, and heterogeneity within the positive and negative psychopathological domains as one of the main factors accounting for them. As to the heterogeneity within negative symptoms, it is largely documented that these symptoms may be secondary to positive symptoms, social isolation, depression and treatment with antipsychotics, or might be primary, i.e. an enduring expression of the disease process. The distinction has important therapeutic implications, as secondary negative symptoms may improve following therapeutic interventions, while the latter ones are likely to persist in spite of treatment with either conventional or second-generation antipsychotics.

The concept of deficit schizophrenia (DS) introduced by Carpenter et al[1], is aimed to identify a relatively homogeneous subgroup of patients with a diagnosis of schizophrenia, characterized by the presence of primary and enduring negative symptoms.

Patients with DS differ from those with non-deficit schizophrenia (NDS) on variables related to the syndrome construct (i.e., more negative symptoms), but also for a lower prevalence of suspiciousness, dysphoria, hostility, suicidal ideation and substance abuse;[2,3] positive symptoms, instead, show a comparable severity. Patients with DS, as compared with NDS ones, have more severe neurological impairment. According to Galderisi et al.[3] they are more impaired than those with NDS on the NES subscales "sensory integration", "motor coordination" and "sequences of complex motor acts"; after partialling out the influence of extrapyramidal symptoms, the deficit/non-deficit categorization was significantly associated to the factor "sequencing of complex motor acts", while negative symptoms on the whole were associated with the factor "sensory integration".

DS does not coincide with Negative Symptoms, Simple Schizophrenia, Process Schizophrenia or Residual Schizophrenia. Negative Symptoms include both primary and secondary negative symptoms, independent of their being temporary or persistent. Simple Schizophrenia involves an insidious but progressive development of oddities of conduct, inability to meet the demands of society, and decline in total performance. While in DS psychotic symptoms are generally as severe as in other forms of schizophrenia, in Simple Schizophrenia this is not the case: delusions and hallucinations are not evident and the negative features are not preceded or accompanied by any overt psychotic symptoms.

Process schizophrenia is a somehow obsolete concept, that refers to severe forms of schizophrenia in which chronic and progressive brain structural and/or functional abnormalities represent the primary cause (so far, this is not part of the Deficit Schizophrenia concept); onset is insidious and at a young age and prognosis is poor. At odds with DS, the clinical picture sometimes involves unconventional character traits, great anxiety, bizarre hypochondriacal symptoms and unstable emotional state: irritability and acts of violence may occur. Work and study performance is decreased, ability to concentrate is markedly reduced loss of patience.

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Different from DS is also Residual Schizophrenia in which evidence in the past of at least one clear-cut psychotic episode meeting the diagnostic criteria for schizophrenia is required; however, for at least 1 year before the diagnosis of Residual Schizophrenia is made, the intensity and frequency of psychotic symptoms such as delusions and hallucinations has to be minimal or substantially reduced while the negative schizophrenia is present.

Deficit schizophrenia is a rare but persistent condition: its prevalence is 25-30% in clinical samples and 14-17% in population studies.[4] Its longitudinal stability is suggested by both retrospective and prospective studies reporting a degree of agreement higher than 80% between the first and the second diagnostic evaluation.

The Schedule for the Deficit Syndrome (SDS)[7] is the gold standard for the diagnosis of deficit schizophrenia. It is a semistructured interview requiring a large clinical experience in patients with schizophrenia, a training led by an expert of the use of the instrument. The diagnosis is based on the interview with the patient, and the use of information provided by clinical records, relatives and health professionals well acquainted with patient's past and present psychopathological state. Information should focus on times of clinical stability, as the categorization has no validity when made during acute psychotic states.

Before the appearance of psychotic symptoms, psychosocial functioning is poorer in patients with DS compared with NDS.[3] Long-term prognosis is worse in DS compared with NDS. The poorer outcome in deficit schizophrenia patients may also result from inefficacy of antipsychotic drugs on primary negative symptoms.[8] In fact, both first and second-generation antipsychotics may act on secondary negative symptoms by removing, in part or completely, some of their causes, such as positive symptoms, depression or extrapyramidal symptoms, but so far no conclusive evidence has been provided of their efficacy on primary and persistent negative symptoms.

The majority of Magnetic Resonance Imaging (MRI) studies did not find more abnormalities of the same type in DS than in NDS patients. Three studies found no ventricular enlargement in deficit *vs.* non-deficit schizophrenia patients;[8] this is surprising, as this is one of the most replicated findings in schizophrenia and has often, but not consistently, been reported in association with negative symptoms and poor outcome. Galderisi et al[10] hypothesized that two distinct processes may occur in deficit and non-deficit schizophrenia: more abnormal scans in patients with non-deficit schizophrenia might reflect progressive ventricular enlargement, possibly related to the excitotoxic effect of repeated psychotic episodes, and be associated with normal early premorbid adjustment and general cognitive abilities, while in patients with deficit schizophrenia less abnormal scans might result from an early onset non-progressive developmental process, allowing for more compensatory brain structural reorganization, but interfering since childhood with the acquisition of basic cognitive and social skills.

Several functional brain imaging studies reported a reduction of glucose metabolism and of cerebral blood flow in the frontal and parietal regions in patients with deficit as compared with non-deficit schizophrenia.[8] A recent Diffusion Tensor Imaging study reported reduced fractional anisotropy, an index of white matter integrity, in the right hemisphere superior longitudinal fasciculus and frontal white matter in the deficit subjects in comparison with NDS ones.[11] Abnormalities confined to the right hemisphere in DS patients were also reported by Galderisi et al[10] and might suggest a different laterality imbalance in DS than in NDS subjects, in which a more impaired right fronto-parieto-temporal network contributes to greater impairment in social functioning, in particular in social relationship, given the role of these brain regions in important aspects of social life, such as emotion and facial processing or language prosody.

Electrophysiological investigations supporting the hypothesis that deficit and non-deficit schizophrenia represent distinct disease entities were also carried out.[8] Mucci et al[12] recorded event-related potentials during an auditory discrimination task and found evidence of a double dissociation: abnormalities of the N1 ERP components were found only in DS patients, as compared with healthy controls, while P3 abnormalities were detected on non-deficit patients only.

Evidence for double dissociation was also shown by studies investigation season of birth in DS and NDS patients. In fact, at odds with the repeatedly reported finding of a predominance of winter birth in schizophrenia, an association between summer birth and deficit schizophrenia has been found by several independent groups.[8] Messias et al[13] analyzed pooled data from six different countries in the northern hemisphere and reported an increased birth in June and July in deficit schizophrenia patients (odds ratio 1.9).

Genetic research on DS is in its infancy. In the absence of a strong candidate gene, large multicenter studies based on genome-wide scan seem to be the most appropriate strategy for future investigations. Fanous et al[14] and Holliday et al[15] carried out two such studies. Fanous et al. reported suggestive linkage of their "deficit" class to a region in chromosome 20. Holliday et al, also used latent class analysis and identified a class resembling DS. For this class, they detected genome-wide significant linkage to 1q23-25 (not detected by using the DSM-IV diagnosis of schizophrenia).

In conclusion, most of the studies carried out so far to characterize the schizophrenia subtype described by

Carpenter as DS provided evidence that abnormalities observed in deficit schizophrenia are not more of the same observed in NDS, as we would expect in more severe forms of the same disease. Instead, some studies suggest that deficit schizophrenia is a separate disease entity.

In my opinion, for the time being, neither conclusion should be considered as the final one, because of the limited number of studies correctly addressing the topic, discrepancies in findings and small size of the enrolled patient samples. Last but not least, not all patients considered as having "deficit schizophrenia" or "deficit state" actually correspond to the subtype described by Carpenter and coworkers.

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What do Drug-Induced Psychoses tell us about Schizophrenia?

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The prevalent view among researchers today is that schizophrenia is a syndrome rather than a specific disease. Liability to this syndrome is highly heritable but the fact that concordance between monozygotic twins is less than 50% suggests an important role for environmental influences. It appears that multiple genetic and environmental factors operate together to push individuals over a threshold into expressing the characteristic clinical picture. Currently there is a great deal of research into identifying genes which may increase risk but much less into establishing the reciprocal environmental factors.

One environmental factor which has been curiously neglected is the evidence that certain drugs can induce schizophrenia-like psychosis. Since the mid 20th century, more knowledge has accumulated concerning this than any other cause of psychosis. Unfortunately, this has not been integrated into our knowledge of schizophrenia because drug-induced psychosis has been considered as quite separate from the supposedly distinct disease of idiopathic schizophrenia. However, in recent years much evidence has suggested that liability to psychosis in general, and to schizophrenia in particular, is distributed though the general population in a similar continuous way to liability to medical disorders such as hypertension and diabetes. As with these disorders, some people have a high liability to the condition and can be readily precipitated into expressing symptoms while others further down the liability continuum, are much more resistant. Just as blood pressure can be increased by a range of environmental factors such as obesity, lack of exercise, and cigarette smoking, so exposure to a range of environmental factors including neonatal hypoxia, urbanicity, migration, and certain types of social adversity can increase an individual's likelihood of expressing minor psychotic symptoms and ultimately crossing a threshold to express frank schizophrenia.

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THE SEROTONERGIC HYPOTHESIS

There is widespread evidence that people diagnosed as having schizophrenia-like psychoses are more likely to use illicit drugs than the populations from which they are drawn. It has become accepted that drugs such as LSD, amphetamines, PCP, and cannabis can induce psychosis. The first model psychosis was that consequent upon LSD. Although this produced predominantly visual hallucinations, it gave rise to great interest in hallucinogens and eventually to the serotonin hypothesis of schizophrenia. This hypothesis continues to have an influence on present day psychiatry through the atypical antipsychotics one of whose abilities is to block serotonin receptors.

THE DOPAMINE HYPOTHESIS

The similarity of amphetamine psychosis to schizophrenia was first clearly described in the 1950s by Connell. Subsequently, it was established that amphetamine administered experimentally produced a paranoid psychosis in healthy individuals and exacerbated psychotic symptoms in approximately one-third of schizophrenic patients; moreover neuroleptic drugs blocked these psychotogenic effects of amphetamines. Amphetamine was found to stimulate dopamine outflow, while, in contrast, chlorpromazine and other antipsychotics were found to act by blocking dopamine receptors in the brain. Subsequently SPET and PET studies demonstrated enhanced striatal dopamine release induced by an acute amphetamine in first-episode schizophrenia patients compared to healthy controls. Together these observations provide the basis for the dopamine hypothesis of schizophrenia.

THE GLUTAMATE HYPOTHESIS

PCP and ketamine were found to have a propensity to induce psychosis-like symptoms particularly negative symptoms and this gave rise to the glutamatergic theory of

schizophrenia. According to the glutamate deficiency theory, drugs which enhance glutamate neurotransmission should improve psychotic symptoms. Trials of glutamate potentiation using glycine and related compounds have not reported any antipsychotic effects but in 2007 Lilly developed a new treatment option for schizophrenia, which is a selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors.

THE ENDOCANNABINOID HYPOTHESIS

In recent years interest in drug-induced psychoses has centred on cannabis. Cannabis is the most widely abused illicit drug in the world, and has been causing some concern because of a) the general increase in consumption over the last 25 years, b) increased potency of street preparations available in many countries, and c) decreasing age of first use. Among those with established psychosis, its consumption results in a worse outcome. In addition, over the past 7 years, a series of cohort studies have produced evidence that regular use of cannabis increases the risk of schizophrenia in a dose related manner. Several factors have been suggested as increasing vulnerability i) variation at the COMT locus ii) having a psychosis prone personality iii) frequent use of skunk and other high potency types. There are also some, not always confirmed, suggestions that initiating use in early adolescence may carry more risk.

Although our knowledge of the endocannabinoid system remains primitive, the fact that tetrahydrocannabinol (THC) can induce psychosis and another cannibinoid cannabiniol (CBD) appear to have some antipsychotic actions, has given rise to the idea that endocannabinoids may be involved in the pathogenenesis of psychosis.

CONCLUSIONS

We have seen that the major pharmacological models of schizophrenia have their origins in the effects of drugs of abuse; in chronological order, the effects of LSD initiated the serotonergic model; amphetamines the dopamine hypothesis, PCP and ketamine the glutamatergic model. Most recently the effects of cannabis have provokes interest in the role of endocannabinoids.

None of these models account for the complete picture of schizophrenia, rather the various drugs mimic different aspects of psychosis. Stimulants and THC are particularly likely to induce paranoia beliefs, whereas LSD almost invariably elicits visual illusions/hallucinations. The non competitive NMDA antagonists phencyclidine (PCP) and ketamine appear to induce negative symptoms, and oneroid states (characterized by perceptual illusions, perplexity and delusional thinking in the context of clouding of consciousness) (135). THC particularly induces paranoid thinking.

An argument can be made that all of the drugs which induce psychosis impact upon the dopamine/endocannabinoid system either directly or indirectly. This fact is compatible with the idea that endogenous psychotic symptoms arise out of pathological dysfunction of the 'reward' pathway. However, not all addictive drugs which impact on the dopamine system appear to be able to induce psychotic symptoms. For example, neither cigarette smoking, nor use of opiates induce schizophrenia-like psychosis. One possible reason is that the fact that nicotine and opiate receptors (and responses) show a rapid de-sensitisation following exposure to their respective agonists. This illustrates the fact that determining the neurochemical differences between those drugs whose effects do and which do not mimic particular aspects of schizophrenia is worthy of investigation.

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Cannabis and Psychosis

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It is reasonably well established that there is an association between cannabis use and psychosis, however, the specific nature of the association remains unclear.

There has been a significant increase in cannabis use in Spain in recent years, particularly among the youth and women. This would appear to be a public health concern, in part because of the relatively high percentage of hospital admissions related to cannabis (16.9%), in part because of the apparent increase in concentration of the active substance, and, in large part, because of the putative relationship between cannabis use and schizophrenia.

A number of recent reviews and studies all point to a dose response association between cannabis use and psychosis, although the specific nature of the relationship remains unclear, in large part because of the complexity of demonstrating causality and related methodological difficulties, including ethical ones, that result in a research base that shows strong limitations. An important conceptual complication is that despite the increase in population level use of cannabis and earlier age of initiation of use, there is not concomitant rise in the overall prevalence of schizophrenia in the general population.

Notwithstanding the methodological limitations, the research demonstrates the following:

1. Cannabis use facilitates appearance of psychotic-like or psychotic symptoms
2. An elevated percentage of schizophrenics use cannabis
3. Cannabis use is a risk factor for the development of schizophrenia
4. The impact of cannabis use is elevated in individuals with a specific vulnerability
5. Cannabis use increases the positive symptoms of schizophrenia
6. The higher the dose and the earlier age of initiation of use the greater the risk

What remains unclear is the specific nature of the relationship. The following possibilities have been identified:

1. Cannabis use causes schizophrenia
2. Cannabis use precipitates and aggravates schizophrenia
3. Cannabis use is the *stressor* that provokes schizophrenia in those with a specific vulnerability (diathesis-stress model)
4. Cannabis is used by chronic schizophrenia as a means of self-medication

To a large extent, the question at hand is whether cannabis use is a risk factor for schizophrenia in the general population or only for those with a specific vulnerability. A review of recent cohort studies, which follow a specific population over time can shed light on this issue. McLaren et al.[1] identified 10 cohort studies, five of which focused on symptoms and five on disorders.

The Swedish Conscript Study was the first to systematically examine the relationship between psychotic disorders and cannabis use in a sample of more than 45,000 male conscripts in Sweden.[2] The participants were evaluated at age 18 for substance use, psychiatric status, and psychosocial data, and then followed up for 15 years. The majority of those participants who received treatment for schizophrenia did not use cannabis. Cannabis consumption was identified as a predictor and the higher the dose the greater the risk. With all other factors controlled, relative risk for developing schizophrenia for those that used cannabis was 2.4. The odds ration increased to 3 (95% CI: 1.6-5.5) for those who consumed cannabis between 11 and 49 times, and 6 (CI: 4.0-8.9) for those who used cannabis more than 50 times over the course of their lifetime. The study results suggest an association between cannabis consumption and schizophrenia and that the more cannabis consumed, the greater the risk for developing schizophrenia. The authors concluded that cannabis should be viewed as a risk factor within a multifactoiral model.

In a more rigorous reanalysis of the data, which included a follow-up period of 27 years, Zammit et al.[3] concluded that cannabis use was predictive of schizophrenia and found a dose-response relationship between cannabis use and schizophrenia, with a relative risk of 2.2. The authors suggested that cannabis may increase the risk of schizophrenia by 30%, which suggests that 13% of all schizophrenia cases could be prevented were cannabis consumption to be eliminated.

In a Dutch study with more than 4,000 participants, between the ages of 18 and 64, none of whom had psychotic symptoms at baseline, Van Os et al.[4] found that baseline cannabis use predicted the presence of psychotic symptoms (OR= 2.76; 95% CI: 1.18-6.47) as well as the number of severe symptoms (OR=24.7; 95% CI: 5.44-107.46), and clinical evaluation of the necessity of treatment (OR=12.01; 95% CI: 2.24-63.34) at 3 year follow up. The authors concluded that the development of psychosis could be reduced by as much as 67% were cannabis consumption to be eliminated in the group with a pathological level of psychosis and 50% in the group requiring treatment for psychotic symptoms. Cannabis use, then, increases the risk for the development of psychosis in individuals without a history of psychosis in a dose-response relationship. Finally, the authors argue that cannabis use worsens the prognosis in those vulnerable to psychosis.

The cohort studies, using Hill's[5] criteria for causality, suggest a causal relationship between cannabis and psychosis. Cross-sectional studies support this in that the co-occurence of cannabis use and schizophrenia is higher than what would be expected by chance.[1] Methodological problems that could give rise to bias, include the use of other substances, the presence of other psychiatric disorders, the means by which drug use is evaluated (e.g. self report, which may underestimate use) and the evaluation of psychotic symptomatology versus disorder. Despite the difficulties in establishing a time sequence, selection bias, and the influence of personality, the cohort studies rather consistently demonstrate that consumption is a risk factor if not a causal factor for the development of schizophrenic disorders or psychotic symptoms.

Two consistent findings are that of dose-response and age of onset. Repeated use of cannabis may indeed increase the likelihood of developing schizophrenia, particularly with more than 50 consumptions. Using cannabis before the age of 15 years would appear to be a strong risk factor both for greater likelihood of developing psychosis as well as greater risk behaviors.

The research evidence suggests that cannabis poses a serious public health risk, and appropriate steps should be taken, that include large-scale information campaigns, and, perhaps, a similar sort of response that has been taken in the face of adverse effects of a pharmaceutical drugs.[1]

Cannabis use constitutes a clear risk factor for the development of schizophrenia. The data suggest that were cannabis consumption to be eliminated, around 10% of schizophrenias could be avoided. Perhaps the clearest conclusion of the research is that those vulnerable to psychosis are particularly affected by cannabis, with use of the drug doubling the risk.

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Functional relevance and activity-dependent regulation of neurogenesis in the adult brain

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Three out of 15 presentations at this conference mentioned adult neurogenesis in their title, two of them (including this one) specifically dealt with the topic, one additional lecture reviewed relevant aspects of the literature on adult neurogenesis. This simple observation highlights how the finding of "new neurons in the adult brain" has began to change psychiatry. At clinically oriented conferences a cell biological topic attracts considerable attention. Some of the expectations are not correct, however. Adult neurogenesis does not provide a means of regeneration, for example. Rather adult neurogenesis itself seems to be susceptible to the (elusive) mechanisms of psychiatric disease. But a few increasingly specific, albeit still highly controversial hypotheses attempt to explain diseases like major depression and schizophrenia by failing or altered adult neurogenesis.[1-4] The still greater relevance, however, might arise from the fact that adult neurogenesis plays a central role for plasticity of the hippocampus, one of the only two regions in the adult brain that produces new neurons lifelong, and thus influence how the brain can deal with pathology.

ADULT NEUROGENESIS IS NEURONAL DEVELOPMENT IN THE ADULT BRAIN

Adult hippocampal neurogenesis produces new granule cells and does so in an activity-dependent way. Precursor cells that have glial properties produce new excitatory neurons in the dentate gyrus that make connections to area CA3, thereby strengthening the mossy fiber connection. Regulation occurs at the level of precursor cell proliferation and of selected survival and functional integration. For the selection process a critical time window exists. Neurons that have passed this recruitment period are likely to persist for very long times. In animals, the different stages of neuronal development can be investigated by means of immunohistochemistry with antibodies against numerous markers that are expressed in the course of neuronal development. Glial (e.g. GFAP), radial-glial (BLBP, Id1) and stem cell markers (Sox2, Nestin) characterize the initial precursor cell stages. Neuronally determined progenitor cells express Doublecortin (DCX), which remains expressed into early postmitotic stages, when cells extend their dendrites and axon. After about eight weeks (in rodents) the new cells have become functionally and by standards of marker expression indistinguishable from surrounding older granule cells.

MARKERS OF ADULT NEUROGENESIS ARE ROBUSTLY IN THE ADULT HUMAN HIPPPOCAMPUS

Doublecortin expression has also been found and characterized in the adult human hippocampus. DCX is not strictly specific to adult neurogenesis but the combination of DCX with other neurogenesis-related markers both sensitivity and specificity will increase, although the ultimate validity remains difficult to address in humans. The marker-based assessment offers important additional circumstantial evidence in a situation, where no method exists that would allow to study adult neurogenesis in humans directly. The method routinely employed in rodents, based on bromodeoxyuridine (BrdU) incorporation into the DNA of dividing cells and consecutive identification of labeled neurons, cannot be used in humans, because BrdU is not applied to humans any more. Thus the pivotal BrdU study, on which our knowledge about adult neurogenesis in humans rests, was done at a time, when BrdU was still used in humans for tumor staging purposes. The co-localization between DCX and neurogenesis markers known from rodents in the human brain revealed a picture that is very similar between the two species. There was also a decrease in neurogenesis-associated markers across the lifespan. Again, as in rodents, the decrease largely occurred in early periods of life, childhood and young adulthood, and remains rather stable, albeit very low, thereafter. Even in the oldest samples, up to 100 years of age, characteristic markers were identified.

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PHYSICAL AND COGNITIVE ACTIVITY HAVE ADDITIVE EFFECTS ON ADULT NEUROGENESIS

Cell proliferation in the hippocampus is robustly stimulated by physical activity.[5-6] Physical activity also prevented the age-related decrease in precursor cell proliferation early in life (of a rodent) but this increase did not translate into a net-production of new neurons.[7] Presumably, an appropriate additional stimulus was lacking that would recruit the new neurons. Exposure to an enriched environment and learning represent such stimuli. So the obvious experiment to do was a sequential challenge by physical activity and environmental enrichment. As in other studies before, exercise and enrichment increase adult neurogenesis. But in the sequential paradigm the two effects turned out to be additive.[8] This finding indicates that increasing the potential for neurogenesis by rather non-specific means to some degree determines how well specific presumably more specific (cognitive) stimuli can recruit neurons.

NEW NEURONS IMPROVE LEARNING OF REVERSAL TASKS

But what are these "more specific" stimuli? Or, with a slightly broader perspective, what are the specific functions of the new neurons? A large number of studies has now allowed to devise concrete hypotheses, what this function might be. These studies have used different strategies to suppress adult neurogenesis, most notably cytostatic drugs, irradiation and genetical ablation, and have applied various behavioral tests. But, obviously, the result can only be as good (and specific) as the question asked. Consequently, in studies applying very general parameters of "learning", results have been mixed at best. But based on theoretical considerations we developed concrete hypothesis that could first be tested in a computational model.[9] The idea is that new neurons act at a bottleneck situation in the network and allow to optimize the strength of the mossy fiber connection between dentate gyrus and CA3. The computational model suggested that new neurons are a more efficient way to prevent "catastrophic interference" in such network situation than the synaptic plasticity employed in other networks brainwide. The new neurons would allow to cope with novelty in situations of complexity arising in a familiar (e.g. learned) environment. This was tested in an animal model, in which neurogenesis was suppressed by means of a modern cytostatic drug.[10] The test consisted of a particular version of the Morris water maze, in which the mice learn to navigate to a hidden escape platform in a pool of water by using cues in the room and increasingly forming a mental representation of the room. Learning the task was not affected in mice with reduced neurogenesis. But when the platform was suddenly moved to a new position, mice without adult neurogenesis showed severe problems to adjust to the new situation. They persevered at the old position but eventually learned the new site again.

THE NEUROGENIC RESERVE HYPOTHESIS

From these results a comprehensive hypothesis can be derived that tries to explain what the benefits of adult neurogenesis over the life-course are. Activity and exposure to complex environments early in life maintains a greater level of precursor cell activity later, so that in addition to the experience made there is additional benefit from a "neurogenic reserve". Few experiences and low activity levels reduce the animals ability to cope with novelty and complexity later in life and, importantly, reduce the range of compensation that is available for the individual.[11] Here lies the importance and relevance of adult neurogenesis to both aging research and psychiatry.

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Brain circuits involved in antidepressant response

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The pathophysiology and treatment of major depression are still controversial issues. Theories based on abnormalities of monoaminergic neurotransmitters have dominated the scene for about 4 decades, mainly due to the fact that most antidepressant treatments enhance serotonergic and noradrenergic function.[1] The discovery that stress reduces synaptic contacts in the limbic system while antidepressant drugs increase the expression of genes related to synaptic plasticity, such as neurotrophic factors (particularly BDNF) and hippocampal neurogenesis led to propose a trophic action for antidepressant drugs.[1, 2] More recent views, however, have focused on the key role of certain cortical areas, such as the prefrontal cortex. Hence, deep brain stimulation of Broadman area 25, in the subgenual cingulate gyrus, was able to bring about a rapid and effective recovery in depressed patients refractory to antidepressant polipharmacy.[3] This opened new perspectives, suggesting that major depression may be associated to the improper function of one or several brain circuits.

Indeed, depressive symptoms include anhedonia, depressed mood, cognitive impairment, fear and anxiety, feelings of guilt and worthlessness, sleep disturbances as well as somatic changes such as tiredness and motor impairment, which suggests the involvement of neuronal networks controlling a variety of brain functions. Actually, some of these symptoms can be associated to the improper function of one or more brain areas/networks. Hence, anhedonia and a poor recollection of pleasant memories can be linked to a malfunction of the ventral striatum and the associated mesolimbic dopamine pathway. Fear and anxiety can be associated to a hyperactive amygdala whereas cognitive impairment can be linked to an improper function of certain cortical areas. Moreover, somatic and sleep disturbances can result from hypothalamic abnormalities and an improper function of thalamocortical networks.

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The brain is an extraordinary biological tool that integrates sensory information from the environment and combines it with a vast array of stored information to produce a single, yet extremely complex product: behavior. One of the crucial and still unresolved questions in Neuroscience is how behavior can emerge from the coordinated activity of billions of neurons distributed in many different brain areas. The prefrontal cortex (PFC) is a key cortical area exerting a top-down control of many brain networks. Automatic or stereotyped behaviors do not require its engagement of the prefrontal cortex (PFC). For instance, directing our attention to a spot where we hear a sudden noise is carried out by an innate connectivity between sensory and motor areas that does not involve the PFC. This type of behavior is carried out through "bottom-up" processing of sensory signals. In contrast, the PFC plays a key role in situations with a large number of degrees of freedom, i.e., when flexibility is required to behave in a novel, unexpected environment or when behavioral rules change.[4] The PFC receives sensory information from the external world, stored emotional and contextual information from limbic and temporal areas, and has a large number of intrinsic connections between different subregions of the PFC itself.

Interestingly, the PFC exerts a tight, top-down control of monoaminergic systems putatively involved in major depression. Anatomical and functional studies have revealed that 1) the PFC projects to these brainstem nuclei, and 2) that activity changes of PFC projection pyramidal neurons result in immediate changes of the activity of monoaminergic systems, often with complex patterns. Hence, the physiological stimulation of PFC can excite or inhibit serotonergic neurons of the dorsal raphe.[5, 6] Complex patterns of activity in response to PFC stimulation have also been reported for noradrenergic and dopaminergic neurons.[7-10] Thus, gene x environment alterations of PFC function can alter the activity of the ascending monoaminergic systems whereas antidepressant drugs can normalize their function through the blockade of the respective membrane transporters. On the other hand, the normalization of these reciprocal PFC-monoamine brain circuits can be achieved through the suppression/stimulation

of the activity of certain PFC areas, as observed with high-frequency stimulation of Broadman area 25.[3]

One key aspect in the required enhancement of monoaminergic function for depression treatment is the observation that antidepressant activate a physiological negative feed-back mechanism involving monoaminergic autoreceptors (5-HT_{1A} and 5-HT_{1B} in serotonergic neurons; α_2-adrenoceptrs in noradrenergic neurons).[11, 12] The acute excess of serotonin or noradrenaline concentration in the extracellular fluid induced by reuptake or MAO inhibition activates these autoreceptors, reducing neuronal activity and monoamine release. Thus, full effects of antidepressant drugs occur only after autoreceptor desensitization, a time-course consistent with the 2-3 weeks of treatment required to observe clinically meaningful effects. These observations led us to propose the use of autoreceptor antagonists as potential enhancers of the clinical action of antidepressant drugs. The non-selective 5-HT_{1A} (partial) antagonist pindolol has been used to accelerate and enhance the clinical effects of SSRIs.[13-15]

However, pindolol is a non-selective agent which also blocks ß-adrenoceptors. The development of 5-HT_{1A} antagonists selective for 5-HT_{1A} autoreceptors is hampered by their similar blockade of pre- and postsynaptic 5-HT_{1A} receptors, which clearly limits their usefulness since activation of postsynaptic 5-HT_{1A} receptors appears necessary for antidepressant effects of SRIs.[16] Thus, our more recent studies have focused on the use of interference RNA technologies (siRNA; small interference RNA) in order to selectively knockdown presynaptic autoreceptors while preserving postsynaptic 5-HT_{lA} receptor function. Pilot studies have revealed that the stereotaxic application of siRNA molecules directed towards 5-HT_{1A} receptors in the dorsal raphe markedly reduced 5-HT_{1A} receptor expression and function, and that this effect was associated with an antidepressant-like response in behavioural tests and with an enhancement of the increase of extracellular serotonin induced by the SSRI fluoxetine.[17] Work is in progress to selectively deliver siRNA molecules to serotonergic neurons via systemic routes.

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Hippocampus changes and remission: Relevance for Depression

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HIPPOCAMPAL INVOLVEMENT IN MAJOR DEPRESSION

There is credible evidence that the hippocampus (HC, Figure1) is part of a network that, when dysregulated, could contribute to a variety of depressive symptoms. Hyperactivity of the HPA axis and the resulting increase in glucocorticoid levels in the brain are associated with early stage reversible dendritic remodelling in the C1 and C3 pyramidal granule neurons, paralleled by reversible remodelling of synaptic terminal structures. As the HC provides negative modulation to the hypothalamus–pituitary–adrenal stress hormone axis through its projections to the hypothalamus, HC dysfunction may contribute to the sustained dysregulation of the stress response that is commonly observed in MDD. Prolonged stress and increased levels of glucocorticoids disrupt HC neurogenesis.[1, 2] High levels of glucocorticoids[3] or behavioral stress[4, 5] result in atrophy and retraction of the apical dendrites of HC pyramidal cells. A reduction in the amount of neuropil without frank cell loss has also been observed, a finding that appears consistent with observations from post-mortem studies of the HC in patients with MDD.[6] In structural MRI investigation smaller hippocampal volumes have been demonstrated in patients with MD compared to healthy comparison subjects.[7]

CLINICAL RELEVANCE OF SMALL HIPPOCAMPAL VOLUMES

Small HC volumes were apparent before the manifestation of clinical symptoms of MDD in at-risk adolescents, particularly in those who experienced high levels of adversity during childhood. Both early-life adversity and smaller HC volume were associated with a higher probability of depressive episodes during prospective follow-up.[8] Moreover, 23 daughters of mothers with a history of MDD had reduced HC volumes compared to 32 daughters of mothers with no history of psychopathology, indicating again that neuroanatomic anomalies may precede the onset of a depressive episode. In another recent study, adults at-risk for MDD had HC volumes that were not significantly different from those already affected with MDD, suggesting that small volumes may precede the onset of MDD and might render subjects more vulnerable to MDD.[9]

There are a number of studies reporting associations between HC volume and probability of achieving and sustaining a clinical remission.[10-15] There may be an iterative relation between HC volume and illness burden, with small HC volumes contributing to poor clinical outcome, which in turn may put further stress on the HC leading to structural changes that increase the likelihood of a poor clinical response. Whether such relations contribute to the development of illness chronicity remains to be determined.

THE EFFECTS OF EARLY CHILDHOOD STRESS ON HC VOLUMES

A recent meta-analysis based on 14250 participants demonstrated that early adverse life events confer significant risk of subsequent MDD.[16] Youth and adults exposed to early-life adversity appear to have small HC volumes[17]. Vythilingam and colleagues reported 18% smaller left HC volumes in patients with early life trauma and MDD compared to non-abused patients with MDD who did not differ from healthy controls.[18] Moreover, patients with MDD and childhood emotional neglect had smaller HC volumes compared to patients with MDD without emotional neglect.[19] In summary, there is evidence from studies of healthy subjects, patients with PTSD, and patients with MDD that early childhood stress is associated with small HC volumes. Whether variables such as the type of stress, the developmental period during which a child experiences the stress, or the chronicity and intensity of the stress can determine HC structure and function later in life needs further investigation.

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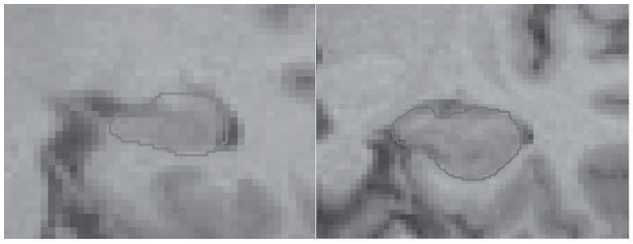

Figure 1 Example of hippocampus measured using magnetic resonance imaging. The hippocampus is smaller in patients with MDD compared to healthy controls

STRESS X GENE INTERACTIONS ON HC VOLUMES

Early life stress and variations in the serotonin transporter promotor polymorphism 5-HTTLPR may interact to predict development of MDD[20]. In a recent study, patients carrying the s-allele had smaller HC volumes when they had a history of emotional neglect compared to patients who had only one risk factor (environmental or genetic). Childhood stress further predicted HC alterations independent of genotype[21]. Significant interactions between BDNF genotype and early life stress were apparent in HC and amygdala volumes, heart rate and working memory[22]. The gene x environmental interaction seems to be particularly relevant in patients with MDD.

SUMMARY

Although the factors associated with small HC volumes are not fully described, there is evidence that genetic polymorphisms and early life stress may contribute to HC volumes prior to onset of illness. Furthermore, subjects at risk for MDD have reduced HC volumes before the clinical onset of illness. Repeated episodes of illness may further contribute to loss of HC volume, and speculatively, the changes in the HC may then contribute to treatment resistance or chronicity. Consistent with this are studies reporting that small HC volumes predict poor short and long term responsiveness to treatment.

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Prognosis and staging in bipolar disorder

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INTRODUCTION

Bipolar disorder is a chronic and recurrent illness which represents a major public health problem, and can lead to incomplete functional recovery, substance abuse, social/family disruptions and cognitive impairment, in addition to increased suicide risk and mortality. Several pharmacological[1-3] and psychological trials[4, 5] have shown that the earlier the intervention is implemented, the better the response to treatment.

Only recently specific proposals have been made to apply clinical staging to bipolar disorder. The staging model suggests a progression from prodromal (at-risk) to more severe and refractory presentations (Stage IV). A staging model implies a longitudinal appraisal of different aspects: clinical variables, functional and cognitive impairment, comorbidity, biomarkers and neuroanatomical changes. Staging models would allow clinicians to guide prognosis and therapy according to the different stages of the illness.[6-7]

BASIS FOR THE STAGING MODELS IN BIPOLAR DISORDER

Together with the fact that there is a poorer response to treatment when it is implemented later in the course of the illness, it has been reported that the risk of subsequent recurrence increases with each new episode. Post (1992) suggested that multiple episodes lead to permanent alterations in neuronal activity, which may be transduced at the level of a greater liability to relapse and the potentially poorer response to medication in patients with multiple episodes.[19]

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Biological markers and neuroanatomical changes

A staging model for bipolar disorder should differentiate the neurobiological correlates of the disorder's distinct stages.[6-8] Some brain alterations such as enlargement of the third and lateral ventricles, reduced gray matter in the hippocampus and cerebellum, reduced volumes in some areas of the prefrontal cortex and an increased size of the amygdala have been found in bipolar patients. It has been reported that such neuroanatomical changes tend to be more pronounced with repeated episodes and correlate with length of illness.[9] Anatomical changes could be a reflection of changes in neurotrophic factors and increased pro-apoptotic routes.[10] Among the neurotrophic factors, the BDNF, NT3, NT4, and GDNF were altered in bipolar disorder mood episodes. Furthermore, recent findings have showed that biochemical markers may change significantly from the early to late stages of bipolar disorder.[11, 12] The TNF-alpha and IL-6 cytokines were shown to be increased in early and late stage of bipolar disorder compared to controls, whereas BDNF levels and the levels of the anti-inflammatory cytokine IL-10 were decreased in the late but not early stage of bipolar disorder.[11] In addition, some parameters of oxidative stress, such as 3-nitrotyrosine, are also altered in the early stages of bipolar disorder; while others, such as glutathione transferase (GST) and glutathione reductase (GR), differ from controls only in those patients with multiple episodes in later stages of bipolar disorder.[12] Oxidative stress plays a key role in the induction of DNA damage, endothelial dysfunction and telomere shortening.[13] Taken together, these findings suggest that with multiple episodes and longer duration of illness, the neuroprotective mechanisms become less effective and the deleterious effects of these biological changes become more apparent. Early therapeutic interventions may play a neuroprotective role reducing neurobiological abnormalities linked to the illness.

Neuropsychology and functioning

Cognitive deficits seem to be related to the severity of the disease, being more evident in patients with a worse prior course of the illness. Significant functional impairment

Table 1 A potential clinical staging model for bipolar disorder from Berk et al.[8]

Clinical Stage	Definition	Potential interventions
0	Increased risk of severe mood disorder (e.g., family history, abuse, substance use) No specific symptoms currently	Mental health literacy Self help
1a	Mold or non-specific symptoms of mood disorder	Formal mental health literacy Family psychoeducation Substance abuse reduction Cognitive behavioural therapy
1b	Prodromal features: ultra high risk	1a plus therapy for episode: phase specific or mood stabilizer
2	First-episode threshold mood disorder	1b plus case management, vocational rehabilitation
3a	Recurrence of sub-threshold mood symptoms	2 plus emphasis on maintenance meds and psychosocial strategies for full remission
3b	First threshold relapse	2a plus relapse prevention strategies
3c	Multiple relapses	3b plus combination mood stabilizers
4	Persistent unremitting illness	3c plus clozapine and other tertiary therapies, social participation despite disability

Table 2 Clinical Staging in Bipolar Disorder from Kapczinski et al.[9]

Stage	Clinical features	Biomarkers	Cognition	Maintenance treatment	Prognosis
Latent	At-risk for developing BD, positive family history Mood or anxiety symptoms without criteria for threshold BD	Polymorphisms that confer susceptibility to BD	No impairment	↓ Exposure to pathogens	Good prognosis when protected from pathogens
I	Well defined periods of euthymia without overt psychiatric symptoms	↑ TNF ά ↑ 3-Nytrotyrosine	No impairment	Mood stabilizer monotherapy; psychoeducation	Good prognosis with careful prophylaxis
II	Symptoms in inter-episodic periods related to comorbidities	↑ TNF ά ↓ BDNF ↑ 3-Nytrotyrosine	Transient impairment	Combined treatment (pharmacotherapy + psychotherapy; focus on the treatment of comorbidities)	Prognosis depends on how well comorbidities can be managed. Worse than stage I
III	Marked impairment in cognition and functioning	Morphometric changes in brain may be present ↑ TNF ά ↓ BDNF ↑ 3-Nytrotyrosine	Severe cognitive impairment associated with functioning impairment (unable to work or very impaired performance)	Complex regimens usually required; consider innovative strategies	Reserved prognosis; rescue therapy needed
IV	Unable to live autonomously due to cognitive and functional impairment	Ventricular enlargement and/ or white matter hyperintensities ↑ TNF ά ↓ BDNF ↑ Glutathione reductase and transferase ↑ 3-Nytrotyrosine	Cognitive impairment prevents patients from living independently	Palliative; daycare center	Poor prognosis

Legend: BD: Bipolar Disorder; TNF-α: Tumor Necrosis Factor-alpha; BDNF: Brain Derived Neurotrophic Factor.

has been found in bipolar patients even in remission.[15] A recent study showed that cognitive deficits were predictive of worse functional outcome at 4-year follow-up (Bonnín et al., 2010). Neurocognitive symptoms can have a clinical value as they can lead to the acquisition of more information about the brain areas and functions involved in the pathogenesis of the disease, and they might also be useful as potential endophenotypes.

Subsyndromal symptoms and comorbidity

Other aspects that have also been related to a poor outcome are subsyndromal symptoms and psychiatric comorbidity. Particularly, subsyndromal depressive symptoms have been consistently associated with poor cognitive and occupational functioning.[15] Psychiatric and medical comorbidity is common in bipolar disorders, being substance-use disorders and anxiety disorders the most frequent. Comorbidity can have a negative impact on the illness prognosis, it could be reduced by an early diagnosis and appropriate treatment; which is not always the case in bipolar disorders.

SUGGESTED STAGING MODELS FOR BIPOLAR DISORDER

Clinical staging was developed by the McGorry group (2006) for psychotic and severe mood disorders.[17] Different staging models have been proposed in bipolar disorder although they need to be better operationalized and validated by empirical research.[8, 7] A staging model may be constructed in parallel to therapeutic algorithms, linking stage to specific treatment needs and possible therapeutic options.

Berk et al.[8] has suggested a model (Table 1) adapted from McGorry et al.[17] In contrast to the early phases in which the focus would be on early intervention and neuroprotective strategies, in the later stages the emphasis would be more rehabilitative treatments dealing with the disabilities of the illness. It implies that early intervention is the critical ingredient if the promise of neuroprotection is to be actualised.

The proposal by Kapczinski et al.[12] implies a longitudinal appraisal of clinical variables as well as assessment of comorbidity, functioning, neurocognition and biomarkers in the inter-episodic period (Table 2).[7] It suggests a progression from at-risk period to more severe and refractory presentations engendered by cumulative exposure to acute episodes, substance abuse, life stress and inherited vulnerability. The authors have also made some therapeutic and prognostic suggestions linked to the illness stage. Staging facilitates understanding the mechanisms underlying progression of the disorder, assists in treatment planning and prognosis, and underscores the imperative for early intervention. This understanding additionally identifies the first illness episode as a critical target for early intervention, creating the hope of being able to prevent some of the consequences of the illness).[10]

Based on the clinical and functioning factors proposed by Kapczinski et al.[7] Reinares et al.[18] carried out a post-hoc analysis of a controlled-randomized study on caregiver psychoeducation. For the purpose of this study, the bipolar sample was divided into two groups (Stage I, and Stages II, III and IV taken together). Psychoeducation for caregivers of bipolar patients on Stage I showed improvement in long-term outcome regarding time to recurrence, highlighting the importance of early intervention as some treatments can be especially useful in patients with lower severity.

CONCLUSIONS

Although different staging models have been proposed in bipolar disorder they need to be better operationalized and validated by empirical research. Early intervention in bipolar disorders depends on the ability to identify individuals at high risk for developing the illness. A model of staging might not only help to predict response to treatment but also general outcome measures.

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Deep Brain Stimulation for Depression

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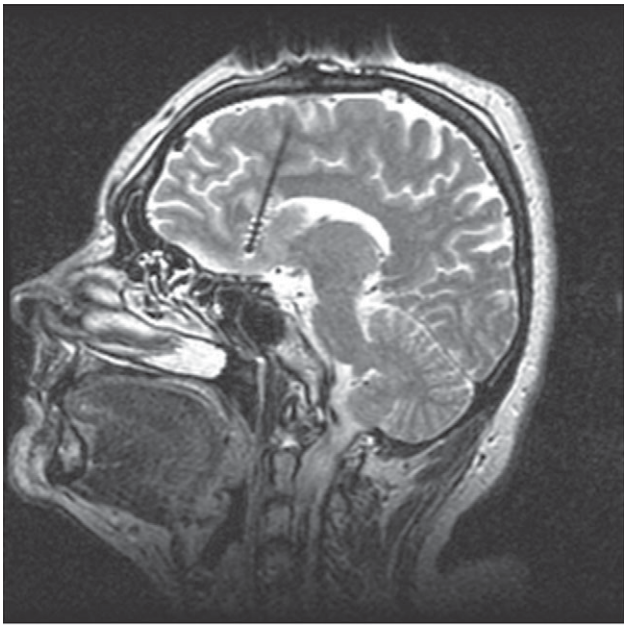
The electric modulation of dysfunctional circuits has transformed the treatment of Parkinson's disease. Approximately 70,000 patients worldwide with Parkinson's disease have been treated with this form of therapy called Deep Brain Stimulation (DBS). This type of surgery involves implanting of electrodes in circuits that control motor function and the application of chronic electric stimulation delivered by a fully implanted pulse generating device or "pacemaker" to block pathological activity, or to drive function across the circuits. With the vast experience and the record of safety and efficacy of DBS to treat Parkinson's disease, the possibility of intervening in other circuits particularly circuits involved in psychiatric disease, has become a reality.

For those patients in whom standard drug therapy, psychiatric therapy and electroconvulsive therapy have had sufficient trials and who continue to be disabled by depression, new alternatives are required. Among therapies that have been tried are vagus nerve stimulation and transcranial magnetic stimulation. Our group has been interested in the possibility of using DBS to treat major depression.[1-3] The work of Helen Mayberg has implicated the subgenual cingulate gyrus as a key area of dysfunction in patients with severe depression and indeed successful depression therapies are associated with modulation of the activity in this area.

We have directly targeted the subgenual cingulate gyrus with DBS electrodes in 38 patients to date in Toronto (Figure 1). Our initial results in the first four patients showed approximately that 2/3 could achieve a response as defined by a >50% reduction in the Hamilton 17 Depression Rating Scale.[1] A more recent analysis in 20 patients that one year suggests that 55 – 60 % of 20 patients can achieve this level of response[2] and Figure 2.



Sagittal MRI showing position of DBS electrode in Subcallosal cingulate gyrus

Figure 1 DBS electrodes implanted in the subgenual cingulate area in a patient with depression

Our imaging studies have shown that introduction of electrodes and current stimulation in this area is associated with striking changes, not only in the subgenual cingulate gyrus with a turning-down of hyperactivity, but also increases in frontal and distant cingular areas that were previously metabolically altered.

The surgery has a very good record of safety with no patients suffering any major neurologic deficits or permanent deficits of any kind related to the surgical intervention to date. Challenges for the future will be to try to improve the efficacy of the surgery and to try to identify biological markers of those patients that may be more likely to respond

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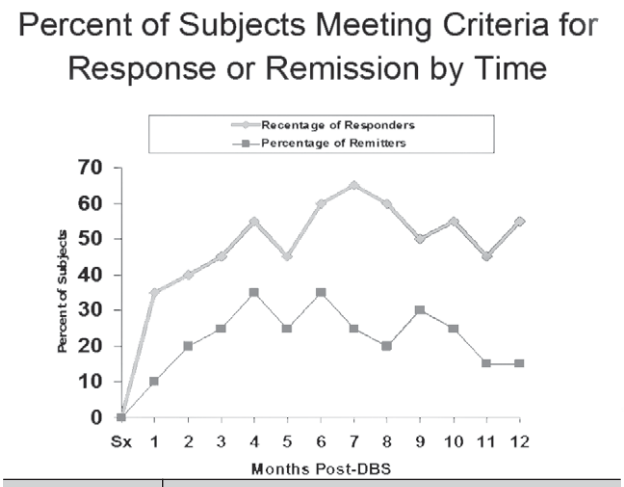

Figure 2 Response after 12 months of DBS in 20 patients. A response is defined as > 50% reduction in HAMD-17 Score

than others. The application of DBS within this target is not unique and indeed there may be other targets that could also be amenable. Similarly, the use of DBS could expand to other psychiatric illnesses, e.g. Tourette's or Obsessive Compulsive Disorder (OCD). Clinical studies which involve double-blinded assessment of stimulation on *vs* off will be required to establish the safety and efficacy of DBS in depression and in other psychiatric disorders. Finally, we are developing animal models of DBS and have shown so far that stimulation but not lesioning of the rodent homologue of the subgenual cingulate gyrus produces an antidepressant-like effect[3] and that chronic electrical stimulation at parameters that are analogous to those used in human can drive neurogenesis in the rodent hippocampus[4], an observation that has implication in the mechanism of action of antidepressant therapies.

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Contribution of adult hippocampal neurogenesis to depression and response to antidepressants

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ABSTRACT

The neurogenesis hypothesis of depression was originally formed when it was demonstrated that stress impacts levels of adult neurogenesis in the hippocampus. Since then much work established that newborn neurons in the dentate gyrus are indeed required for mediating some of the beneficial effects of antidepressant treatment. Recent studies combining behavioral, molecular and electrophysiological approaches have demonstrated a potential role for young neurons in regulating circuitry in the brain that underlies mood.

INTRODUCTION

Elucidating the neurobiological basis of depression and determination of improved treatments is one of the foremost challenges for modern psychiatry. Mood disorders impact 7% of the world's population and severe forms of depression affect 2–5% of the US population. The heterogeneous nature of depression, which includes a multitude of diverse symptoms, suggests a dysfunction of multiple distinct brain regions. Consistent with this idea, human imaging and post-mortem studies have implicated areas including the prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus. Together, these brain regions operate a series of highly interacting circuits involved in depression. The development of improved treatments will rely on identification of cellular mechanisms within these brain regions.[1]

Over the last decade, it has become accepted that new neurons are produced throughout life in two locations, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. The neurons born in the SVZ migrate through the rostral migratory stream into the olfactory bulb and become interneurons, while those born in the SGZ migrate into the granular layer of the DG and eventually become mature granule neurons. The process of adult neurogenesis involves several steps including the proliferation and fate specification of neural progenitors, neuronal migration, neuronal maturation, and synaptic integration of the young neurons into the existing neuronal circuitry. Various well-established histological markers can be used to mark or identify the cells at distinct points during this process, and the electrophysiological membrane properties of cells throughout the steps are well understood.[2]

Much work has now suggested an important role for the hippocampus in the etiology of depression and mediation of the antidepressant response. Specifically, adult neurogenesis in the dentate gyrus has gained considerable traction as a cellular substrate underlying the treatment of depression. The neurogenesis hypothesis of depression postulates that a decrease in the production of newborn granule cells in the dentate gyrus is related to the pathophysiology of depression while enhanced hippocampal neurogenesis is required for the beneficial effects of antidepressant treatment. Current evidence suggests that this hypothesis is at least partially true. While decreasing neurogenesis alone is not sufficient to drive a depression-like phenotype, there is a requirement for adult neurogenesis in mediating some of the beneficial effects of antidepressants.[3]

STRESS, ANTIDEPRESSANTS AND THE HIPPOCAMPUS

Several classic studies provided a foundation for the idea that the hippocampus is involved in the regulation of mood by demonstrating the vulnerability of the hippocampus to various hormones induced by stressful experiences. As for adult DG neurogenesis, there is also much evidence for regulation by stress. Exposure to multiple different forms of chronic stress can suppress adult neurogenesis. From these results demonstrating effects of stress on adult neurogenesis in the DG arose the question whether antidepressant

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treatment could possibly reverse or mitigate these effects. In other words, would antidepressant treatment result in a change in adult DG neurogenesis? In line with this hypothesis, chronic antidepressant treatment indeed increases adult DG neurogenesis as measured by uptake of BrdU in the SGZ.[3, 4] Importantly, this increase is seen only in the SGZ and not in the SVZ, suggesting a specificity of the antidepressants to regulate hippocampal neurogenesis. This result holds true for multiple classes of antidepressants including SSRIs, monoamine oxidase inhibitors (MAOIs), tricyclics (TCAs), and norepinephrine reuptake inhibitors (NRIs). The proneurogenic effects of antidepressants are only seen with chronic, and not with acute, treatment, mirroring the time course for therapeutic action of antidepressants in humans. In addition to increasing proliferation in the adult dentate gyrus, chronic fluoxetine accelerates the maturation of young neurons by increasing dendritic arborization.[5] Administration of various antidepressants can also reverse the effect of stress on neurogenesis. Taken together, these results hint at an important role for adult neurogenesis in mediating the antidepressant response. However, it remained unclear whether increased neurogenesis is required for mediating the behavioral effects of antidepressant treatment.

REQUIREMENT FOR NEUROGENESIS IN MEDIATING THE ANTIDEPRESSANT RESPONSE

The next set of critical experiments ablated adult neurogenesis in the DG and tested if the subjects were still responsive to antidepressants. The first attempt to address this problem used focal X-irradiation of the hippocampus (Santarelli *et al.*, 2003). Low doses of x-rays to the hippocampus, while sparing the rest of the body and most of the brain with a lead shield, resulted in a persistent 85% reduction in BrdU incorporation into the SGZ. To test the importance of adult DG neurogenesis in the antidepressant response, irradiated and sham-irradiated mice were then treated chronically with antidepressants (either the SSRI fluoxetine or the TCA imipramine) and subjected to behavioral testing. Sham-irradiated mice chronically treated with antidepressants display a decreased latency to enter the center and take a bite of a food pellet in the Novelty Suppressed Feeding (NSF) test. Critically, mice that have been exposed to focal X-irradiation of the hippocampus, resulting in a loss of adult hippocampal neurogenesis, do not show this response to either fluoxetine or imipramine. Further controls demonstrated that mice exposed to X-irradiation of the SVZ or cerebellum responded normally to the antidepressants. The results in the NSF test are of particular significance since mice only show responsiveness to antidepressants in this test after chronic treatment, unlike other tests such as the forced swim or tail suspension where acute treatment is sufficient. These results suggested a necessary role for adult DG neurogenesis in mediating the antidepressant response.

POTENTIAL MECHANISMS UNDERLYING THE REQUIREMENT OF NEUROGENESIS IN MEDIATING THE ANTIDEPRESSANT RESPONSE

While some work has been done that has laid a foundation for the understanding of how antidepressants increase neurogenesis, much less is known about why the increase in neurogenesis is required for the antidepressant response. One potential mechanism would be negative feedback regulation of the HPA axis and the stress response. A recent study demonstrated that in mice with ablation of neurogenesis there was an increased HPA axis response to an acute stress.[6] Since stimulation of the subiculum, CA3 or DG can yield an inhibitory effect on the HPA axis through well-described circuitry, it is possible that young neurons may contribute to hippocampal-dependent negative feedback of the HPA axis. Future studies will need to use genetic methods to more direcly determine if young neurons impact the negative feedback circuit to the HPA axis.

Another hypothesis, which is not mutually exclusive, that has gained traction is whether neurogenesis in different areas of the SGZ play distinct roles in the regulation of mood. Due to participation in different circuitry, it has been suggested that the dorsal and ventral hippocampus may be distinct structures. In the hippocampus, the dorsal dentate gyrus receives inputs from lateral and caudomedial entorhinal cortex and medially located cells of the medial septal nucleus.. Outputs of the dorsal hippocampus are to the mammillary complex, dorsal lateral septum and lateral entorhinal cortex. In contrast ventral dentate gyrus receives inputs from the rostromedial entorhinal cortex and laterally located cells of the medial septal nucleus while ventral hippocampus outputs are to the prefrontal cortex, amygdala, nucleus accumbens, hypothalamus, medial entorhinal cortex, bed nucleus of stria terminalis and rostral and ventral lateral septum.[1] This different circuitry may suggest that the dorsal hippocampus is more important for learning and memory while the ventral hippocampus is more involved in emotion. Some lesion studies have further supported this hypothesis. Therefore, neurogenesis along the dorsal-ventral axis may play distinct roles in learning and mood. Genetic models and ablation techniques that are restricted to dorsal or ventral SGZ need to be developed in order to test this hypothesis.

Much work has also been done to advance the understanding of the synaptic and physiological properties of the young neurons and these unique properties allow for distinguishing young neurons from their mature granule neuron counterparts. Of particular relevance to antidepressant treatment is a form of long-term potentiation derived from a weak stimulation paradigm in the absence of GABA blockers (ACSF-LTP) that is sensitive to manipulations that block hippocampal neurogenesis. After chronic, but not acute, fluoxetine treatment, ACSF-LTP is enhanced in sham animals and completely blocked in animals subjected to

X-irradiation, suggesting an effect of fluoxetine on the electrophysiological properties of young neurons that have integrated into the hippocampal circuitry.[5]

Relatively little work has addressed the function of young neurons in an intact hippocampal circuit in vivo. In hippocampal slice work, fluoxetine treatment enhances activity of the dentate gyrus relative to CA1 in a neurogenesis-dependent manner,[7] suggesting a network effect of the young neurons. Furthermore, one very recent study used multiple methods to ablate adult neurogenesis in vivo and assessed hippocampal activity.[8] In anesthetized mice after X-irradiation or thymidine kinase mediated pharmacogenetic ablation, perforant-path evoked responses were reduced in magnitude. In striking contrast, there was an increase in the amplitude of spontaneous gamma-frequency bursts in the dentate gyrus and hilus, as well as increased synchronization of dentate neuron firing to these bursts. This striking result may suggest that the young neurons can serve to modulate activity in the much larger population of mature granule cells rather than acting solely as independent encoding units. It remains to be tested whether antidepressant treatment may modulate hippocampal circuitry by enhancing the effect of the young neurons on the mature granule neurons.

MODELS OF DEPRESSION

There are multiple chronic stress paradigms that can be used to induce a state of anxiety and depression in animals that render them responsive to antidepressant treatment, such as unpredictable chronic mild stress (UCMS). UCMS has been effectively used to investigate the requirement for neurogenesis in antidepressant treatment.[9] In this study, UCMS effectively decreased proliferation in the dentate gyrus and induced a state of anxiety/depression as measured by the NSF test and the splash test of grooming. Fluoxetine and imipramine effectively reversed the neurogenesis and behavior phenotypes in sham but not irradiated mice. Potential negatives of the UCMS paradigm is that it is notoriously labor-intensive and can be difficult to establish.

A second useful paradigm for inducing anxiety/depression-like states in animals is chronic corticosterone treatment. Long-term exposure to exogenous corticosterone has been successfully used to induce an anxiety/depression-like changes in behavior, neurochemistry and, importantly, proliferation in the adult dentate gyrus in mice.[10] Furthermore, these effects are reversible by antidepressant treatment. Importantly, using X-irradiation, some but not all of the effects of antidepressant treatment were neurogenesis-dependent. More specifically, fluoxetine-induced reversal of anxiety/depression measures in the NSF test is neurogenesis-dependent while reversal in the Open Field is neurogenesis-independent. Taken together, chronic corticosterone is also a useful paradigm for studying the effects of antidepressants. Compared to UCMS, chronic corticosterone is much less labor intensive (the corticosterone is placed in the animals' drinking water). Potential negatives of the chronic corticosterone paradigm is that it may not be useful for studying the role of the HPA axis in the neurogenesis-mediated effects of antidepressants because the chronic exogenous corticosterone leads to blunting of the HPA axis.

REVISITING THE NEUROGENESIS HYPOTHESIS OF DEPRESSION

The neurogenesis hypothesis of depression postulated that a decrease in the production of newborn granule cells in the dentate gyrus is related to the pathophysiology of depression while enhanced hippocampal neurogenesis is required for the beneficial effects of antidepressant treatment. With few exceptions, ablation of hippocampal neurogenesis alone is not sufficient to induce a phenotype reminiscent of anxiety or depression. It will be critical for future work to determine how the addition of new units to the dentate is involved in mediating the effects of antidepressants.

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The Human Mind, Psychotherapy and EMDR*

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EMDR (Eye Movement, Desensitization, and Reprocessing) is a psychotherapeutic approach that has been proven to be effective for the treatment of trauma in approximately 20 controlled studies, including comparisons with drugs[1] and other treatments.[2] Based on this evidence, EMDR has been recommended as first line treatment in the Clinical Practice Guidelines of the many organizations, including the American Psychiatric Association.[3]

During the past decade, the rapid effects of treatment with EMDR have provided neurophysiologists and clinical investigators a « window to the inside of the brain» as is seen in several neurobiological studies that have demonstrated pre- and post changes, supporting the efficacy of EMDR.[4-7] One of these studies[8] revealed that the hippocampal volume deficit in patients with posttraumatic stress disorder (PTSD) compared with normal controls decreased with EMDR treatment. Specifically, it was demonstrated that eight memory processing sessions with EMDR correlated with a 6% increase in the hippocampal volume of these participants, with effects that were sustained in a follow-up at one year. In a significant way, one of the patients with PTSD who had left hippocampal atrophy at the onset of the study responded to treatment with EMDR, presenting 10% growth in the right hippocampus and 12% in the left one. This evolution is very promising and indicates the need for future studies to investigate not only the underlying mechanisms of the EMDR treatment but also those regarding cerebral neuroplasticity in general. EMDR has a special advantage in this type of investigations, in which it can be applied on consecutive days. Compared to the Trauma-focused Cognitive-Behavioral Therapy that needs one to two hours of daily homework, the effects of EMDR are achieved only within the session. In this way, treatment with EMDR can be completed in days rather than in months.

EMDR is characterized by a combination of standardized procedures that include repeated use of bilateral stimulation (e.g.: eye movements, hand tapping and auditory tones), eye movements being the ones that have received the greatest attention by the memory investigators.[9] Twelve randomized studies that have investigated the underlying mechanisms, such as orientation response and working memory, have found that eye movements facilitate memory recovery, mental imagery vividness and attentional flexibility, and reduce negative emotions.[10] All of them can be identified during the processing with EMDR therapy.

EMDR is guided by the Adaptive Information Processing (AIP) model that postulates that, except for organic injury or deficits, dysfunctional perceptions, responses, attitudes, self-concept and personality traits are all non-processed memory symptoms.[9] In accordance with this model, a high level of disturbance during an event makes the information processing system fail to adequately assimilate the experiences in the normal global neural networks. Consequently, these unprocessed memories contained emotions, thoughts, sensations and behavioral responses that were coded when the event occurred. The primary objective of treatment with EMDR is aimed at dysfunctional memories that are triggered by daily life circumstances of the subject, and are transmuted into functional memories, taking advantage of the natural neural process of memory consolidation.[9,11]

It has been proposed that EMDR is related with the same process that occurs in the REM phase (rapid eye movements) of sleep.[12] These reprocessed memories would then be stored functionally and successfully integrated with similar experiences. The final outcome is assimilation of the new information in the existing memory structures, in semantic memory more than the implicit or episodic memory, which allows the individuals to respond adaptively to daily life. Contrary to the cognitive-behavioral models of information processing, AIP/EMDR guides an associative memory process by which clusters of memory are simultaneously processed, with generalization to both present and future events. The

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EMDR processing differs from exposure therapies, that function by means of extinction. The latter is «... conceptualized as the development of an inhibitory association specific to a context which, in contrast to the acquisition of fear, is not easily generalized to new contexts.»[13] It is argued, rather, that EMDR involves assimilation and reconsolidation processes by which the original memory is altered and restored.[11]

EMDR is an 8-phase approach that treats the condition by (a) accessing and processing the memories related with the dysfunction, (b) identifying and focalizing the current problems that triggered the problem and (c) incorporating memory templates for appropriate future actions, including those aimed at evolutive deficits, useful skills and necessary behaviors for optimum functioning. A systematic evaluation has demonstrated that a wide variety of diagnoses are caused or exacerbated by unprocessed memories.[9] Thus, the EMDR tries to directly address the stored memory networks that underlie both psychological problems and mental health.

During the EMDR treatment sessions, the rapid changes in cognition, emotions and somatic response reflect consistent patterns of associated internal memory networks. In a typical EMDR session, the clinician will routinely observe that each new set of bilateral stimulation is accompanied by rapid appearance and alteration of emotions, insights, sensations and memories, together with a concurrent reduction of subjective disturbance. The patients not only experience a reduction of their emotional difficulties (and other clearer symptoms, but also, and more important, an extensive psychological reorganization of the affective regulation and personality traits.[14,16] The final result is not only the elimination of the clinical diagnosis but also a positive change in interpersonal dynamics.

As a comprehensive therapeutic approach, EMDR has been successfully applied to an extensive range of clinical problems, including some generally considered to be untreatable or very difficult to treat. For example, it has recently been reported that 80% of the patients in a group of 5 different evaluations obtained substantial relief or elimination of pain in the phantom limb after processing of the key memories, an improvement that was sustained at one year of follow-up.[15] EMDR has also been used in combination with a program of standard cognitive-behavior therapy (CBT) to treat a subgroup of sexual child molesters who had also been victimized when they were children. Specifically, Ricci, Clayton, & Shapiro (2006) showed that adding six sessions of the memory processing with EMDR to the standard CBT meant the elimination of the denial of the perpetrator and of the deviated arousal, when compared with the absence of change in these aspects with the CBT condition alone.[16] The perpetrators were capable of accepting adequate responsibility for their acts, admitting the harm they had caused their own victims, and to discontinue becoming aroused with children, this aspect being measured with the plethysmograph. The effects of the treatment were sustained at one-year of follow-up. Finally, positive effects of the EMDR treatment have been reported with three psychotic patients with Cotard Syndrome, Delusional Dysmorphophobia and Schizophrenia, who were symptom (and medication) free at three years post-treatment.[17] These findings have important clinical implications and need future rigorous studies.

The mentioned results provide strong support for the view that EMDR processing eliminates the emotions, cognitions and physical sensations associated to dysfunctional memories and in this way, changes the experience of the subject in the present. While the cognitive-behavioral conceptualization considers the dysfunctional behaviors and beliefs as the causes of the condition, the EMDR/AIP simply considers them as symptoms, the cause being the dysfunctionally stored memories that contain the perceptions that were coded during the original disturbing event. Thus, adequate memory processing serves to eliminate depression, whether it has been caused by critical events consistent with the diagnosis of PTSD[1] or by other types that are more omnipresent in the disturbing life experiences, such as family discussions, divorce and humiliation.[18] Furthermore, the processing of the key memories has been shown to normalize the «attachment style» in both adults and in children,[19] with a concomitant alteration of the automatic behavioral responses that indicate the interruption of the intergenerational transfer of the dysfunction.

Although EMDR reduces the clear symptoms of different clinical diagnoses, its most important goal is to change the underlying conditions that generate the dysfunctional response in the present and to lead the patient to a stronger mental health condition. This is achieved by focusing the conceptualization of the cases and the treatment on the memory and information processing networks. The resulting rapid and consistent effects of EMDR treatment allow the investigators to discriminate between the contributions regarding the genetic-natural and experiential factors. This also provides a tool for the evaluation of the neurophysiologic concomitant factors of the condition, treatment, recovery and health.

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Fundación Lilly
Distinguished Career Award
Neuroscience/Psychiatry
2010

La profesora Carmen Leal recibe el Premio Fundación Lilly a una Carrera Distinguida por su contribución a la investigación de las enfermedades mentales en España.

Carmen Leal Cercós, catedrática de Psiquiatría y jefe de Servicio de Psiquiatría del Hospital Clínico Universitario de Valencia, a propuesta de la Sociedad Española de Psiquiatría, ha recibido el Premio Fundación Lilly a una Carrera Distinguida. El premio le fue entregado en el marco del 17º Simposio Científico "Desde la neurobiología a la nosología de las enfermedades mentales", ante más de 450 compañeros asistentes, por su destacada contribución al desarrollo de la psiquiatría moderna en España y al conocimiento de patologías de gran impacto social como la esquizofrenia o el trastorno bipolar.

El Premio Fundación Lilly a una Carrera Distinguida, ya en su quinta edición, pretende reconocer trayectorias científicas ejemplares como la de la profesora Carmen Leal.

El doctor José Antonio Gutiérrez, director de la Fundación Lilly, destacó las aportaciones de Carmen Leal al mundo de la neurociencia y su total entrega a los pacientes, y puso de relieve su dedicación al estudio de los factores de riesgo prevalentes que afectan a la salud mental y a dilucidar la forma más eficaz de abordar los trastornos psiquiátricos.

Por su parte, la profesora Leal, manifestó su satisfacción y agradecimiento por este reconocimiento, otorgado por sus compañeros.

CONOCER LA MENTE Y AL PACIENTE

Licenciada en Medicina y Cirugía por la Universidad de Valencia y Premio Extraordinario de Doctorado por su tesis sobre "Trastornos psiquiátricos en los traumatismos cráneo-encefálicos". Realizó estancias en las áreas de psiquiatría de los hospitales de Murcia, Vancluse y Distrito XIII (París) y en diferentes hospitales y servicios de Salud Mental en Nueva York.

Desde el año 2005 es miembro honorario de la Asociación Mundial de Psiquiatría, y recientemente, nombrada miembro de la Real Academia de Medicina de la Comunidad Valenciana.

Además de sus actividades asistenciales, la profesora Leal cuenta con una dilatada experiencia docente y ha sido decana de la Facultad de Medicina de Valencia y vicedecana de la Facultad de Medicina de Cádiz. Directora de 16 tesis doctorales, ha participado en los programas educativos de esquizofrenia y formación en psiquiatría de la Asociación Mundial de Psiquiatría. Asimismo, es miembro del Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), y ha participado en múltiples proyectos de investigación.

Es autora de 102 artículos en revistas científicas españolas, 20 en publicaciones extranjeras con alto índice de impacto y numerosas ponencias en congresos nacionales e internacionales.

Carmen Leal es miembro honorario de la Asociación Mundial de Psiquiatría y ha presidido sociedades científicas tan prestigiosas como la Sociedad Española de Psiquiatría Biológica (SEPB), la Sociedad Española de Psiquiatría (SEP) y la Fundación Española de Psiquiatría y Salud Mental (FEPSM).

En las ediciones previas, el Premio Fundación Lilly a una Carrera Distinguida fue otorgado, a los profesores Alfonso Castro Beiras en la especialidad de Cardiología; Mariano Barbacid, en la de Oncología; Manuel Serrano Ríos, en la de Diabetes; y José Elguero en la de Química Médica.