***TOWARDS AN EPISTEMOLOGY OF NEUROPSYCHIATRIC CONSTRUCTS***

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**ABSTRACT**

The purpose of this article is to present an epistemological analysis of neuropsychiatric constructs. We characterize the concept of academic neuropsychiatry: a theoretical and research-based field of interdisciplinary work which is concerned with the full scope of psychopathological phenomena and its relationship with the neurosciences. Then, we define clinical neuropsychiatry as a practical field of medicine operating in the borderline of neurology and psychiatry to care for patients with neuropsychiatric conditions. To explain the logic of neuropsychiatric constructs, we define neurological constructs as well as psychiatric constructs, leading us to conceptualize and to distinguish between the neurological and the psychological, by means of a clarification of seven critical points of debate: structural lesions, physiologic abnormalities, causal agents, behavior, psychological functions, phenomenal experience, and clinical patterns. We discuss the traditional logic of brain-behavior relationships as well as the need for closer academic feedback between neuroscientific research and clinical practice. We argue that some neuropsychiatric cases are well explained by the current science of brain-behavior relationships, but many other cases located at the boundaries of this science require a transdisciplinary approach, including the study of sociocultural contexts and biographic timeline.

**Key words**: neurology; psychiatry; neuropsychiatry; neuroscience; psychopathology; phenomenology

**I. OPENING REMARKS:**

**THE MIND-BODY PROBLEM IN CLINICAL PRACTICE.**

The purpose of this article is to provide conceptual clarity to the concepts of academic and clinical neuropsychiatry, and to present an epistemological analysis of neuropsychiatric constructs. Neuropsychiatry has been defined as “a field of scientific medicine” which is “rooted in clinical neuroscience and provides a bridge between the disciplines of Psychiatry, Neurology and Neuropsychology.”(P. Sachdev, 2005). It may be regarded as an *inter-field* integrating results from all these disciplines. Neuropsychiatry combines principles derived from clinical neuroscience, mainly neurology and psychiatry, and is often placed in the borderland between these specialties (P. S. Sachdev, 2005). The neuropsychiatric activity includes a research dimension, and a clinical one that can be thought of as an attempt to provide a science-based practice. As part of the enterprise of scientific medicine, neuropsychiatric research shares the general principles of the factual sciences: the collective search for objective knowledge by means of the acquisition of empirical data, based on methodic observation and experimentation, which are then integrated into theoretical models. The path from data to theory requires analytical methods provided by logical rules, mathematics, and critical thinking, to achieve self-correction and gradually improve models(Bunge, 2017). As these general attributes of science have been widely discussed elsewhere, this article will focus on some of the specific aspects of neuropsychiatric epistemology.

According to Ivana S. Marková and German E. Berrios “epistemology” has been defined as “the theory or science of the methods of grounds of knowledge”. Epistemology remains “the study of the nature, limits and justification of knowledge.” (Marková & Berrios, 2012) In this article, we delineate a neuropsychiatric metatheory, to deal with the knowledge of neuropsychiatric constructs. What is the characterization of a neuropsychiatric condition? Is there a logical basis involved in the construction of neuropsychiatric concepts? How are these concepts used by clinicians at the practical level to reach diagnostic judgments? This discussion may be of value for neurologists and psychiatrists, but also it may be informative outside the field of medicine, in the context of two philosophical lines of inquiry: In the first place, there are renewed debates regarding the mind-body problem, with several arguments coming from the monistic, dualistic, and pluralistic positions (G. E. Berrios, 2018; Jerotic & Aftab, 2021; Maung, 2019; O’Leary, 2021; Pernu, 2021). Neuropsychiatric problems may be useful as bridges between the formal and the empirical levels of this discussion. In the second place, and closely related to the metaphysical mind-body problem, there is an intense interdisciplinary debate on the nature of mental disorders, mental illnesses or mental health problems, including several variations of the following thesis: a) Mental disorders are not real, only neurological diseases are real; b) Mental disorders are real and should be regarded as brain-based diseases; and c) Mental disorders are real, but they should be regarded as mutually exclusive with regards to neurological disease, and thus, their nature is not biologically based. Although the purpose of this article is not to address that discussion, the case of neuropsychiatric constructs may be of value to pose a fourth perspective to the general problem of mental disorders and their nature. To answer these questions, we will first outline a definition of clinical neuropsychiatry.

**II. THE CONCEPT OF NEUROPSYCHIATRY**

Alwyn Lishman, author of the canonical textbook *Organic Psychiatry*, conceptualized this discipline as the field of medicine that deals with the borderland between neurology and psychiatry, with two complementary aspects (as two sides of a coin): academic neuropsychiatry and clinical neuropsychiatry. **Figure 1** attempts to summarize both concepts.

**II. 1 ACADEMIC NEUROPSYCHIATRY** is a theoretical discipline concerned with the neuroscientific explanation of the full scope of psychopathologic phenomena, encompassing the neurobiological study of mental symptoms, syndromes and disorders, and the psychiatric phenomena observed in neurological disease. In this perspective, neuropsychiatry integrates findings and advances from cognitive and behavioral neurology and from biological psychiatry.(J. L. Cummings & Hegarty, 1994) Behavioral neurology is the branch of neurology dedicated to the study and clinical care of patients that present with behavioral disturbances as a consequence of structural brain abnormalities. Biological psychiatry, on the other hand, can be defined as the study of psychopathological phenomena by means of neuroscientific resources. Both disciplines are related, but the endeavors they accomplish are not equivalent. Behavioral neurology classically deals with neuropsychological syndromes as amnesia, apraxia, agnosia, aphasia, and dementia. Regarding biological psychiatry, the core inquiry has been about the so called “primary psychiatric disorders”: psychopathological constructs described since the XIX century and the early XX century (schizophrenia, bipolar disorder, major depression, obsessive-compulsive disorder, anorexia nervosa, and others) that do not fulfill nowadays the criteria to be considered neurological diseases but remain as significant challenges in terms of mental health(Prince et al., 2007). Academic neuropsychiatry can be understood as a conceptual interdiscipline, dedicated to the integration of information coming from various branches of clinical neuroscience, by means of critical analysis and scientific research towards the progressive development of a neuropsychiatric theory (J. L. Cummings et al., 1998).

**II.2. CLINICAL NEUROPSYCHIATRY**, according to Alwyn Lishman, is a form of medical practice dealing with the psychopathological problems which can be demonstrated (at the clinical level) to owe their origins to brain malfunction of a clearly identifiable nature (Lishman, 1992). This is consistent with the definition provided by German Berrios (neuropsychiatry is the discipline that studies and takes care of the patients with psychiatric complications in the context of neurological disease(German E. Berrios, 2007), and with the statement of the American Neuropsychiatric Association, which clarifies that the word “neuropsychiatry” may be used to describe a medical subspecialty committed to provide care to individuals with neurologically based behavioral disturbances. The clinical problems that appear in this interfield include focal neuropsychological syndromes (aphasia, apraxia, agnosia, alexia, and other cognitive disturbances with a well-defined pathophysiology) but also psychopathological syndromes with a less clear explanation in terms of behavioral neuroanatomy: psychosis, mania, depression, catatonia, and others which may appear in neurological patients or in patients without a demonstrable neurological disease.

Some clinical problems appear in patients with neurological disease but are not fully explained by the current understanding of brain function. This may be due to the incomplete status of neurobiological theories of behaviour and cognition, but also to the fact that clinical problems may be the result of a history of complex interactions between environmental influences and the biologic arrangements of the organism. The clinical outcomes arising from those interactions are multiple, and they do not always fall into the stereotyped patterns that have been described and explained by the clinical traditions. As we encounter some typical cases which are fully consistent with the medical taxonomy, we will also fall upon plenty of atypical cases that indicate the need for more basic, clinical, and social research. The clinician must decrease the initial levels of uncertainty by means of methodic interviews, a thorough examination of the physical and mental state, and by means of diagnostic studies; sometimes, therapeutic procedures are part of the diagnostic process, once there is a strong hypothesis to be tested. A process of logical analysis must take place to interpret and integrate all pieces of information. In any case, the clinical epistemology needs to address the question about neuropsychiatric constructs. How can we define those constructs, and what are the rules for its practical use in medicine? This requires a gradual approach, from “the neurological” to “the psychological” and to the conceptual and operational definitions that allow us to qualify some conditions as “pathological”.

**III. NEUROLOGIC, PSYCHIATRIC AND NEUROPSYCHIATRIC CONSTRUCTS**

Clinical neuropsychiatry shares a common ground with the rational basis of scientific medicine. The construction, transmission and application of diagnostic concepts is a complex process, one by which the experience of the individual clinician is integrated with the general knowledge of scientific medicine. Medical concepts represent a synthesis of collective apprenticeship (although they may be also the result of collective errors), which are verbally codified as diagnostic constructs with variable degrees of scientific validity. These constructs become abstract concepts within a shared semantic network that allows for communication between professionals across time and space, and they acquire predictive value through calibration within a research process. It must be emphasized that diagnostic constructs are highly fallible. The fact that many clinicians use the same concept reliably, does not mean that the concept is valid. An example of this would be the concept of “hysteria”, which has been used for centuries without any scientific validity. This problem should stress the fact that all medical concepts need to be recalibrated periodically according to the new empirical and theoretical advances.(Marková & Berrios, 2012)

In the context of this essay, we aim at discussing the logic of neuropsychiatric constructs. We address this issue step by step, going from the structural evidence of disease observed in neurological disease, to the behavioral patterns classified as pathologic according to clinical psychiatry, and finally into the convergence of brain disease and clinically relevant behavioral patterns.

**III.1. NEUROLOGIC CONSTRUCTS**

Although it is possible to trace a genealogy of neurology in antiquity, including Hippocratic medicine dealing with migraine, paraplegia, epilepsy, and so on, and even if we highlight that some relevant clinical and surgical observations were obtained in other pillars of civilization, as Egypt or Peru, it is generally accepted that the anatomical studies of Vesalius and the development of optical technologies giving rise to microscopy and neuro-histology were critical facts leading to the European revolution of anatomopathological medicine. The cellular pathology developed by Rudolf Virchow, Darwin’s evolutionary theory, the physiological conceptualization provided by Claude Bernard, and the neuronal theory by Santiago Ramón y Cajal, provided a new scientific framework for the clinical phenomena related to sensorial, motor, and mental functions, which were reinterpreted as expressions of underlying bodily pathologies.

Along the XIX century and the early XX century, many attempts were made to provide an explanation to clinical problems by means of anatomical pathology, with a success regarding conditions like Parkinson’s disease, multiple sclerosis, amyotrophic lateral sclerosis, or stroke, which had important sensorimotor disturbances. There were even paradigmatic cases of behavioral disturbances being explained by anatomical pathology. For example, language dysfunction related to lesions in the left hemisphere, as described by George Dax, Paul Broca, and Karl Wernicke. Phineas Gage’s frontal lobe lesion -and his subsequent change in social behavior- is also one of the famous stories of early neuropsychiatry. European psychiatry got involved into the quest for pathological explanations of psychiatric disturbances. While some problems were fully explained, others were explained partially, and most of the conditions that remained without explanation were discarded as part of the neurological field and thus remained within the psychiatric canon.

Many clinical conditions -in the field of psychiatry, but also in neurology and clinical medicine- do not fulfill the classical scientific criteria which have been used to define a disease according to the anatomopathological tradition. When a clinical construct does fulfill the criteria, there is a gain in terms of scientific validity, and a reduction of uncertainty at the practical level. Therefore, it is important to enlist these criteria explicitly and exemplify how to apply them in clinical neuropsychiatry.

**A) STRUCTURAL LESIONS.** Following Virchow, at least one structural lesion should be demonstrated in the nervous tissue of the patient, and a significant relationship between the kind of lesion and the kind of clinical pattern should be demonstrated. Classically, the lesion should be observed by means of cellular pathology in the direct assessment of the tissue, by autopsy or biopsy. After the technological and scientific revolution provided by neuroimaging techniques, the use of computed tomography, magnetic resonance imaging and other imaging techniques became the practical standard for the recognition of structural lesions in the nervous system ( although the direct pathological examination of tissues is still of critical value in many fields, as would be the case of neurooncology). It must be clarified that some neurological conditions -for example, Parkinson’s disease- are generally diagnosed on a clinical basis, without the resource of neuroimaging biomarkers. However, they are not considered merely “functional” disorders because there are consistent studies of brain pathology in autopsy specimens, which demonstrate the relationship between the clinical pattern (a rigid-akinetic syndrome, in Parkinson’s disease) and specific structural abnormalities (neuronal death by apoptosis in the *substantia nigra* of the mesencephalon).

**B) PHYSIOLOGIC ABNORMALITIES.** Following Claude Bernard, the physiological study of the milieu intérieur -or internal environment- became the biological framework to study the health and disease dynamic process. According to Bernard, the stability and constancy of the internal environment (homeostasis) is the condition for life, by means of a coordinated work of all the organs and tissues of the organism to ensure the maintenance, within the internal environment, of all the physical, chemical, and biological conditions that are necessary for cell survival. This presupposes that the systemic and highly coordinated activity of the organism compensates for the continuous variations in the external environment to ensure the dynamic balance of the internal milieu, even by means of a brain-centered, predictive mode of physiological regulation (to achieve stability through change) as has been highlighted by the concept of allostasis(McEwen, 1998; Schulkin & Sterling, 2019; Wen, 1998). Since Claude Bernard, the specific properties of the internal milieu became the main road to clinical physiology, and this is still crucial for clinical practice by means of laboratory studies. The demonstration of a physiological abnormality or the determination of a specific biochemical or cytological biomarker may be of value to establish a causal inference, according to medical theory. A classic situation is described: a patient with a state of behavioral unresponsiveness to any kind of stimuli, including pain, has severe hypoglycemia. Patients with acute hypoglycemia usually have symptoms related to central nervous dysfunction (drowsiness, visual changes, cognitive dysfunction) which, “if left untreated, can lead to seizures and coma”. (Ishii, 2017) If the physician provides the specific physiological treatment, a rapid improvement may be expected. If this treatment is not implemented, irreversible neurological damage or even death may occur. This example highlights that the theoretical knowledge which has been formed by medical research has a direct impact in clinical praxis.

**C) CAUSAL FACTORS.** The third explicit criteria to define the concept of disease is the identification of an agent that is related to the clinical construct by means of a causal relationship. A useful definition of cause has been provided by clinical epidemiology: a factor is a cause of an event if its operation increases the frequency of the event. (Elwood, 2009) As pointed out by Mark Elwood in his *Critical Appraisal of Epidemiologic Studies and Clinical Trials*, there are at least four types of causes in the context of clinical epidemiology: a) necessary causes, when the outcome occurs only if the causal factor has operated, b) sufficient causes, when the operation of the causal factor always results in the outcome, c) necessary and sufficient causes, when the cause and the outcome have a fixed relationship, and neither occurs without the other, and d) contributing causes, when the operation of the causal factor increases the frequency of the outcome, but the outcome does not always result, and the outcome can occur without the operation of the causal factor.(Elwood, 2009) Even if popular culture identifies the meaning of cause only with the concept of “sufficient and necessary causes”, this kind of causal relationship is in fact quite rare in clinical medicine. Perhaps some genetic conditions, as Huntington disease, fulfill the definition. On the contrary, contributing causes, which are not sufficient nor necessary, provide the commonest opportunities for effective interventions. In neurology, causal relationships are well established for many clinical phenotypes, although the exact and precise chain of causality is not fully known in most conditions. The causes may be inherited or acquired, environmental, or arising from the organism’s biology. Most frequently, human disease is the result of multicausal interactions.(Elwood, 2009). Today, we see the example of coronavirus-19 as a causal agent which increases the frequency of mental health disorders (Taquet, Geddes, Husain, Luciano, & Harrison, 2021).

**III. 2. PSYCHIATRIC CONSTRUCTS**

Psychiatric constructs include several categories from the etiological viewpoint: a) psychiatric disorders which are regarded as primary (they are not the consequences of demonstrable brain pathologies or pharmacologic-toxic agents), b) psychiatric problems which are secondary to pharmacologic agents (for instance, psychosis induced by ketamine, a hallucinogenic drug), and c) psychiatric problems which are secondary to general medical conditions or neurological disease (these may be regarded as neuropsychiatric constructs; for instance, psychosis due to systemic lupus erythematosus or catatonia due to autoimmune encephalitis). In any case, psychiatric problems are not defined by the presence or absence of structural lesions, physiologic abnormalities or specific causes: psychiatric constructs are defined by recognizable patterns of psychological signs and symptoms with significant features or suffering and/or functional impairment (American Psychiatric Association, 2013; “WHO | ICD-10 classification of mental and behavioural disorders,” 2010). This leaves us with the task of unpacking the concepts of “psychological”, “clinical pattern”, “suffering” and “functional impairment.”

 As German Berrios wrote, the concepts of “psychic” and “mental” are difficult to define due to their metaphorical origin (*Ψυχń*, *psyche*) and ontological instability.(G. E. Berrios, 2018) The word *psyche* was used in Classical Greece to mean “rush or air, blow, breath, and later -by dint of metaphor- was used to name the soul, conscious self, the source of life.” (G. E. Berrios, 2018) The English word “mind” is related to Old English *Mynd*, Old High German *gimunt*, Gothic *gamund,* and to the latin term *mens*, which was the name a goddess (*Mens Bona*), the personification of “right thinking”.(Adkins & Adkins, 1998) Highlighting the metaphorical and mythological origins of the terms “psyche” and “mind” helps us to understand the relationship of these terms with cultural traditions and folk psychology. However, in the context of medical, neuroscientific, and psychological practice and research, the word “psychological” does not carry necessarily a metaphysical dualistic view, in the sense of a soul-body substance-dualism. Instead, “the psychological” is used as a conventional term with a polysemy which will be addressed here in three levels: a) behavior, b) subjective or phenomenal experience, c) (neuro)psychological functions.

**A) BEHAVIOR.** Following a classic definition, we can start by saying that *behavior is what the organism is doing* (Skinner, 1938). B.F. Skinner states that behavior “is only part of the total activity of an organism, and some formal delimitation is called for.” Although the organism has multiple parts that have multiple “actions” at the physiological level, for the purpose of conceptual clarity, it is better to restrict the concept of behavior to the environmental interactions of the organism as a whole, as an integrated agent, and not to the specific physiological contribution of each part of the organism: “behavior is that part of the functioning of an organism which is engaged in acting upon or having commerce with the outside world”(Skinner, 1938). For clinical purposes, behavior may be regarded as the actions of the individual organism during the interplay with the environment, as this may be verified by an external observer (Skinner, 1938). From an epistemological perspective, the clinical analysis of behavior falls under the terms of a third person perspective (Díaz, 2016). Behavioral signs may be captured by external observers, and other objective signs of disease can be obtained by means of laboratory, electrophysiology, and imaging studies.

**B) PHENOMENAL EXPERIENCE.** Even if the study of overt behavior is optimal for the logic of scientific objectivity, clinical practice relies in the third person as well as in first person and second person accounts, for practical reasons (Díaz, 2016). In any field of medicine, most patients seek attention because of private experiences that may be conceptualized as symptoms (for instance, pain). Clinicians need to take seriously the symptoms reported by their patients: they might be the key towards a relevant pathology, and they are indicators of suffering, which must be alleviated according to medical ethics and deontology. The private aspect of psychological functions, which implies a privileged personal access to certain types of signals processed by the individual’s organism, has been conceptualized by philosophical traditions as a feature of the first-person perspective. If other branches of the scientific and philosophic endeavor are skeptical of the validity and reliability of the first-person perspective, the practical relevance of symptoms emphasizes the need to include this perspective in the clinical epistemology. Even radical behaviorism recognizes the psychological relevance of what can be called private stimuli, covert behavioral responses and private events (Tourinho, 2006). These subjective phenomena are available for the individual as private events, but not for a public examination as an observable, overt behavior, unless the individual communicates these experiences by means of verbal language or any other kind of symbolic system. This privileged access to private information is regarded as a feature of subjective or phenomenal experience, and as a fundamental aspect of conscious activity (Seth, Dienes, Cleeremans, Overgaard, & Pessoa, 2008; Seth & Hohwy, 2021). Psychiatric constructs include many clinical features based on patients’ subjective experiences (for instance, visual hallucinations). The clinical approach in psychiatry requires a phenomenological method to provide a detailed study of the contents and “the structure of human experience itself” (Varela, 1996). This refers not only to private events, but also to the full scope of phenomenal aspects that are captured by means of a first-person perspective during the organism-environment interaction. As pointed out by H.H. Maung, “the phenomenal concept of the mental is that which concerns the subjective quality of experience”(Maung, 2019). The level of phenomenology brings a qualitative, subjective dimension to neuropsychiatric epistemology, and thus it is open to hermeneutical approaches. At the clinical level, phenomenal consciousness cannot be studied directly, but only by means of a second person perspective. The main method to access the patient’s experience is by means of the anamnesis: semi-structured or in depth-open interviews which reveal the subjective qualities of psychopathologic phenomena. The paralinguistic aspects of communication -facial and bodily expressions, as well as prosody- are relevant also to make inferences about the other’s experience. Other forms of non-verbal behavior are important symbolic resources as well (drawing, dancing, singing) and they may be valuable sources of information in persons with impaired verbal behavior (for instance, patients with aphasia).

**C) PSYCHOLOGICAL FUNCTIONS.** The concept of neuropsychological functions (which are often described also as “mental functions”) is used here to categorize the cognitive-affective functions of the central nervous system which mediate the organism’s interaction with the environment: the neural processing of signals that is necessary to organize the overt behavior, as well as the subjective dimension of personal experience. A “mental status exam” is undertaken in the clinical setting to assess the neuropsychology of alertness, attention, language (and the paralinguistic aspects of communication), memory, constructional abilities and other aspects of spatial cognition, numerical cognition, reasoning abilities, categorization and abstraction, executive functioning, decision-making processes, praxis, and the evaluative processes which have been traditionally conceptualized as “emotional or affective”. A critical analysis of all these categories is needed, as there are specialized controversies regarding the scientific validity and the boundaries of these functions.(Pessoa, 2008; Pessoa, Medina, & Desfilis, 2022) The categories of mental function are controversial at the ontological and epistemological level. Our current mental concepts are used in neurological, psychiatric and neuropsychological clinical practice as they are helpful to clinicians to organize the wide scope of behavioral and phenomenological disturbances, and to attempt preliminary explanations of their relationship to brain processes. However, these categories represent a problematic confluence of philosophical and clinical traditions, popular psychology, and empirical research provided by clinical and cognitive neuroscience. It is expected that the continuous dialogue between basic, clinic and theoretical research will be able to provide a scientific reconceptualization of cognitive-affective functions with value at the practical level.

**D) CLINICAL PATTERNS.** The medical conceptualization of psychiatric problems usually starts with subjective complaints by the patient, and/or with behavioral problems observed by the interpersonal network. These complaints reach a level in which, according to cultural, historic, and socioeconomical standards, a medical or psychological consultation takes place. This implies a social dimension related to cultural values. In the context of psychiatric medicine, the clinician generally attempts to make sense of the initial complaints by means of an interview, a mental status examination, and a general medical examination as well, to see if the complaints should be categorized as symptoms and/or signs which could be understood as parts of a syndromic clinical pattern. In general medicine, a “sign” is defined as an objective manifestation of disease which can be captured during the physical examination of the patient, by means of inspection, palpation, percussion, and auscultation. In the context of psychiatry, there are behavioral signs (for instance, psychomotor agitation, aggressive behavior, or the signs of catatonia). It has been pointed out that behavioral signs are not as objective or stable as physical signs in general medicine, due to significant differences regarding the temporal dynamics of the sign (behavior is changeable and requires longer periods of observation to capture the specific behavior under study) and due to the historical-cultural context in which the clinical judgment is stated.(Marková & Berrios, 2009) Regarding mental symptoms, these refer to atypical and problematic events that appear in the patient’s subjective experience (for instance, hallucinations or feelings of depersonalization and derealization). According of Marková and Berrios, mental symptoms are “personal constructs” or personal interpretations of subjective experiences, described by the patient according to his/her catalogue of verbal categories, and influenced by personality factors, education, and sociocultural factors as well (Marková & Berrios, 2009). To be conceptualized as symptoms, these problematic subjective experiences need to be communicated by the patient and then judged as abnormal or pathological by the clinician. It is clear that the historical, social and cultural factors in which the clinical relationship is immerse are variables influencing this diagnostic decision (Marková & Berrios, 2009). However, there are also intrinsic variables which influence the diagnostic decision making, as the degree of suffering, or how unusual the experience is (for instance, a patient would hear a cat crying inside his stomach and thus would seek for help). To be considered a clinical pattern, there are two current conventional requisites: a) suffering, and b) functional impairment (American Psychiatric Association, 2013). These may have many sources, including social, political, cultural, and economical dimensions, as well as interpersonal sources. This should be assessed in each case, as these sources frequently coexist with the psychopathologic pattern. To be valid, the diagnosis should delineate clearly to which extent the psychopathologic phenomena is related intrinsically to suffering and functional impairment. As an example, some patients with a first episode of psychosis may show a significant reduction in cognitive functioning before the use of antipsychotic drugs (Saykin et al., 1994). This may be considered a functional impairment related to the psychopathologic pattern. Also, some patients with this condition experience intense emotional distress (suffering) related to the hallucinatory experiences, which may involve persistent and involuntary voices that are offensive or that give orders to the patient to commit harmful acts to their beloved ones. The evaluation of suffering and functional impairment (disability) involves a qualitative, contextual and interpersonal clinical judgment, which requires an axiological discussion.

**III.3. NEUROPSYCHIATRIC CONSTRUCTS**

How do we decide in clinical practice if a patient has a neuropsychiatric problem? What is the relationship between the clinical concepts used in practice and the theoretical knowledge provided by scientific research in the fields of psychopathology, neuroscience, and medical science? Neuropsychiatric constructs are not fixed objects with a perfectly stable ontology, but instead, pragmatic diagnostic concepts allowing for a rational connection between the level of clinical care and the level of scientific research. As any diagnostic concept in medicine, neuropsychiatric constructs change over time when empirical data and improved analyses show that the terms -or the operational criteria- should be reformulated, usually on a gradual basis. Neuropsychiatric constructs must fulfill both the criteria previously exposed for neurological constructs and for psychiatric constructs, but also, a significant relationship between the psychopathological pattern and a specific neurologic condition should be demonstrated. How can we know if it is not merely a casual or a trivial coexistence of two independent phenomena? The scientific answer to that question involves the longitudinal study of the individual case, and a clinical epidemiology approach, but also a clinical neuroscience approach, given that the clinician needs a scientific theory of the relationship between the behavioral events that may be classified as pathologic (the psychopathologic phenomena) and the structural and/or functional abnormalities which are seen in nervous system pathologies.

**A) BRAIN-BEHAVIOR RELATIONSHIPS AND THE CONSTRUCTION OF A NEUROPSYCHIATRIC DIAGNOSIS.** The nervous system functioning includes sensory-motor functions, autonomic functions, and the intermediary processing that organizes complex behavior. Behavior is not the result of a mere set of inherited sensory-motor reflexes. Instead, overt behavior is the external aspect of the sensory-motor integration that results by virtue of the intermediary neuronal processing. As Marsel Mesulam has explained, if the behavioral response is fixed as the result of direct connections between sensory and motor neurons, what is observed is the simple and stereotyped pattern of reaction that characterizes nervous reflexes (for instance, stretch reflex). In the nervous system, these involuntary responses are the result of simple pathways that include one motor neuron, one sensory neuron and one or more intermediate “interneurons” located in the spinal cord or the brainstem (Purves, Augustine, & Fitzpatrick, 2019). These responses are executed without reaching higher processing centers in the brain. On the other hand, when it comes to complex forms of overt behavior, sensory inputs are subject to intermediary processing before reaching motor neurons. This comprehends different brain centers including the association cortices, paralimbic cortices, allocortical structures and subcortical nuclei traditionally encompassed as parts of the limbic circuits. As a result, we observe adaptive, flexible patterns of behavior through which the organism interacts in different ways with an everchanging environment, according to the individual’s learning history. (M.-M. Mesulam, 2000; M. M. Mesulam, 1998)

At the level of neurobiology, the interactions between the organism and the environment induce physiological and structural changes by means of neuronal plasticity mechanisms (synapse formation, long term potentiation, long term depression, neurogenesis)(Asok, Leroy, Rayman, & Kandel, 2019; Marín-Burgin & Schinder, 2012; Ramirez, 2018). These structural modifications are necessary to stabilize the changes in verbal and motor outputs which are obtained by learning. As an example, a written text can be shown to a person with preserved visual abilities before alphabetization, but the individual cannot read aloud nor access the semantic content of the text. After learning to read, the same text elicits a complex set of phenomenal experiences and verbal behaviors. It has been observed that “the maturation of a functional response to letter strings in the visual word form area closely tracks the acquisition of reading”(Hannagan, Amedi, Cohen, Dehaene-Lambertz, & Dehaene, 2015). This functional response is observed in the ventral occipitotemporal cortex, and it collateralizes to the same hemisphere as spoken language. Alexia results from an unilateral left hemisphere lesion in this area, leading to a persistent word reading disability.(Michel, 2008) This fulfills the criteria to be considered a clinical pattern of behavioral/mental dysfunction: alexia implies a cognitive and behavioral deficit at the level of the reading behavior and experience. If the patient has a structural lesion in the left ventral occipito-temporal cortex, a valid relationship can be established between the clinical pattern and the neuroanatomical condition, and thus a neuropsychiatric diagnosis can be provided by the clinician.

Since the late XIX century, and until the first half of the XX century, many case studies established clinico-pathological relationships between the level of behavior and the existence of structural brain lesions. Initially, many cognitive and affective problems were observed to be present after focal lesions: amnesia as related to damage in the hippocampus(Penfield & Milner, 1958; SCOVILLE & MILNER, 1957), disinhibited behavior after lesions of the ventral parts of the frontal lobe(Price, Carmichael, & Drevets, 1996), expressive aphasia in patients with lesions of the third frontal gyrus in the left hemisphere(M.-M. Mesulam, 2000), or receptive aphasia in patients with lesions of the left parieto-temporal junction(M. M. Mesulam, 1998). Soon, other focal neuropsychological syndromes were described: alexia, agraphia, acalculia, Balint’s syndrome, visual agnosia, amusia, ideomotor apraxia, and many others. These syndromes may be subject to a critical review regarding the precise definition of the behavioral phenotype and the specific lesion location, and specialized controversies may appear, but they are robust facts which have been regarded as empirical data with a high scientific validity.

Consider the following case: a 29-year-old male patient with right hand dominance has a new onset disturbance in speech production, characterized by a reduced verbal output and grammar deficiencies. The brain-language relationships previously established by clinical neuroscience dictate that the clinician must solicit a brain imaging study to rule out a structural lesion affecting Broca’s area. **Figure 1** presents the brain image, as well as the essential facts for a scientific discussion. The general issue to be considered is that, in certain clinical scenarios, the knowledge of brain-behavior relationships imposes a deontological imperative to assess carefully -by means of clinical and technological resources- the possibility that some patterns of behavior and experience are due to an objective, demonstrable neurological condition which typically requires therapeutic maneuvers beyond the traditional management provided by psychiatrists and clinical psychologists.

There are clues that help the clinician to recognize which patients require a differential diagnosis with a more thorough technological analysis by means of brain imaging, electrophysiology, and laboratory tests, as described in **table 1**. If the clinician decides to do the proper testing, the results may be normal, but if the results are abnormal, an interpretative procedure takes place. If the anatomical or pathophysiologic explanation of a behavioral syndrome has been confirmed by means of reliable neuroscientific studies, a causal relationship may be established between the structural lesion (or the physiologic abnormality) and the clinical pattern. However, there is a great variability in the degrees of certainty regarding brain-behavior relationships, according to the heterogeneity of clinical circumstances. How do we establish a valid and reliable relationship between a psychopathological pattern and a neurological pathology when both are present in the same patient? How do we know there is a significant relationship instead of a merely casual coexistence?

**B) THE EPISTEMOLOGICAL FEEDBACK BETWEEN CLINICAL PRACTICE AND NEUROSCIENTIFIC RESEARCH.** During the last century, focal neuropsychologic syndromes, tied to brain lesions, have provided a robust framework to understand brain-behavior relationships. But there are neuropsychiatric patterns of severe cognitive dysfunction (as would be the case of delirium or rapidly progressive dementia) which are also of neurological origin, although not as the result of a focal lesion, but as the manifestation of a diffuse, generalized encephalic dysfunction (encephalopathy)(Maldonado, 2013; Oldham & Holloway, 2020; Trzepacz, Teague, & Lipowski, 1985). These patterns are hard to explain from perspectives in which mental function results from the activity of a circumscribed brain region. New perspectives of modern neuroscience such as connectomics suggest that mental function is the product of the activity of a set of dynamically interconnected brain regions, which provides a biological framework to tie diffuse brain pathology to psychiatric symptomatology(Cao, Wang, & He, 2015; Deco & Kringelbach, 2014).

There are many psychiatric signs, symptoms and syndromes that are not well explained in terms of focal or generalized demonstrable deficits, or that are subject to many controversies. Psychosis, catatonia, mania, depression, anxiety, obsession-compulsion, dissociative phenomena, aggressive behavior, and many other psychiatric phenomena may be seen in neurological patients but also in patients without a demonstrable neurological condition. This fact presents a difficulty at the theoretical and practical levels. If one of the stereotyped patterns which are usually identified with primary psychiatric disorders (for instance, a schizophrenia-like psychosis) is observed in a patient with a neurological condition, how can it be established that there is a significant relationship between the psychiatric and the neurological facts? As mentioned above, there are three main approaches to answer that question: a longitudinal study of the individual case, a clinical epidemiology approach, and a clinical neuroscience approach. When the three approaches converge, there is a gain in clinical certainty.

It is well-known that individual cases only rarely provide sufficient information on matters of causality because chance variation cannot rarely be controlled. The clinical epidemiology approach is based in the collection of many cases with similar selection criteria, which allows for inferential statistics, improving our capacity to establish causal inferences beyond chance, and beyond the effect of confounding variables. For instance, the case of Augusta D. -which lead to the clinico-pathological description of Alzheimer’s disease- shows that she suffered from delusions one year before the cognitive deficit was observed(Ramirez-Bermudez, 2012). There is a scientific consensus regarding the causal relationship between Alzheimer’s neuropathology and the progressive cognitive decline in patients with Alzheimer’s disease. Both the neuropathological abnormalities and the cognitive dysfunction are always present in Alzheimer’s disease. But delusions are present only in some cases. The question would be: Alzheimer’s pathology was the cause of delusions in the case of Augusta D.? By looking at her individual case, it is impossible to reach a conclusion. However, clinical epidemiology studies have shown that delusions are significantly more common in patients with Alzheimer’s disease (22%) as compared to age matched individuals without dementia (2%)(Leroi, Voulgari, Breitner, & Lyketsos, 2003). This statistical relationship has been confirmed by multiple studies(J Cummings et al., 2018; Jeffrey Cummings et al., 2020; Leroi et al., 2003). By using the epidemiological definition of cause(Elwood, 2009), it is reasonable to state that Alzheimer’s pathology is a causal factor of delusions in the elder, even if the process of symptom formation is not perfectly established and involves multicausality, and even if not all patients with Alzheimer’s disease present delusions.

According to the classic Bradford Hill criteria(H. Fletcher, Fletcher, & Fletcher, 2014), a strong theory constructed by means of empirical data provides a framework for biological plausibility, which is a relevant criterion in the assessment of causation. This is pertinent when we ask if a structural lesion or a physiologic abnormality is a likely explanation for a psychopathologic pattern in a specific case. In the context of neuropsychiatric constructs, clinical neuroscience provides a plausibility framework. If a patient has a subjective complaint of visual loss (homonymous hemianopia) and she or he has a lesion in the occipital lobe, the lesion explains the subjective complaint, according to an extensive body of neuroscientific research. If the lesion is located, however, in the frontal lobe, it is unlikely that the lesion explains the same symptom, as the research from animal, clinical and cognitive neuroscience studies does not support the relationship(M.-M. Mesulam, 2000; Zunt, 2010). The gradual construction of an integrated theory of the relationships between the nervous system and the psychological requires neuroscientific studies done in healthy subjects, in patients with brain lesions, and in subjects receiving a diagnosis of primary psychiatric disorders. This integrated theory -the ambition of academic neuropsychiatry- is necessary to approach the difficult cases that lie in the borderland between neurology and psychiatry.

**C) HYBRID CONSTRUCTS AND PLURALISTIC APPROACHES.** Some neuropsychiatric cases are well explained by the current science of brain-behavior relationships, while other cases located at the borderlands between neurology and psychiatry require a transdisciplinary approach, which should include contextual variables and idiographic trajectories. **Figure 2** shows the case of a young woman with a brain lesion affecting the medial frontal lobe and the cingulate cortex. This explains some cognitive and behavioral signs (a reduction in spontaneous activity, catatonic signs, dysexecutive syndrome). However, a severe delusional behavior is present, which seems to be influenced by the brain lesion but could also by influenced by biographical events including forced isolation, abuse for many years and the loss of her mother. The patient requires surgical treatment and use of steroids, which improves the catatonia, apathy and dysexecutive syndromes. But the psychotic features persist, so she is given antipsychotic and antidepressant medication, as well as individual and family therapy. This brings the issue raised by German Berrios: even in the patients with well-defined neurological conditions, the psychosocial and biographical variables have an influence over certain symptoms that are not well explained by mechanical brain-behavior relationships. “Neurological patients have reasons for their symptoms, that is, neurological diseases happen to real people and hence have semantic contexts. This adds an entire new layer of meaning, hermeneutics and therapeutic response”(German E. Berrios, 2007). These hybrid cases pose the need for psychotherapy and social actions in many patients even when the neurological factors are demonstrable at the clinical level. At the ontological level, the study of hybrid cases does not support a reductionist perspective according to which neuroscientific studies are sufficient to understand mental health problems in general, and not even in the context of neurological disease, but it does not support a substance-dualism that considers the psychological to be independent from the neurological, as brain lesions are demonstrable causes of psychiatric clinical patterns. Psychiatric constructs are not mutually exclusive with regards to neurological constructs, as there is a partial overlap between both categories.

**IV. CLOSING REMARKS:**

This article aimed at characterizing the concept of academic neuropsychiatry: a theoretical and research-based field of interdisciplinary work which is concerned with the full scope of psychopathological phenomena and its relationship with the neurosciences. Then, we defined clinical neuropsychiatry as a practical field of medicine operating in the borderline of neurology and psychiatry to care for patients with neuropsychiatric conditions. To explain the logic of neuropsychiatric constructs, even if superficially, we defined neurological constructs as well as psychiatric constructs, leading us to conceptualize and distinguish structural lesions, physiologic abnormalities, causal agents, behavior, psychological functions, phenomenal experience, and clinical patterns. We discussed the logic of brain-behavior relationships as well as the need for closer academic feedback between neuroscientific research and clinical practice. Some neuropsychiatric cases are well explained by the current science of brain-behavior relationships, but many hybrid cases located at the boundaries of this science require a transdisciplinary approach including the study of sociocultural contexts and biographic timeline. Moreover, an integration of the third-person perspective of science with the second person perspective of clinical practice, and with the first-person perspective of illness, is most needed.

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**Figure 1.** The two sides of Neuropsychiatry: at the left, academic psychiatry is conceived as a theoretical discipline dedicated to the medical study of brain pathology and behavior, which integrates the scientific knowledge of behavioral neurology and biological psychiatry, with the support of several disciplines, including neuropsychology and the cognitive, affective, and social branches of neuroscience. At the right: clinical neuropsychiatry is depicted as a practical interdiscipline dedicated to the study and clinical care of patients with psychiatric patterns caused by a brain pathology which is demonstrable at the individual level.

**Figure 2.** A neuropsychiatric clinical case which is consistent with the best-known brain-behavior relationships. A 29-year-old male patient with right hand dominance has a new onset disturbance in speech production, characterized by a reduced verbal output and grammar deficiencies. However, he is able to understand language. He is found with disorientation and psychomotor agitation. The patient has a history of a recent dental infection, with extraction of a tooth. Magnetic Resonance Imaging revealed a lesion localized in the left hemisphere, affecting the opercular region of the frontal lobe, the insular cortex, and the anterior and lateral part of the temporal lobe. A bacterial abscess was diagnosed and treatment with antibiotics was successful. The recovery of mental state and language abilities was complete.

**Figure 3.** An example of a clinical case in the borderland between neurology and psychiatry. A young woman has aggressive behavior. She is locked by her family, physically abused and isolated in a room for many years, receiving only minimal quantities of food and water. She experiences a progressive headache, and a brain tumor is detected in a hospital. She is kept in forced isolation by her family for a couple of years, until her mother dies, and she is taken by her brother to the hospital when she is 37 years old. She states that her brother is an impostor (Capgras delusion) and that her mother is still alive. Also, she has gait apraxia, urinary incontinence, a marked reduction in cognition and spontaneous activity, and a refusal to eat and drink. After the surgical removal of the tumor, there is a significant improvement in her cognitive and spontaneous activity, and a remission in gait apraxia and urinary incontinence. Capgras syndrome and the delusion of her mother being alive persisted for a year and only remitted with the use of an antipsychotic , an antidepressant and psychotherapy.

**Table 1.** When caring for patients with psychopathological problems, the clinician must consider whether there is an underlying condition if any of these criteria is fulfilled:

|  |  |
| --- | --- |
| **CRITERIA**  | **EXPLANATION** |
| Abnormal neurological examination  | A neurological clinical exam showing abnormal sensitive, motor or autonomic signs[56] |
| Focal neuropsychologic syndrome | Presence of cognitive deficits with a well-known neurological basis (aphasia, apraxia, agnosia, amnesia, dysexecutive syndrome, Balint syndrome, Gertsmann syndrome, etc)[37, 56] |
| Atypical psychiatric patterns | Atypical psychiatric phenomenology in the context of a common psychiatric syndrome, and/or uncommon age of onset, as may be the case of a syndrome outside the expected epidemiological profile (for instance, a case of first episode mania after age 50)[58] |
| Psychiatric syndromes suggesting a neurological condition | Some psychopathologic syndromes are always indicative of the need to assess neurological or general medical conditions (delirium, dementia, Klüver-Bucy syndrome, etc), whereas other psychopathologic syndromes increase the probability of finding underlying neurological conditions but may also be seen in primary psychiatric conditions (Capgras syndrome, Cotard syndrome, Ekbom syndrome |
| Unexpected therapeutic response | Lack of therapeutic response or worsening after adequate therapeutic procedures (psychotherapy, pharmacotherapy or other biological treatments as ECT).[59] |
| Additional red flags | Data that increase the suspicion of an underlying neurological condition in patients with psychopathologic patterns. Fever, infectious syndrome, headache, seizures, autonomic abnormalities, and abnormal movements. |