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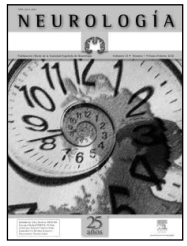

REVIEW ARTICLE

Apathy in Parkinson's disease

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KEYWORDS
Apathy;
Parkinson's disease;
Striatum;
LARS scale;
Negative symptoms

Abstract
Introduction: Apathy is a behavioural syndrome due to dysfunction of the process that gives rise to actions induced by external or personal stimuli. Apathy is very common in Parkinson's disease, with a prevalence that ranges between 16-48% Three subtypes of apathy are currently accepted, which are anatomically and functionally different: cognitive, emotional and due to a deficit in auto-activation. Each of these subtypes is involved to a variable degree in the apathy of Parkinson's disease. The diagnosis is supported by clinical, diagnostic and neuropsychological tests. The evaluation of the apathy must be done simultaneously along with with depression cognitive deficit.
Conclusions: Apathy has become a very important symptom to bear in mind in Parkinson's disease patients as it has significant repercussions on the quality of life of the patient. It is very important to do a differential diagnosis with the depression and the cognitive deficit since the therapeutic approach is different. Specific scales to measure this symptom should be included in the evaluation protocols of cognitive function in Parkinson's disease.

PALABRAS CLAVE
Apatía;
Enfermedad de Parkinson;
Estriado;
Escala LARS;
Síntomas negativos

Apatía en la enfermedad de Parkinson

Resumen
Introducción: La apatía es un síndrome comportamental por disfunción del proceso que origina los actos inducidos por estímulos externos o los propios. Es muy frecuente en la enfermedad de Parkinson, con una prevalencia que oscila en el 16-48% Actualmente se aceptan tres subtipos diferentes de apatía con un correlato anatómico-funcional distinto

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en cado uno de los casos: cognitiva, emocional y por déficit en la autoactivación. Cada uno de estos subtipos está implicado en un grado variable en la apatía de la enfermedad de Parkinson. El diagnóstico es fundamentalmente clínico apoyado en escalas neuropsicológicas. La evaluación de la apatía debe hacerse simultáneamente con la de la depresión y el deterioro cognitivo.
Conclusiones: La apatía es un síntoma muy importante y de reciente consideración a tener muy en cuenta en los pacientes con enfermedad de Parkinson por la repercusión en la calidad de vida del paciente. Es importante el diagnóstico diferencial con la depresión y el deterioro cognitivo, pues el abordaje terapéutico es diferente. Para ello es necesario incluir en los protocolos de exploración escalas específicas para valorar este síntoma.

Introduction

Apathy is a modern concept within cognitive and behavioural disturbances of neurodegenerative diseases. It is now accepted that apathy is one of the most common behavioural disorders associated with dysfunction and injuries of the prefrontal cortex and basal ganglia and that the cause of apathy is the interruption of the frontal-subcortical circuits (basal ganglia)[1]. It is also a very common feature in basal ganglia diseases, such as progressive supranuclear palsy, Huntington's disease and Parkinson's disease (PD); moreover, it is almost constant in focal lesions of the caudate, pallidum internum and mediodorsal thalamus[2].

Since it is a very common and incapacitating syndrome in patients with PD, with an estimated prevalence of 16-48%, it must be taken into account when diagnosing and treating non-motor symptoms. The main problem we face in apathy associated with PD is differential diagnosis with depression and cognitive impairment. Moreover, the diversity in the underlying physiopathology of this syndrome is the reason why the development of therapeutic strategies is still in its early stages.

The following article is a review of apathy in order to provide an update on it and to position it in the evaluation of patients with PD.

Development

The dictionary of the Spanish Royal Academy[3] defines apathy as "a mood of impassiveness" and "laziness, indolence, lack of vigour or energy?. Its origin is from the Latin *apath¥a* and the Greek *¿n¿jÂÈa*. Etymologically, this word refers to the absence of passions (*pathos*: passion).

More than two thousand years ago, the Greek philosophers of the Stoic school defined *aphathês* as a state of mind consisting of emotional indifference to the vicissitudes of our existence. The Stoic philosophers believed that happiness could only be achieved when a subject obtained a mood through which he or she became emotionally indifferent to the circumstances or events that life brought. Marco Aurelio expressed this point of view graphically in his "Meditations": "You should be like a rock on which all the waves crash. She is firm and tames the swell around her"; "The first precept: do not be impressed by anything". When the various vicissitudes of life do not arouse in us any passion or emotion, we attain spiritual tranquillity and we reach the maximum happiness we can expect. An echo of this cold and indifference nature towards the adverse circumstances can be found in phrases like "to stoically endure suffering" and "taking things philosophically". It is clear that they were religiously and philosophically influenced by Eastern conceptions, particularly the doctrine of Buddhism and Jainism on nirvana as absolute repose and the highest state of the human mind[4].

In the principles of Christianity, Christians adopted the term "apathy" to describe the contempt of all worldly concerns, a state of mortification, as described in the Gospel. The word has been used since then among the more devout writers. In particular, Clement of Alexandria gave the term an excessive popularity, believing that this would drag philosophers to Christianity, aspiring to such a sublime extreme of virtue. During the Renaissance, the term apathy was used in its ancient meaning "free from passion" by all the great humanists from Erasmus to Vives.

The concept of apathy gained popularity during the First World War, in which the atrocious conditions on the Western Front led to apathy. Here we begin to observe a new concept of apathy developed during the nineteenth century in which the term is used to refer to an unresponsive state, both psychologically and physically. This state has received other names such as adynamic stupor, affective apathy or intellectual apathy[5].

The current concepts and definitions of apathy cannot be more different from those considered by the Stoics. Apathy is currently considered a pathological condition of a patient and is becoming the subject of many research studies. Conventionally defined, apathy is the absence or loss of feelings, emotions, interests or concerns. Traditionally and in currently existing terminology glossaries, such as the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM IV) and the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), apathy is considered as an abnormal personality change secondary to a medical illness. Therefore, it is considered more as an aspect of depression and not as a syndrome with its own identity.

In the early nineties, Robert Marin[6] proposed a definition of apathy with clinical and practical purposes and was the first to give it a separate and distinct entity from that of

depression. Marin defined apathy as a "loss of motivation not attributable to a decreased level of consciousness, cognitive impairment or emotional stress". The latter definition has several problems: the first is that it considers the loss of motivation as the primary symptom of apathy and that defining apathy as a lack of motivation is a psychological interpretation of a behavioural state; secondly, apathy defined in this way may be the clinical expression of different underlying physiopathological mechanisms[5].

The definition of motivation proposed by Marin[7] is "sense, intensity and persistence of goal-directed behaviour". Based on this, Marin's definition of apathy[7] is structured around the following concepts: *a*) reduced goal-directed behaviour, *b*) reduction in target-directed thoughts and *c*) reduction of the emotional constraints of the behaviours directed by objectives. This definition was adapted and slightly modified by Starkstein et al.[8] to create diagnostic criteria (Table 1).

Levy et al.'s alternative definition of apathy[9] proposed considering apathy as a quantitative reduction in actions compared to previous behaviour, although the patient's environment and physical condition remain the same. In other words, they propose as a definition of apathy the quantitative reduction of voluntary behaviour determined by the subject him/herself. This is an objective and quantifiable concept. This replaces the concept of apathy, understood as an alteration in motivation, for a measurable and observable behavioural syndrome.

Under the latter definition, apathy is a disorder of the voluntary acts or behaviour, directed at achieving our objectives[10]. The goal-directed behaviour include a series of steps that go from the processing of external and internal determinants that influence the intention to act, developing a plan of action and initiating and implementing the plan, to the regulation of action by feedback (Fig. 1). Apathy can therefore be seen in a dysfunction at any point in the development, implementation and monitoring of acts directed by goals. Because the condition may occur in any part of this process, Stuss et al.[11] proposed that apathy should be split into three subtypes based on the altered phase: emotional, cognitive and behavioural or self-triggering (modified by Levy). This last modification by Levy et al.[12] is geared towards emphasising that apathy is not only an emotional and cognitive deficit that can be reverted by external stimuli (hetero-activation), but it may be a deficiency in the conduct itself or in conduct induced by the subjects themselves (auto-activation).

In conclusion, apathy (initially considered as a problem of expression of feelings and emotions), became, in the early nineties, according to Marin, an alteration of motivation. This concept is now being discussed and apathy is considered to be a behavioural syndrome or a dysfunction of the process that gives rise to acts induced by external or self stimuli.

Currently, according to new theoretical and physiopathological models, we can classify apathy into three subtypes: emotional apathy, cognitive apathy and apathy from auto-activation deficits.

Table 1 Diagnostic criteria for apathy

Loss of motivation relative to the patient's previous functioning or according to the standard marked by his/her age or culture as referred by the subject or by the observation of others
Presence for the past 4 weeks, and during most of the day, of at least 1 symptom belonging to each of the following 3 domains:
Decreased goal-directed behaviour s
Pérdida de esfuerzo o energía para llevar a cabo las actividades de la vida diaria
Dependence of the stimulation of other people to make and organise the activities of daily living
Decreased goal-directed thinking
Loss of interest in learning new things or having new experiences
Lack of concern about personal problems
Decrease in emotional constraints of goal-directed behaviour
Affective flattening
Loss of emotional response to positive or negative stimuli
The symptoms cause clinically significant dysfunction and interfere with the patient's social, occupational and other functions
The symptoms are not due to a decreased level of consciousness or to the effects of drugs or other substances

Taken from Starkstein, 2000; adapted from Marin, 1991.

Emotional apathy

Emotional apathy refers to a reduction in one's own goal-directed behaviour and actions, due to the inability of associating affective and emotional signals with the closer ongoing actions. Any alteration between affection-emotion and behaviour-actions can cause apathy, either by reducing the willingness to carry them out, by the inability to finish tasks or by the inability to assess the consequences of future actions[13]. The areas involved are the orbitomedial area of the prefrontal cortex[14] and the limbic area of the basal

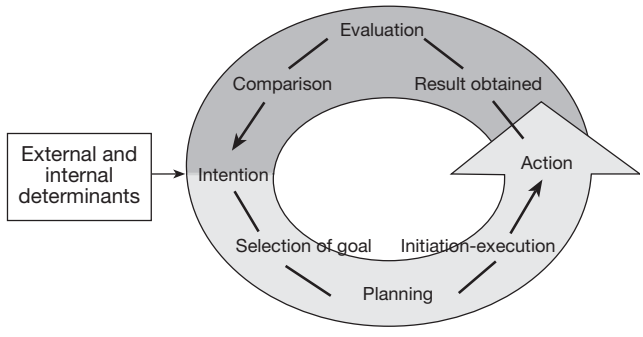

Figure 1 Model of the functional organisation of goal-directed behaviour. Modified from Brown et al.[48].

ganglia (ventral striatum and ventral pallidum), that is, the limbic cortico-thalamic-striatal circuit (Fig. 2).

Injuries in the frontal orbitomedial region cause apathy, as has been observed in frontotemporal dementia or focal lesions in this area. Apathy appears in more than 70% of patients in the early stages of frontotemporal dementia[15]. A reduction in reaction to emotions and in personal sensitivity to reward has been observed in patients with focal lesions in the frontal orbitomedial region, leading to a decreased capacity to make decisions and an inability to accurately assess the consequences of one's own choices and actions on an emotional-affective basis[16]. These consequences induce a quantitative decrease in actions motivated by our own objectives.

The frontal orbitomedial region has connections with the limbic system (amygdala, *subiculum*, ventral tegmental area) and the visceromotor areas (hypothalamus, periaqueductal grey matter). The more lateral areas of this region have connections with the sensory areas (olfactory, gustatory, somatosensory, visual and primary and secondary auditory areas). The afferents from the sensory and limbic areas provide the orbitomedial region with the necessary emotional input for developing voluntary, present actions[17].

Studies on monkeys and recent findings in humans have proven that the orbitomedial area is an essential part in the mechanism of reward, especially when the value of the reward determines the development of a behaviour[18]. Lesions to this area produce insensitivity to reward, which may lead to a reduction of voluntary acts, secondary to both endogenous and exogenous stimuli. Dopamine, the neurotransmitter involved in the mesolimbic and mesocortical connections in these pathways, is involved not only in natural rewards, but also in addictions, through a mechanism of dopaminergic sensitisation and neuronal plasticity[19].

Part of the orbitomedial region output is projected onto the medial and ventral parts of the caudate nucleus, which in turn is projected on the pallidum internum and the substantia nigra of the *pars reticulata*. Pallidal projections terminate in the mediodorsal area of the thalamus and from there return to the frontal orbitomedial area. This cortico-subcortical-cortical loop has connections with the amygdala and is known as the "limbic loop". Based on this physiological observation, the participation of the medial area of the striatum as a key structure involved in the relationship between emotional states and voluntary actions has become accepted. However, studies in humans who have suffered isolated lesions of the ventral part of the striatum show that these do not produce apathy, while extensive lesions of all basal ganglia do produce it[20].

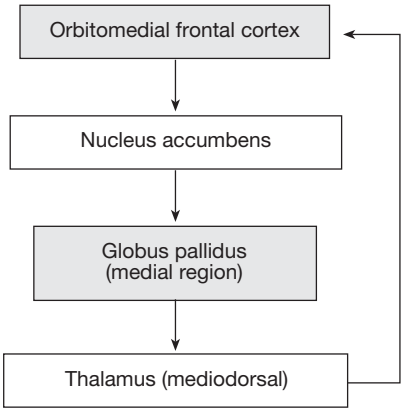

Figure 2 Diagram of the anatomical-functional correlate of emotional apathy. Modified from Tekin et al.[2].

Therefore, we can consider that emotional apathy, secondary to a dysfunction of the affective-emotional processing of actions, may be secondary to a lesion of the frontal orbitomedial region rather than to a lesion of the medial area of the striatum, mainly involved in reward systems.

Cognitive apathy

Cognitive apathy refers to a decline in behaviour and actions directed by one's own objectives by the alteration of the cognitive functions needed to develop the action plans to accomplish them. These functions are grouped under the name of executive functions. Patients may be apathetic from the disruption of working memory (the one responsible for keeping the memory of events in progress) or from the difficulty in generating new rules and strategies or in changing from one action or mental process to another[21]. The area involved is the lateral part of the prefrontal cortex and the cognitive territory of the basal ganglia (caudate and dorsal pallidum)[22] (Fig. 3).

A reduction in target-directed actions can be produced by lesions in the lateral area of the frontal cortex, which produces executive dysfunction. The lateral part of the prefrontal cortex (composed of the dorsolateral, ventrolateral and frontopolar areas) is the neuronal area that produces executive functions. An alteration in event planning and working memory causes a secondary difficulty in sequencing ideas and mentally representing a motor sequence, as well as in developing them and achieving them completely[24]. This dysfunction causes a quantitative reduction and qualitative dysfunction in goal-directed actions.

The lateral part of the prefrontal cortex has connections with the caudate nucleus, mainly on its dorsal part. Lesions to the lateral part of the caudate nucleus produce executive dysfunction, similar to the executive dysfunction caused by prefrontal lesions. There is evidence that both unilateral and bilateral lesions of the dorsal portion of the caudate nucleus produce severe apathy and executive dysfunction. All these studies indicate that the dorsal portion of the caudate nucleus and the lateral part of the frontal region are the regions that contribute most to the executive functions. Cognitive apathy therefore appears by lesions to these two areas and is directly related to the presence of a dysexecutive syndrome.

Apathy as a result of auto-activation deficit

Apathy from a dysfunction in auto-activation is the most severe subtype of apathy. It is characterised by a difficulty

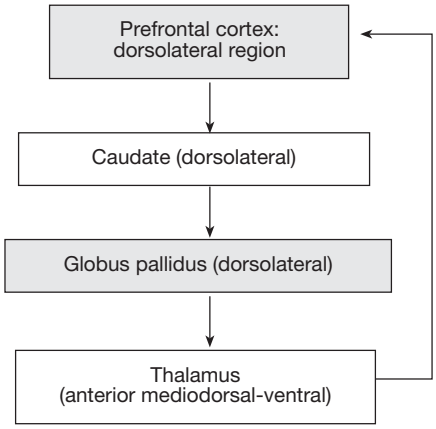

Figure 3 Diagram of the anatomical-functional correlate of cognitive apathy. Modified from Tekin et al.[2].

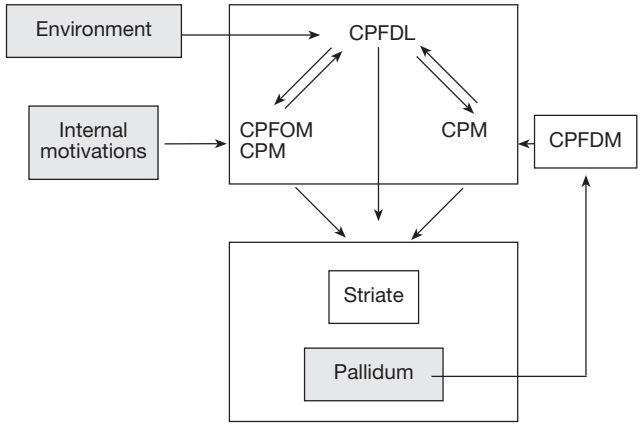

Figure 4 Diagram of the anatomical-functional correlate of apathy by auto-activation deficit and of the auto-activation mechanism. Pallidal lesions cause a disruption of the entire circuit. Modified from Levy et al.[25].

in initiating self-motivated actions and thoughts, while retaining the ability to initiate actions motivated by external stimuli[25]. It occurs because of an inability to reach the triggering threshold required by thoughts and actions when the subject acts on an inner voluntary impulse, not based on automatic responses to external perception. The area involved is principally the cognitive and limbic part of the basal ganglia and, to a lesser extent, the dorsomedial area of the prefrontal cortex[12] (Fig. 4).

Motor activities can be classified into two groups. First, intentional actions controlled by their consequences (goal-directed actions) and, second, habits (which are related to specific stimuli). When a result is dependent on a particular response (pressing a switch by making a movement), it is said that the behaviour is instrumental. These actions are different from reflex ones; there is no dependence between conduct and consequence. The basal ganglia control instrumental behaviour. Their injury causes a decrease in goal-directed actions.

Auto-activation deficit apathy reflects the joint dysfunction of emotional and cognitive processing. Auto-activation represents the central role of the basal ganglia. This function can also be divided into a motor domain (that would be reflected, in the event of injury, by symptoms such as akinesia, freezing or reduction in the number of spontaneous movements) and a non-motor domain represented by the cognitive and limbic parts of these territories. The main consequence of an injury to the non-motor domain is a deficit in auto-activation of voluntary actions (that is, a decline in deliberate instrumental actions), but this is partially reversible by external stimuli[25].

The most serious patients suffering from this type of apathy are those who spend all day in the same place and in the same situation, without speaking and without any initiative. When asked about their state, they say that their mind is empty. This produces a drastic reduction in activities of daily living. In contrast, these patients may present pseudo-obsessive behaviours and stereotypes in this state.

Apathy caused by auto-activation occurs in medial frontal lesions that affect the subcortical white matter, the medial region of the promoter area and the dorsal part of the anterior cingulate cortex, as well as in basal ganglia lesions, mainly those affecting the pallidum internum bilaterally[27].

Auto-activation deficit indicates that lesions to the basal ganglia produce a deficit in triggering inputs to the frontal lobe, particularly those that come from internal decisions. In patients with progressive supranuclear palsy (PSP), in whom there is global dysfunction of the basal ganglia, a frontal hypometabolism can be observed[28]. A model has been proposed that gives the basal ganglia the role of selecting the actions to be undertaken in auto-activation. In a normal state, the frontal cortex receives the necessary external and internal stimuli to carry out possible actions; the basal ganglia process this information and validate the most relevant action. This is handled by extracting the most important signal out of the noise constantly being received and this decision is then communicated to the effector organ, which is the frontal cortex[29].

In short, auto-activation deficit apathy is that in which voluntary actions do not reach the necessary activation threshold due to a decrease in the signal/noise ratio at the level of the prefrontal cortex. In the case of a lesion of the basal ganglia, the ability to select and amplify the relevant signal is reduced[30].

Apathy from auto-activation is a consequence of lesions in the limbic and cognitive territory of the basal ganglia (mainly pallidum internum) and of lesions in the dorsomedial region of the prefrontal cortex. In apathy caused by auto-activation, self-motivated responses are dramatically diminished in comparison with responses induced by external stimuli.

Apathy as an independent syndrome of depression and cognitive impairment

The current discussion is whether apathy is a syndrome of depression or dementia or if it is a syndrome on its own. According to the DSM-IV, depression can be diagnosed without the presence of a depressed mood if there are symptoms of loss of interest and anhedonia; and according

to the ICD-10, patients without a depressed mood, but with loss of interest or lowered vitality, can be diagnosed with mild or moderate depression. Diagnostic criteria as well as the major scales that measure depression, such as the Hamilton rating scale for depression (HAM-D) and the Montgomery-Åsberg depression rating scale (MADRS), treat apathy as an aspect of depression. In depression, apathy is a result of anhedonia or a greater sensitivity to negative feelings that interfere with attention or executive functions[31]. While it is accepted that apathy can be another symptom of depression, there are many clinical situations in which apathy can be completely independent from depression[32].

The first characterisation of apathy as an entity with its own clinical, physiological and pathogenic features, independent of depression, was made by Marin. This author was the first to design a study[33] to discriminate between the two symptoms. He studied patients with Alzheimer's, stroke and major depression using his apathy evaluation scale and the HAM-D. He noted that the relationship between apathy and depression in different groups varied considerably. A high frequency of apathy and low frequency of depression was observed in patients with Alzheimer's. Patients with left hemispheric lesions had higher frequencies of apathy and lower frequencies of depression, while patients with right-sided lesions presented both symptoms in similar frequencies.

Levy studied a series of 154 patients with five neurodegenerative diseases (Alzheimer's, frontotemporal dementia, Parkinson's, PSP, Huntington's) to analyse the characteristics distinguishing apathy and depression. He found a higher frequency of apathy than of depression in Alzheimer's, frontotemporal dementia and PSP, as well as a positive correlation between apathy and cognitive impairment in patients with Alzheimer's and Parkinson's but not in PSP and Huntington's. Of all these diseases, PSP is the one that produces the highest frequency and severity of apathy. That study concluded that apathy is a common neuropsychiatric symptom and can be clearly distinguished from depression[34]. The confusion with depression in many studies may be because many of the scales that measure depression include items that measure apathy, but also because apathy and depression, according to recent research, share similar physiopathological circuits and it may be that a simple imbalance of neurotransmitters produces different symptoms. A dopaminergic and cholinergic deficit is implicated in the physiopathology of apathy; in contrast, serotonergic agents that clearly improve depression worsen apathy.

Neither is there any doubt that apathy is a symptom that often occurs in PD, irrespective of depression. To confirm these data, Kirsch-Darrow et al.[35] designed a study to assess apathy and depression in Parkinson's disease, which had as its main objective to assess whether apathy is a characteristic or a core symptom of the disease. This study compared patients with PD (n = 80) with others who also presented subcortical dysfunction, such as patients with dystonia (n = 20). The study result was that, using Marin's scale, the frequency of apathy in patients with PD was 51% compared with 20% in patients with dystonia. In 28.8% of the patients with PD and apathy, this was not associated with depression, a feature not evidenced in any patient with dystonia. The conclusion of the study was that apathy is a characteristic, very important symptom of PD and that it occurs independently of depression. Apathy, therefore, is not a symptom that appears in any subcortical dysfunction, but is associated with a dysfunction of the non-motor circuits between the prefrontal cortex and the basal ganglia.

These facts make the diagnosis of depression more difficult in patients with PD because its symptoms overlap with those of apathy. Both apathy and depression can cause psychomotor slowness in the patient, changes of facial expression, decreased voice volume, and disturbances in sleep and cognitive skills. This is what is known as anhedonia, which is the inability of individuals to experience pleasure. The nosological relationship between apathy and anhedonia depends on the definition of apathy that we consider. If apathy is considered as a loss of feelings or an emotional reaction, then anhedonia is a symptom of it. However, if we consider apathy as a decline in motivation, then anhedonia is not part of the concept. Starkstein et al.[36] conducted a study in patients with dementia in which they observed that patients with apathy but without depression rarely suffered anhedonia: this suggests that anhedonia is a symptom of depression rather than apathy. In this case a problem arises: depression may be underdiagnosed in PD because apathy is considered a further symptom of PD, all the more so considering that many patients with Parkinson's suffer mild forms of depression. Differentiating these conditions is very important to prevent misdiagnosis and, therefore, errors in treatment[5]. Apathy should be treated with methylphenidate, levodopa or dopaminergic drugs[37], in the case of Parkinson's disease, and cholinesterase inhibitors in Alzheimer-type dementia or dementia with Lewy bodies. On the other hand, if we mistakenly treat depression, serotonin reuptake inhibitors worsen apathy.

Marin's 1991 definition of apathy indicated that apathy should be diagnosed in the absence of altered mental status, moderate or severe cognitive impairment and significant emotional stress. This definition allows us to diagnose the syndrome of pure apathy. Many studies show that apathy is more common in patients with cognitive impairment or dementia[38]. Conceptually, when a problem is considered as a syndrome, it refers to a constellation of symptoms that characterise a given situation, but not to its aetiology. Therefore, when we refer to apathy as a syndrome today, the aetiology may be very diverse. However, in certain conditions such as dementia, there are still doubts about whether it is a separate syndrome or a symptom of the disease. As in the case of other psychopathological syndromes such as depression, which often appear in many neurodegenerative diseases, apathy can also occupy a parallel place[8]. Although in many studies executive dysfunction is associated with more severe forms of apathy[39], cognitive impairment in itself is not sufficient to cause apathy, given that many other studies show that patients with cognitive impairment do not have apathy[40]. The syndrome of apathy associated with dementia may have a different origin of the syndrome of apathy present in other neurological diseases (Parkinson's, frontal lesions...) or in psychiatric illnesses. This remains to be clarified by studying its physiopathology in each of the diseases in which it appears.

Apathy in Parkinson's disease

What is the physiopathological mechanism of apathy in Parkinson's disease? There are many neurochemical systems considered potential candidates for causing apathy. Dysfunctions of the following pathways are thus considered: ascending dopaminergic, including the nigrostriatal and mesocorticolimbic; cholinergic; ascending serotonergic and noradrenergic[25].

The underlying physiopathology of this syndrome in PD is very important; to find new treatments, there have therefore been many studies aimed at identifying not only which pathway is the most involved in the apathy of PD, but also what factors influence this.

Adrenergic pathways have been studied in PD using an *in vivo* adrenergic marker (serotonin, noradrenaline) with PET scans[41]. In patients with both PD and apathy, it is observed that there is a decreased uptake of adrenergic receptors in the ventral striatum that is proportional to the degree of apathy. A study carried out by the group of Levy[42] showed in 28 patients a difference in the severity of apathy between the *on-off* stages, suggesting that apathy in PD is, at least partially, a syndrome related to dopamine. Dopaminergic stimulation mediates in reward processes and is believed to be the main cause of the physiopathology of apathy in Parkinson's disease[43]. Dopamine is involved in the learning process dependent on rewards and in decisions made despite the risk of not obtaining an expected reward[44]. Since these processes depend on the mesocorticolimbic pathway, a dysfunction of this pathway in PD could cause apathy, specifically emotional apathy[45]. However, there is evidence to rule out that emotional apathy is the only mechanism of apathy in PD: *a*) the existence of apathy in the early stages of the disease when the dopaminergic mesocorticolimbic system is still intact[46], and *b*) the normality of tests evaluating reward mechanisms in PD patients even in states off medication[42].

There is data supporting the presence of the cognitive apathy subtype in PD, that is, that which occurs by a dysfunction of the prefrontal dorsolateral pathway and the dorsal part of the caudate nucleus. Cognitive dysfunction in patients with PD is equal to that which occurs in patients with lesions in the prefrontal dorsolateral region[47]. Apathy in patients with PD is more common in those with executive dysfunction and cognitive impairment[48].

Finally, an alternative to the previous hypotheses explaining apathy in PD would be one that takes into account the role of the striatum as the selector of relevant signals out of the environmental noise constantly being received[49]. As with the motor symptoms of PD, following striatal dopamine depletion, there would be a failure in selecting and amplifying relevant signals in the striatum, thereby contributing to the production of apathy because striatal afferents would be unable to select relevant signals. Dopamine acts as a non-specific modulator of the firing threshold of striatal neurons; its depletion results in a decrease of their activity and their triggering frequency[50]. Dopamine depletion can therefore cause problems in the patient's decision-making process, slowing it down or even suppressing it. There are functional neuroimaging studies[51] in non-demented PD patients in the *off* stage that show that they have a frontal hypometabolism in relation to controls. This hypometabolism, reversed by apomorphine and dopamine agonists, would receive a contribution from GABAergic hyperactivity of the pallidum internum that would produce a thalamocortical hypofunction. This theory is more involved with the function of the striatum in the participation of goal-directed or auto-activated actions.

Considering that the loss of dopamine is not homogeneous throughout the striatum, an explanation could be that, depending on the most affected circuit (motor, cognitive, associative), the clinical manifestations and form of apathy prevailing in a patient with PD are different. This is supported by the lack of association between apathy and the severity of motor symptoms.

Recently, it has been reported that the main system involved in cognitive dysfunction in PD is cholinergic deficit[52]. The implication of this system as a cause of apathy is supported by the relationship existing between apathy and executive dysfunction and the presence of apathy in patients with Alzheimer's disease without dopaminergic deficit[53]. Recent studies[54] have observed that cholinesterase inhibitors improve neuropsychiatric symptoms in PD, especially apathy.

Substances with multiple action mechanisms (amphetamines, dopamine, cholinesterase inhibitors) improve apathy and the variety of neurotransmitter systems involved. This fact implies that more research and clinical studies are needed to explore the physiopathology of this syndrome and to be able to apply new treatments.

It is clear from all the studies that apathy in PD at this time cannot be considered as the result of a single causal mechanism, but is probably due to the participation of cognitive apathy, emotional apathy or auto-activation deficit in variable percentages (depending on the type of patient). It will be interesting in future studies to attempt to clarify these theories further and identify phenotypes of patients that correlate more with one kind of apathy or another in order to apply individualised treatments.

Epidemiology of apathy in Parkinson's disease

Apathy is one of the negative symptoms characteristic of frontal-subcortical dysfunction. This symptom produces great impact on and is of great weight in the degree of patient disability and results in a very substantial reduction in activities of daily living appropriate to their ages, regardless of other aspects of the disease.

Apathy in PD was first studied in the early nineties; since then, a number of studies have been carried out in this respect (Table 2). Starkstein et al.[55] were the first to study the frequency of apathy in PD, in a 50-patient study that measured the frequency of neuropsychiatric symptoms such as apathy, depression and anxiety. This study, using Marin's apathy evaluation scale, a frequency of apathy in the series of 12% for apathy in isolation and 30% for apathy associated with depression. Apathy in patients with or without depression was associated with specific cognitive deficits such as verbal fluency and response time. At that time, it was concluded that apathy was prevalent in PD and was associated with cognitive dysfunction. It was also proposed

that the causal mechanism is independent and different from that of depression.

Aarsland et al.[56] studied the neuropsychiatric symptoms of a series of 139 patients using the neuropsychiatric inventory (NPI) scale. The results were that 61% of the sample suffered from a neuropsychiatric symptom and 45% from two or more symptoms. Depression was the most frequent symptom, followed by hallucinations and anxiety. The highest scores were for the items of apathy, anxiety and depression. All the symptoms were represented at higher frequencies than in the general population. The exact frequency of apathy found was 16.5%; apathy correlated with greater executive dysfunction. In all symptoms found, their severity was related to disease duration and cognitive impairment but not to age, disease duration, levodopa dose, dyskinesias and *on-off* phenomena.

The same group[39] carried out a new study in a large, 537-patient series, initially selected to evaluate the efficacy of rivastigmine in patients with PD. With the NPI scale, they found a frequency of neuropsychiatric symptoms of at least one symptom in 89% of the patients and two or more in 77%. The severity of all symptoms was moderate in 64% of patients. Depression was the most common symptom (58%), followed by apathy (54%), anxiety (49%) and hallucinations (44%). The patients with more advanced PD and greater cognitive impairment had neuropsychiatric symptoms more often.

A study by an Italian group[45] in 30 patients with PD and 25 controls, designed to study the level of apathy using Marin's apathy scale, observed a frequency of apathy of 43.3%. A relation was observed between apathy and impairment of executive functions. Pluck et al.[48] also studied apathy in PD in a series of 45 patients using Marin's scale, finding a frequency of 37.8%. They did not find a connection with disease duration. There were no differences in the frequency of depression and anxiety and between the different severities in apathetic patients. Apathetic patients have more executive dysfunction and it is greater in the most apathetic.

The French group who created the Lille apathy scale (LARS)[57] has studied a series of 159 patients with PD. The prevalence of apathy found in this study was 32%. Apathetic patients, with respect to the non-apathetic, did not show significant differences in the main demographic and clinical parameters, except that the former presented higher dysexecutive dysfunction and more severe depressive symptoms. The contribution to the total score of the four dimensions of apathy studied (emotion, intellectual curiosity, self-awareness and onset of action) was different; the variables related to executive dysfunction had a more important participation.

One of the most recent studies published in this regard is that of a Norwegian group that has estimated, in 232 patients, the prevalence of apathy in a sample population[58]. Part I, item 4 (motivation/initiative score) on the unified Parkinson's disease rating scale (UPDRS) was used to diagnose apathy. The rate of apathy obtained was 38%; of this, depression and dementia coexisted in 11%, 6.5% of apathetic and demented patients did not have depression, 10% of apathetic patients had depression without dementia, and 9% were apathetic and without depression or dementia.

Table 2 Percentages of apathy in Parkinson's disease and rating scales used in the existing studies

Studies	Percentage of apathy	Scale used
Starkstein[55], 1992	42%	AS
Aarsland[56], 1999	16.5%	NPI (7)
Pluck[47], 2002	37.8%	AS
Dujardin[57], 2007	32%	LARS
Pedersen[58], 2008	38%	Part I (Item 4), UPDRS
Kulisevsky[59], 2008	48%	NPI

AS: Apathy Scale; LARS: Lille apathy rating scale; NPI: neuropsychiatric inventory; UPDRS: unified Parkinson's disease rating scale.

In this study, apathy was associated with increased cognitive and motor disabilities. Excluding cases with dementia and depression, 5% of the patients in the series presented apathy in isolation.

A Spanish group[59] has also published, over the past year, a study on this matter, focusing on the neuropsychiatric profile of patients with PD. It studied 1,351 patients with PD without dementia. It used the following scales: NPI, hospital anxiety and depression scale (HADS), executive performance (fluencies) and Epworth sleepiness scale. The most common symptom was depression (70%), followed by anxiety (69%), apathy (48%) and irritability (47%). They concluded that apathy emerged as an independent syndrome in patients with PD without dementia, indicating the need to seek specific treatment for this syndrome.

How is the diagnosis of apathy established?

Marin suggested in his early publications that apathy can only be diagnosed after a neuropsychological assessment that includes an evaluation of the subject's social environment and physical conditions. Subsequently, there has been an emphasis on the importance of the great variability of individual goals, interests, activities and emotional expressiveness, which are strongly influenced by cultural factors such as individual experience, education, social class and age. All these circumstances should be taken into account when establishing a clinical diagnosis of apathy. The problem arises when trying to establish a formal diagnosis of apathy in the absence of diagnostic criteria and with limited diagnostic tools available.

In the first place, elaborating a diagnosis requires valid and reliable criteria. So far, only those of Marin[6] adapted by Starkstein[8] are available, as has already been detailed in Table 1. Starkstein's adaptation restructures the original criteria and abandons cognitive impairment as an exclusion criterion. A time criterion was also included in the last review by this author[5].

The first method for assessing apathy is anamnesis carried out by the neurologist or neuropsychologist on the patient and caretakers. In addition, a series of

neuropsychological batteries should be conducted to assess other concomitant syndromes, such as depression and cognitive impairment.

With time and deeper studies into apathy, a series of questionnaires to assess it have been developed. These questionnaires have recently been analysed by the Movement Disorders Society[60].

Marin's Apathy Evaluation Scale (AES)[6] is the most widely used scale for assessing apathy in clinical studies. The AES contains 18 items and has been specifically designed to assess the impairment of behavioural, affective and cognitive elements of motivation. The AES has been validated and used effectively in patients with apathy and with dementia secondary to cerebrovascular accidents[61] and PD[55], as well as in Alzheimer's disease and other dementias. There are several versions of this scale: self-administrated by the patient, completed by the caretaker or carried out by the evaluator of the patient. The data available in PD are reliable, but there is no validity data. The Children's Motivation Scale is a variant of the AES used to assess apathy in children and adolescents. There is also the Apathy Scale (AS), which is an abbreviated version of 14 items that has been successfully validated in patients with PD[55]. The latter is considered as a recommended scale to assess apathy in PD because there are very acceptable validity and reliability data in patients with PD[58].

The Neuropsychiatric Inventory (NPI)[62] is a neuropsychiatric scale that assesses 10 psychopathological domains in patients with dementia and is administered to caretakers. The most widely used scale in research and clinical trials, the NPI includes 10 subscales: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and aberrant motor behaviour (continuous foot movements –pacing–, compulsions, etc.). In addition, two subscales relating to appetite and sleep disorders have been added. The subscale used to investigate apathy (subscale 7) includes questions related to loss of interest, lack of motivation, decreased spontaneity, affection and enthusiasm, loss of emotions and disinterest in carrying out new activities[63]. This scale has been used in numerous studies to assess the frequency and severity of neuropsychiatric symptoms in patients with PD. In a recent review, it was felt that this scale may be indicated for measuring apathy in PD; however, this is not recommended, given that there are no metric data in PD[60].

The Apathy Inventory (AI) is a scale that has 3 ítems[64]. Except for the data in its original description, in which 12 patients were evaluated, no other data are available in patients with PD. It cannot therefore be recommended for assessing apathy in these patients[60].

Item 4 of the UPDRS is also recommended to assess apathy in PD[65]. There are validation data in several series of patients with PD. However, being just a single item, it does not offer much information. It can therefore only be considered a screening tool.

The scale developed by Strauss et al.[66], the Dementia Apathy Interview and Rating, is also available; it assesses changes in motivation, emotional response and commitment in patients with dementia. By an interview with the caretaker, it assesses changes in the last 4 weeks with respect to the previous situation. It is a useful scale that could be applied to patients with dementia, but there is no data available from patients with PD.

Finally, the Lille apathy rating scale (LARS) was created in 2006 as the first scale developed for the diagnosis of apathy in Parkinson's disease in accordance with the new concepts of apathy. According to the authors, the LARS scale is a practical and reliable instrument for assessing multiple areas of the apathy syndrome. The scale consists of 33 items, divided into nine domains. Answers are based on emotions, thoughts and activities experienced by the patient in the previous 4 weeks. Each of the 9 domains constitutes a subscale with equal weight in the global scale score. The range of scores varies between –36 and +36, the highest score corresponding to a higher degree of apathy. Our group has performed a validation of the Spanish version of this scale, with results that are still pending publication.

Conclusions

Apathy is a behavioural syndrome or dysfunction of the process that causes the actions induced by external or internal stimuli. It has a high prevalence in all diseases affecting the basal ganglia, in particular Parkinson's disease. In the latter case, it is related to the degree of executive dysfunction and is independent of motor symptoms. Its diagnosis requires carrying out a clinical interview using the available diagnostic criteria, in addition to a scale-based neuropsychological assessment that also covers depression and cognitive impairment. This global assessment of the patient will allow us to make a differential diagnosis of cognitive-behavioural symptoms and implement the most appropriate therapeutic measures. To do so, it is necessary to have adequate measurement tools, designed specifically for this purpose or at least validated in these patients. At present, we have no drug that has proven, in a clinical trial, its benefit in this syndrome. To improve the management of this syndrome in patients with PD, functional and descriptive neuroimaging studies need to be carried out to establish more precisely the subtypes of apathy and their involvement in PD.

Conflict of interests

The authors declare no conflict of interests.

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