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Frontiers between neurology and psychiatry

Behavioral disorders: The 'blind spot' of neurology and psychiatry

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ABSTRACT

Behavioral disorders occupy the crossroads between neurology and psychiatry, and emerging disorders, such as frontotemporal lobar degeneration of genetic origin and autoimmune encephalitis, can present with both neurological and psychiatric signs. Thus, the primary aim of this introductory article is to review frequently encountered behavioral clinical features, such as apathy and agitation, and their related syndromes, including frontal and anterior temporal syndromes. These behavioral states and their underlying etiologies are also here illustrated with clinical case reports. In addition, this review highlights the idea that in order to progress in the understanding and management of behavioral disorders, there needs to be a strong interest towards developing new forms of cooperation between neurologists, psychiatrists and neuroscientists, such as those who work at university-based hospital neuropsychiatric clinical units.

1. Introduction

Neuropsychiatry refers to that controversial association of neurology and psychiatry initiated in France by Jean-Martin Charcot and eventually leading to an official diploma of neuropsychiatry in 1949. This field of study then served as the 'nurturing mother' of neurology and psychiatry, although the two disciplines separated from each other at the end of 1968 and still remain autonomous – albeit only apparently so [1]. As a consequence, the behavioral symptoms that lie along the borders of both neurology and psychiatry by their expression and their underlying diseases have remained in the 'blind spots' of both disciplines. These behavioral symptoms, which include apathy, impulsivity, agitation and hallucinations, have meant that the many neurological and psychiatric patients with these types of disorders have been either

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neglected or treated within only one of the two disciplines and, when patients were fortunate enough to benefit from dual care, it was rarely concerted, synergistic or concomitant. As a result, for these disorders, there has been a massive lack of knowledge with four consequences: poor clinical characterization (description, assessment, prognosis); (very) limited care; a lack of knowledge of the pathophysiology; and a lack of teaching about these disorders [2,3]. Fortunately, the emergence of the field of neurosciences in clinical practice has prompted an amalgamation of knowledge that allows neurologists and psychiatrists to again speak a common language so that, together, they can now address the pathology of neuropsychiatric disorders.

The purpose of this introductory review is to put behavior at the center of concern for both neurologists and psychiatrists. For this reason, these disorders are here defined and accompanied by examples of the importance of working together, most notably because of the emergence of neuropsychiatric entities that not so long ago were poorly characterized or even unidentified, such as frontotemporal lobar degeneration (FTLD) and, in particular, amplification of the *C9ORF72* gene and the gene coding for progranulin, but also autoimmune encephalitis, attention-deficit disorders, Kleine–Levin syndrome and somatoform disorders.

Behavior can be defined as the observable result of all automatic (unconscious) or voluntary mental activities, while pathological behavior is represented by actions and gestures that alter the course of voluntary and/or automatic thought through impaired sensory (for example, visual hallucinations), cognitive (for example, an attention disorder) and/or emotional (for example, acute anxiety) mechanisms brought into play by the alteration. In fact, two main categories of behavioral disorder can be distinguished: (i) pathological reduction of behavior, including apathy, passivity, hypersomnolence, psychic asthenia, clinophilia, and even catatonia and mutism, thereby leading to social withdrawal or, at worst, a major loss of autonomy; and (ii) exaggeration or emergence of inappropriate conduct in terms of personal behaviors (impulsiveness, disinhibition, stereotypies, automatisms, autoaggressivity, ambulation, aimless agitation, disordered eating behaviors, vegetative homeostasis regulation) or social interactions (violence, loss of social distance, lack of empathy, disinterest in others). Indeed, an analysis of the signs and symptoms presented by 100 patients admitted to the Behavioral Neuropsychiatry Unit (UNPC, Pitié-Salpêtrière Hospital, Paris, France) showed that most of these patients ($n = 74$) had quantitative behavioral reductions leading to severe depression or a neurological disorder expressed by apathy. More rarely, these patients presented with (in association or not with apathy) aggressivity, impulsivity or disinhibition ($n = 17$), hallucinations ($n = 8$) and eating ($n = 5$) or social ($n = 4$) disorders (Azuar, Cohen, Fossati, Levy, Naccache and Mauras, personal communications).

It should also be noted that the origin of behavioral disorders is often multifactorial, combining discrete brain damage or dysfunction (affecting visual integration, memory, executive functioning), sensory factors (deterioration of vision or hearing), visceral somatic factors (such as organ failure and physical stress like general anesthesia, pain, pneumopathy, constipation, urinary tract infections) and/or environmental factors (such as family conflict, change of residence, psychological stress). Furthermore, the opposing features of reduction and exaggeration of behavior may sometimes be artificial, as the same patient may be both apathetic (reduction of voluntary behavior) and hyperactive (exaggeration of involuntary behavior), and the underlying pathophysiological mechanism may be common to both disorders (for example, frontal lobe injury reduces both the ability to activate voluntary behavior and to inhibit reflexive/automatic responses).

2. Apathy and agitation as models for describing behavioral disorders

2.1. *Apathy*

This can be defined as a quantitative reduction of adaptive behaviors while environmental or physical constraints remain unchanged: in other words, apathy is the quantitative reduction of voluntary goal-directed behavior [4]. This is the most common behavioral disorder in pathologies affecting the central nervous system (CNS). It is observed in around 50% of patients in the prodromal stage of Alzheimer's disease (AD) and in $>$ 60% of patients in the dementia phase [5,6]. Similarly, apathy is frequently present in the behavioral variant of frontotemporal dementia (bvFTD), affecting 62–89% of patients [7,8]. Apathy is also commonly seen in pathologies involving the basal ganglia, such as Parkinson's disease, Huntington's disease and progressive supranuclear palsy [9–12], and may be due to any mechanism that alters the development, execution and control of goal-directed behavior. Apathy can therefore be caused by affective/emotional, motivational or cognitive (executive) mechanisms, depending on the disease and topography of damage to the frontal basal ganglia networks. The most severe states of apathy are related to basal ganglia lesions (for example, auto-activation deficit caused by bilateral pallidal or caudate nuclei lesions), and damage to the orbital and ventromedial prefrontal cortices (for example, bvFTD) or anterior cingulate cortex (for example, akinetic mutism due to bilateral lesions of the mesial frontal cortex). In patients with AD, strong correlations have been found between the degree of involvement of the anterior cingulate and ventral orbitofrontal cortices and the severity or presence of apathy [13–21].

Management of apathy as a specific syndrome is virtually non-existent. Whatever the approach (medicinal or physiotherapeutic), the amount of progress yet to be made is massive. To date, treatments proposed for apathy have given no meaningful results in either reported cases or open trials with methylphenidate, bupropion, modafinil or dopaminergic drugs such as levodopa (L-DOPA), amantadine, selegiline and bromocriptine, or double-blind placebo-controlled clinical trials with anticholinesterase inhibitors in AD, diffuse Lewy body disease and Parkinson's disease (PD) [22–27]. Worse, the results have been discordant (positive or negative) and, when statistically significant, the effectiveness has been clinically modest for apathy as assessed by the Neuropsychiatric Inventory (NPI) scale. When methylphenidate was tested in AD in a double-blind placebo-controlled trial, it resulted in a

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