# *Psychotropic medication, psychiatric disorders, and higher brain functions*

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*Conventional psychiatric diagnosis is founded on symptom description; this then governs the choice of psychotropic medication. This purely descriptive approach resembles a description of diphtheria from the premicrobiology era. Based on current advances in basic and clinical neuroscience, we propose inserting an intermediate level of analysis between psychiatric symptoms and pharmacologic modes of action. Paradigm 1 is to analyze psychiatric symptoms in terms of which higher brain function(s) is (are) abnormal, ie, symptoms should be analyzed as higher brain dysfunction: a case study in obsessive-compulsive disorder reveals pointers in four common symptoms to the higher functions of working memory, emotional overlay, absence of voluntary control, and the ability to evaluate personal mental phenomena. Paradigm 2 is to view psychotropic drugs as modifying normal higher brain functions, rather than merely treating symptoms, which they do only secondarily: thus depression may respond to agents that act on related aspects of mental life derived from higher brain functions, eg, the ability to enhance bonding. We advocate a strategy in which psychiatric illness is progressively reclassified through knowledge in clinical neuroscience and treatment targets are revised accordingly.*

The last decades have been a time of active research and discovery in the fields of psychotropic medication, the identification and classification of psychiatric disorders, and the physiology of higher brain functions, such as emotions, memory, or consciousness. A very impressive effort has been made at the international level to reach a consensus for making reliable psychiatric diagnoses, which represents a huge progress. In this article, we explore the nature of the relationship between psychopharmacology, psychiatric symptomatology, and higher brain functions.

## Psychotropic medication

Psychotropic drugs, such as chlorpromazine, imipramine, or diazepam, were developed by astute researchers, at a time when several neurotransmitters had not yet been discovered and when little was known about the physiology of neurotransmitters. The modes of action of these first psychotropic drugs were discovered years after they had been successfully used clinically, and are still undergoing further study. A psychotropic drug can be described according to the way in which it influences receptors, transporters, and enzymes, ie, the cellular sites of its pharmacological actions. These drugs can be selective to a greater or lesser extent. There are the so-called "dirty" drugs that influence a large number of brain systems. Chlorpromazine is an example of such a nonselective psychotropic drug as it acts as an antagonist of many dopaminergic, adrenergic, serotonergic, cholinergic, and histaminergic receptors and has a membrane-stabilizing action. Clozapine is another example of a drug that acts on many cell-membrane receptors or transporters; it is difficult to explain why blocking all

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these systems with clozapine has led to the best results yet seen in the treatment of schizophrenia. Prescribing only clozapine to a patient cannot be said to be monotherapy, because more than 10 different modes of action may be involved in its clinical effects. On the other hand, there are psychotropic drugs with a more selective mode of action, for example, the serotonin (5-HT) transporter (5-HTT) blockers (selective serotonin reuptake inhibitors [SSRIs]). When these drugs are administered, however, physiological systems subserving many brain functions are influenced, as is apparent from the list of their beneficial and adverse effects. Selectivity is also relative if one considers the number of intracellular changes that are induced following drug administration, and the number of different neuronal circuits that are influenced. For example, an agonist of the $M_1$ muscarinic receptor, a drug that may be useful in dementia of the Alzheimer type, has a selective mode of action. However, this selectivity is only at the cell membrane receptor level; stimulation of this cell membrane receptor leads, through secondary and tertiary intracellular messengers,[1] to the expression of more than 100 proteins 60 minutes after administration (Nitsch RM, unpublished data). In the future, clinicians will be able to explain to their patients that psychotropic drugs modify protein synthesis in the brain (demanding patients may ask for the exact list of the proteins that are modified by their medication!). Moreover, because most drugs diffuse throughout the brain and are not target-selective, they probably exert their effects mainly via an influence on volume transmission of several neurotransmitters rather than via the more classic wired transmission.

As already mentioned, the present approach in psychopharmacology is essentially syndromal. For example, antidepressants are drugs aimed at treating depressive symptoms, while antipsychotics are aimed at treating schizophrenic symptoms. Similarly, antihypertensive drugs are prescribed in internal medicine to treat high blood pressure. However, a major difference is that internists know better than psychiatrists what drugs do at the pharmacological level. Internists know that they either substitute for a missing compound (eg, insulin), attack an infectious agent (ie, antibiotics), or "cheat the body" (eg, induce a dysfunction in normal physiology in order to influence a symptom). For example, drugs used for cardiac insufficiency decrease blood volume, increase the muscular capacity of the myocardium, modify vascular resistance, lower heart rate, etc. Internists have a clear idea of what occurs when a patient develops cardiac insufficiency. They know that a diuretic is a regulator of electrolyte homeostasis and so do not call it an "antidyspnea" drug just because it controls the respiratory difficulties of patients with cardiac insufficiency. In psychopharmacology, direct links are often made from receptor or transporter to symptoms, without an intermediate analysis of which physiological functions are modified by the medication. Recent discoveries in the field of antidepressant agents show that extrapolation from the action of SSRIs action on the 5-HTT to improvement in mood is a gross simplification. Indeed, several antidepressants also decrease the expression of corticotropin-releasing hormone (CRH) in the hypothalamus and increase the expression of glucocorticoid receptors in the hippocampus[2]; in addition, they increase the expression of gonadorelin (LHRH),[3] and of brain-derived neurotrophic factor (BDNF).[4] These pharmacological effects might explain, in part, the clinical effects, through an influence on several brain functions.

## Psychiatric disorders

Diagnoses using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* and the *International Statistical Classification of Diseases, 10th Revision (ICD-10)* manuals are based on qualitative classification: a particular disorder is present if the required number of symptoms is found. Only a few mechanisms have been established for these disorders. The problems of a descriptive classification have long been recognized, as illustrated by the following citation, translated from a French book by Nathan[5]: "Until a classification can be based on etiology and pathogenesis, it does exist but is theoretically and practically sterile. If we only described symptoms, we would be like a doctor who described the false-membrane pharyngitis of diphtheria, while ignoring the microorganism that provokes the disease." There are more than 400 clinical codes in the *DSM-IV*. *ICD-10* proposes an even larger number of clinical entities, because, for each corresponding *DSM-IV* diagnosis, synonyms and related entities are mentioned in *ICD-10*. The validity of some of these disorders can be questioned: are they independent entities, do they have different mechanisms, do they respond to specific treatments? Thinking in terms of direct links between the actions of psychotropic medications at a receptor and the changes in symptoms has been fruitful in the sense that many discoveries were made following this rather simple paradigm. An amusing example may be

found in a recent article,[6] where a direct link was made between receptors and symptoms, ie, between 5-HTT on blood platelets and romantic love. The study, which was the work of an Italian group, was based on the fact that there is a superficial resemblance between obsessive compulsive ideas and romantic fascination. The results were that subjects in love have a lower number of 5-HTT, as do patients suffering from obsessive-compulsive disorder. Applying this linear thinking to the mechanisms of disorders can, however, be risky and it would be like internists thinking that a cardiac disorder such as hypertension is a disorder of calcium or β-receptors, just because calcium blockers or β-blockers are clinically useful in this condition. The biochemical organization of the brain is better understood now, and this has consequences for psychopharmacology. The importance of volume versus classic transmission has been recognized.[7] With volume transmission, 5-HT, noradrenaline (NA), and other compounds are secreted into the interstitial space by the axon and neuron, rather than released into the synaptic cleft. Overall, half of serotonergic transmission is said to be volume transmission, but this proportion varies depending on the brain structures. Thus, monoamines are classic neurotransmitters as well as neuromodulators or neurohormones. Psychotropic drugs act at all these various levels of monoamine physiology.

## Brain physiology and higher brain functions

Higher brain functions include perceptions, emotions, memory, thinking (beliefs), attention, consciousness, motivation (desire), and many others. These functions create and regulate our mental world, and the organization of the brain in regard to these functions has been discussed for centuries. René Descartes (1596-1650) recognized the central role of emotions (or "passions" as they were then called) by indicating what information or thought was important for us and what was not. John Hughlings Jackson (1835-1911) proposed that, when a hierarchically higher center became dysfunctional, a more primitive form of the brain function previously regulated by that center was expressed. Paul MacLean (1913- ), who worked with James Papez (1883-1958), has stressed the concept of a triune brain: a reptilian brain (essentially the brain stem), a paleomammalian brain (the limbic system), and a neomammalian brain (the neocortex). The reptilian brain is for basic instincts (feeding, fighting), the paleomammalian brain deals with emotions, and the neomammalian brain is responsible for complex associative functions. The dialogue between these three brains may be difficult, because only the neomammalian brain seems capable of handling information with verbal and symbolic modalities.

Point-to-point (wired or linear) transmission of information is a necessary component of perception and motor activity according to the concept of modularity: a specific brain region is mostly responsible for a specific function. This wired transmission of information is also relevant for higher brain functions, a fact that was elegantly demonstrated by Downer in a paper published in *Nature* in 1961.[8] His paper is about visual gnostic functions and emotional behavior in split brain monkeys, with the corpus callosum and optic chiasma both cut. In such a model, information getting to one eye only goes to the ipsilateral cortex and the two cortices can no longer exchange information as they usually do through the corpus callosum. The next step was to destroy the amygdala in one temporal lobe, leaving the other one intact. When this was done, covering the eye that projected to the lesioned cortex had no consequences: the monkey behaved in a normal manner (reacting aggressively to any human it saw). When the eye projecting to the non-lesioned cortex was covered, behavior became abnormal, with the monkey being indifferent to the potential threat of an approaching human; it "saw" the world through its lesioned amygdala only. This example of a unilateral Klüver-Bucy syndrome supports the notion of point-to-point or wired transfer of information, ie, modularity in behavioral control. It was selective for the visual modality, since, if the monkey was touched by a human, it reacted violently, as usual. Research in human beings who have a lesioned corpus callosum has also illustrated this modularity of brain functions: in these studies, it was established that the right cortex had information that the left one did not have access to. Brain-imaging techniques have now opened fields of knowledge far beyond these early and clever analyses. For example, it has become possible to identify which brain areas are metabolically active after the intravenous injection of nicotine in human subjects. Thus, limbic areas related to higher brain functions such as reward and emotions are more active, specifically the nucleus accumbens, the amygdala, the cingulate, and frontal lobes.[9]

The study of higher brain functions is complex, because each can be analyzed at different levels (from psychol-

ogy to molecular biology), and because few higher brain functions are unitary, a fact that can be illustrated with the many aspects of consciousness. Consciousness can be described in neurological terms, meaning vigilance states (awake, asleep, comatose), or in more psychological terms, meaning awareness. Awareness refers to many higher brain functions. There are so many different things that we can be conscious of (aware of), and we do not always have words for these categories of consciousness. We do have words for dysfunctions of specific aspects of consciousness, such as blindness, prosopagnosia, and phantom limbs, which are problems of awareness in relation to perception of physical realities.

Alexithymia involves both perception and consciousness, in the sense that it is concerned with recognizing our emotions and those of others. The capacity to construct a representation of a person's mental world is called the "theory of mind," and dysfunctions of this higher brain function are observed, for instance, in autism. An important question is how to define higher brain functions: should they be defined in behavioral terms, in physiological terms, or at the level of neuronal circuits? To illustrate this question with schizophrenia, should the disorder of thought be approached by measuring changes in neurophysiological parameters, or should it be described in terms of the filtering capability of corticothalamocortical loops, or in terms of neuroanatomical or biochemical changes? Other issues are the definition and the taxonomy of higher brain functions. The case of the emotions is illustrative of these issues. How many basic emotions are there? How can one classify the many composite (or secondary) emotions? In our text below, we mention the behavioral and psychological level of higher brain functions, and we discuss some quite basic functions (eg, memory), as well as composite (derived or secondary) functions (eg, empathy, social dominance, bonding).

## Proposals concerning diagnosis

We propose that symptoms should not be merely described and classified clinically, but also analyzed in terms of potentially modified higher brain functions. This proposal can be illustrated by the following case of a 50-year-old man suffering from an obsessive-compulsive disorder with predominant ruminations. If he hears a song on the radio in the morning, he can have this music in his mind for the whole day, and, if the text of the song has emotional connotations, he feels compelled to increase what he calls his "corrections," that is, to keep large numbers in his head from becoming even larger, by carrying out mental subtraction. He takes forever to close the door of his apartment, but can go out without checking when his friend closes the door. How could these symptoms be analyzed in terms of higher brain functions? First, it seems that auditory messages, when they are presented in a song, are kept in the phonological loops of his working memory. The second observation is that emotionally charged information induces or aggravates the symptoms, a well-known phenomenon in several neurological disorders. The third observation it that he has no voluntary control over the need for mental calculation, just as we do not have control over a tremor or a dyskinesia. The fourth observation is that he has an awareness of these mental phenomena, and can see them as unusual or abnormal. Finally, it is difficult for him to conclude that a given situation is solved and that he can safely move on to the next action. In order to consider that a given action is safely finished, one must escape or extinguish the need to continue checking what has just occurred and what might occur next. People with obsessive-compulsive disorders cannot stop checking, but they seem to check mostly things or activities that are a problem to them; they worry about "ego-centered," not general, safety. In summary, for each of the above aspects, one could investigate which higher brain functions are abnormal.

Another illustration of how to analyze symptoms in terms of higher brain functions is given below, for the case of depression. If a man becomes depressed because he has not achieved the life goals (education, fame, fortune, etc) that he has set himself, one might consider that his prefrontal cortex is predominantly involved in the causation of his depression: it would therefore be a case of mainly neomammalian brain dysfunction. If another man is depressed because he has suffered two myocardial infarctions within a year, one might consider that the amygdala and other limbic structures are predominantly involved in the causation of his depression, in which case it would be mainly paleomammalian brain dysfunction. Finally, a reptile that seems unhappy in captivity could be suffering from reptilian brain dysfunction, accompanied by excess secretion of cortisol.

Our proposal that a given symptom results from the dysfunction of a particular higher brain function remains schematic. Questions arise such as where does one symptom end and others begin, how often can one isolate one higher brain function from another, what are the hierarchies between global and more selective higher brain

functions? Despite these questions, we feel that adding an intermediate level of analysis between psychiatric symptoms and pharmacological modes of action would be fruitful. Indeed, more and more studies are being conducted along these lines. For example, in the field of schizophrenia, the cognitive abilities of subjects are measured in the prodromal phase, in the acute decompensation phase, and under treatment with antipsychotics. An obvious advantage of linking psychiatric symptoms to higher brain functions is that the clinician is bound to establish a list of functions and to consider which of these functions are normal or abnormal. Indeed, therapies based on the maintenance and care of body or brain functions that have remained responsive are usually more successful.

## Proposals concerning medications

It might be beneficial to consider what normal function(s) is (are) modified by psychotropic drugs and how this might be useful in cases of psychiatric disorders. We illustrate this proposal by listing particular aspects of our mental life that are derived from higher brain functions, and that, if influenced by therapeutic agents, might lead to an improvement in depression. A first function is related to the tendency to be a dominant subject within a group: antidepressant agents facilitate dominance in the hierarchical position of animals within their social group. A second function might be the bonding process and the need for affection between individuals. Oxytocin is involved in bonding, but antidepressants have not yet been developed along that line. γ-Hydroxybutyrate (GHB) seems to lead to enhancement of the pleasure of being with others; analogues of GHB might therefore act as antidepressants. Sildenafil might be an antidepressant agent for some men, directly through reestablishing a sense of bonding and indirectly through higher levels of testosterone. A third function is stress and sensitivity to stress; many antidepressant agents dampen the biological consequences of stress and modify the level of function of major stress axes. Antagonists to CRF are also being studied as potential antidepressants. A fourth function is the construction of beliefs, and their malleability or lack thereof. A substance that could facilitate putting strong ideas or beliefs slightly "out of focus" would be useful in cases of depressed thoughts or melancholic delusions.

## Conclusion

Clinicians describe psychiatric symptoms, but rarely analyze them in terms of higher brain functions, although these symptoms certainly result from alterations in these functions. However, establishing direct links between symptoms, higher brain functions, and modes of action of psychotropic drugs remains difficult. While discrete neuronal circuits are being discovered for particular higher brain functions, most psychotropic drugs have an overall effect on the brain, without much neuroanatomical selectivity. In addition, we do not have a definitive taxonomy of higher brain functions. In this article, we have proposed two shifts in paradigms. First, psychiatric symptoms should be analyzed in terms of which higher brain function(s) is (are) abnormal, ie, they should be analyzed as dysfunctions of higher brain functions. Second, psychotropic drugs should be seen as modifying normal higher brain functions, rather than merely treating symptoms, which they do only secondarily. Our proposal may facilitate comprehension of the links between psychotropic medications and their clinical effects. The challenge is to confront theoretical and pathophysiological models with the present descriptive clinical approach, and to establish a new classification of psychiatric disorders based on the elaborate psychological and physiological concepts derived from the neurosciences. ❑

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### *Psicofármacos, trastornos psiquiátricos y funciones corticales superiores*

*El diagnóstico psiquiátrico convencional se basa en la descripción de los síntomas, y a partir de esto se hace la elección de los psicofármacos. En su falta de rigor científico y su potencial de daño iatrogénico colateral, esta aproximación parece como una descripción de la difteria en la época premicrobiológica. En base a los avances actuales de las neurociencias (aspectos básicos y clínicos), se propone insertar un nivel intermedio de análisis entre los síntomas psiquiátricos y los mecanismos de acción farmacológicos. El paradigma 1 se refiere al análisis de los síntomas psiquiátricos en términos de cuál(es) función(es) cerebral0+(es) superior(es) es(son) anormal(es); es decir, los síntomas se deben analizar como una disfunción cerebral superior: un estudio de caso en un trastorno obsesivo compulsivo revela índices de cuatro síntomas comunes para las funciones superiores de memoria de trabajo, sobrecarga emocional, ausencia de control voluntario y capacidad para evaluar fenómenos mentales personales. El paradigma 2 consiste en ver a los psicofármacos como modificadores de las funciones cerebrales superiores normales, más que sustancias que meramente tratan síntomas, esto lo realizan sólo secundariamente: así la depresión puede responder a agentes que actúan sobre aspectos relativos a la vida mental derivados de funciones cerebrales superiores, por ejemplo, la capacidad del γ-hidroxibutirato para incrementar el grado de afinidad. Se defiende una estrategia en la que la enfermedad psiquiátrica es reclasificada progresivamente por las neurociencias y los enfoques terapéuticos se reformulan a consecuencia de esto.*

### *Médicaments psychotropes, troubles psychiatriques et fonctions cérébrales supérieures*

*En psychiatrie, le diagnostic est classiquement posé d'après la description des symptômes cliniques et détermine ensuite le choix du traitement psychotrope. L'absence de rigueur scientifique de cette attitude et le risque potentiel d'effets iatrogènes collatéraux rappelle la situation dans laquelle on se trouvait pour décrire la diphtérie à l'ère où la microbiologie n'existait pas encore. Nous proposons de créer un niveau intermédiaire d'analyse entre les symptômes psychiatriques et les modes d'action pharmacologiques en se fondant sur les avancées actuelles en neuroscience fondamentale et clinique. La première étape est d'analyser les symptômes psychiatriques en termes de quelle(s) fonction(s) cérébrale(s) supérieure(s) est/sont affectée(s) : l'exemple de l'étude du cas d'un patient souffrant de trouble obsessionnel-compulsif a montré que ses symptômes affectent quatre domaines de ses fonctions supérieures : mémoire immédiate ; élément émotionnel surajouté ; absence de contrôle volontaire ; enfin, capacité d'évaluer ses propres mécanismes mentaux. La deuxième étape est de prendre en considération le fait que les traitements psychotropes ont un effet sur l'ensemble des fonctions cérébrales supérieures normales et non pas seulement sur les symptômes, leur action thérapeutique intervenant en fait en un second temps : ainsi, la dépression pourrait répondre à des thérapeutiques qui agissent sur les aspects relationnels de la vie mentale dérivant des fonctions cérébrales supérieures, comme par exemple au γ-hydroxybutyrate qui aurait la faculté d'accroître les liens affectifs. Nous préconisons de reclasser progressivement les pathologies psychiatriques en se fondant sur les données neuroscientifiques et de redéfinir en conséquence les cibles thérapeutiques.*