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Apathy Syndrome in Neurological Diseases – State of the Art and Current Research Directions

Magdalena Roessler-Górecka[1]
Institute of Psychiatry and Neurology in Warsaw
Second Department of Neurology
https://orcid.org/0000-0002-1375-5643

Abstract

Aim: Apathy is sometimes indicated as a symptom in various diseases, among others in psychiatry. However, for several decades it has also been distinguished as an independent syndrome accompanying many neurological diseases. Although still omitted from current medical classifications, apathy syndrome is the subject of numerous theoretical and clinical analyses. The spreading of knowledge on it among clinicians – including the possibility of recognizing and differentiating it, especially from depression – is of fundamental importance for the effectiveness of therapeutic interventions. The paper presents definitions and diagnostic criteria of apathy syndrome proposed in the literature. It presents data on its prevalence in various diseases, its relationship with brain pathology, and several clinical variables.

Theses: Contemporary concepts emphasize the syndromic character, multidimensionality of apathy syndrome and links with the broadly understood functions of frontal lobes. The domains of functioning in which symptoms of apathy may be revealed include the cognitive sphere, the emotional sphere, social interactions, and behavior (initiating and maintaining any intentional activity). The relative independence of apathy syndrome from depression is indicated, the importance of apathy syndrome as a prognostic factor for dementia is emphasized, as well as its relationship to quality of life, effectiveness of rehabilitation and psychological burden on caregivers. As for neuronal basis of apathy, a few partially overlapping processes are considered, with significant role of basal ganglia and certain areas of prefrontal cortex.

Conclusion: Dysfunction of any link of complex prefrontal-subcortical circuits may be crucial for occurrence of apathy symptoms, which explains high frequency of this syndrome

[1] Correspondence address: mroessler@wp.pl.

in brain diseases, especially those with damage to basal ganglia and/or prefrontal cortex. Different severity of symptoms in particular domains and recurrence of abnormality profiles observed depending on the analyzed disease and/or location of brain pathology prompt the search for subtypes of apathy syndrome.

Keywords: apathy syndrome, basal ganglia, prefrontal cortex, executive dysfunctions

Definitions and Main Concepts of Apathy

The term *apathy* is sometimes used imprecisely to describe various conditions, determined biologically and situationally (Jorge et al., 2010). In psychiatric literature, it has for decades been synonymous with indifference or "blunted" , "flat" affect, often indicated as an element of mood disorders; in neurology, apathy has been mentioned, among others, as a component of abulia syndrome (Fisher, 1983). Clinical ambiguity may also be caused by the coexistence of concepts with a similar range of meanings, such as "psychic akinesia" (*psychic akinesia*, Laplane et al., 1984) or *athymhormia* (Habib, 2004). In 1990, Marin, to clarify the meaning of the term apathy, defined it as "a decrease in motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress" (Marin, 1990, p. 22). Therefore, conditions such as depression, dementia, delirium, but also, for example, akinetic mutism have been eliminated from the medical definition – and the psychological (motivational) nature of apathy has been mainly emphasized. A year later, while acknowledging that clinically apathy can sometimes be identified as a symptom of other disorders, Marin emphasized that it can also occur as a complex independent syndrome (Marin, 1991). He indicated the presence of a motivational deficit in any domain of behavior, affect, or cognition as sufficient to diagnose apathy; proposed exclusion criteria were disorders of consciousness, depression, and cognitive disorders as primary causes of apathy (Marin, 1991; Marin & Wilkosz, 2005).

On the other hand, Stuss and Benson (1986) defined apathy as "an absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action" , which, according to them, provided a better framework to measure such a variable. They emphasized that apathy is not a causally and behaviorally homogeneous syndrome, but rather a certain possible group of conditions, with different clinical manifestations and neural mechanisms (e.g., drive disorders primarily associated with damage to medial frontal regions of the brain and disorders of arousal regulated by lower neural axes, cf. Stuss & Benson, 1986; Stuss et al., 2000). These authors proposed to divide apathy syndromes into three main subtypes: "emotional" , "cognitive" and "behavioral" . Levy and Dubois (2006) considered the term "behavioral apathy" to be a tautology – they introduced the term "auto-activation deficit" instead, emphasizing the contrast

between the presence of actions undertaken by the patients due to external stimulation and the limitation of those undertaken on their own initiative. In later years, Levy (2012), defining apathy as a "quantitative reduction of goal-directed behavior," described the "auto-activation deficit syndrome" as its most severe form.

An attempt to organize these issues was presented by Radakovic and colleagues (2017, 2018), who proposed a multidimensional model of apathy, referring its various forms to Stuss's (2011) concept of frontal (including executive) functions. In their opinion, most forms of apathy described in the literature can be classified as: initiation apathy, executive apathy or emotional apathy. The first group includes, among others, behavioral apathy or "auto-activation deficit" , the second includes clinical problems referred to as cognitive apathy and/or decreased intellectual curiosity, and the third group includes affective "flattening" or emotional "blunting" . All three dimensions of apathy (i.e., initiating, executive and emotional) are associated with specific functions of frontal lobes and their connections, respectively: energization (that is, the process of initiating and sustaining response to stimuli), executive (meaning here, among others, task setting and monitoring goal-directed action), and the aspect of behavioral/emotional self-regulation (including integration of emotional and social aspects of action as well as its assessment in terms of risk, punishment and reward). An additional element of the model is self-awareness, which may vary depending on the dimension of apathy analyzed (Radakovic et al., 2017).

Diagnostic Criteria for Apathy

In 2001, Starkstein and colleagues proposed the first structured diagnostic criteria for apathy syndrome, based on the original concept of Marin (1991). These included:

A. Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture, as indicated either by subjective account or observation by others.
B. Presence, with lack of motivation, of at least one symptom belonging to each of the following three domains during the last four weeks, for most of the day:
   B1. Diminished goal-directed behavior
      1. Lack of effort to perform daily activities.
      2. Dependence on the encouragement of others to carry out complex structure activities.
   B2. Diminished goal-directed cognition
      3. Lack of interest in learning new things or in new experiences.
      5. Lack of concern about one's personal problems.
   B3. Limitations of emotional aspects of intentional behavior:
      5. Unchanging affect.
      6. Lack of emotional responsivity towards positive and negative events.

C. Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D. Symptoms are not due to diminished level of consciousness or direct psychological effects of a substance (e.g., medications).

A further modification of criteria of apathy was proposed by Robert and an international group of experts (2009), who distinguished between behaviors, emotional responses, and cognitive curiosity dependent on external stimulation and those initiated spontaneously: interestingly, according to these authors, a diagnosis of apathy can be established regardless of whether the first, second, or both forms of activity are disturbed. They also postulated impairment of at least two of the three domains of functioning (i.e., intentional behavior, cognitive and/or emotional activity) as necessary for diagnosis, (cf. Robert et al., 2009). In 2018, the proposed criteria were updated: the term "motivation" was totally removed and replaced by "goal-directed activity," cognitive and behavioral domains were merged into a single dimension, and the dimension of social interaction was added. References to age or cultural norms were removed: apathy was defined as a quantitative reduction of goal-directed activity in comparison to the patient's previous level of functioning, with consideration for individual differences. For each of the three dimensions (i.e., cognitive-behavioral, emotional and social interaction), five examples of problems are provided to facilitate clinicians' assessment. Exclusion criteria were supplemented by situational/environmental factors (e.g., terrorist attack) since they can induce changes resembling apathy syndrome in everyday behavior of an affected person (Robert et al., 2018). In the most recent proposal of diagnostic criteria, the main domains of apathy are defined as: diminished initiative, diminished interest and diminished emotional expression/responsiveness (cf. Miller et al., 2021). A decrease in initiative was defined as being less spontaneous and/or active than usual self: less likely to initiate usual activities such as hobbies, chores, self-care, conversation, work-related or social activities (dimension B1). Symptoms of decreased interest include reduced participation in activities even when stimulated, less persistence in maintaining or completing tasks or activities, being less interested in, or less curious about events in one's environment, activities and plans made by others, being less interested in friends and family (dimension B2). Among the features of reduced emotional expression/responsiveness, there are: less spontaneous emotions, being less affectionate compared to one's usual self, expressing less emotion in response to positive or negative events, experiencing less concern about the impact of their actions on other people, and less empathy (dimension B3). Importantly, the authors propose the co-occurrence of cognitive impairment/dementia as a necessary criterion for diagnosing apathy in patients with neurocognitive disorders (criterion A). The other criteria are like those proposed by Robert et al. (2009, 2018): for a diagnosis of apathy, a constant or frequent presence of at least one symptom from two or three domains is necessary, observed over the last four weeks, reflecting a change in the patient's usual behavior reported by the patient or an observer (criterion B). Symptoms cannot be exclusively explained by psychiatric illness, intellectual disability, change in level of consciousness, motor or sensory deficits, or direct effects of a substance

(criterion C) but must cause clinically significant impairment of an important area of functioning (personal, social, occupational) (criterion D).

Methods of Diagnosing Apathy

Symptoms of apathy can be identified based on three sources: interview, observation of the patient's behavior and clinical examination – a combination of the above methods is considered optimal (Seniów et al., 2005). It is important to determine the patient's pre-morbid personality traits in anamnesis, exclude situational causes (e.g. lack of stimulation, loneliness) and – during appropriate medical examinations – somatic problems (e.g. hormonal or metabolic disorders) whose clinical picture may imitate apathy syndrome. A full diagnosis should also include a detailed assessment of cognitive functions and the emotional/personality domain (among others for depressed mood, anxiety, guilt, resignation thoughts, suicidal thoughts, and vegetative symptoms of depression). Apart from depression, fatigue may also make a proper diagnosis difficult – fatigue is a common consequence of brain damage, but according to studies it does not correlate with apathy (Douven et al., 2017).

Using the standardized methods of assessment makes it possible to record the nature of apathy, its severity, changes in response to various stimuli (among others, therapeutic strategies), as well as relationships to other elements of the clinical picture. For several decades, there has been a development in diagnostic methods for apathy, based mainly on structured interviews (Lázaro-Perlado, 2019). These tools differ significantly due to diagnostic criteria as well as clinical populations for which they are intended. Some of the methods are fully intended for assessment of apathy symptoms, while others contain only some subscales concerning this aspect of functioning. One of the first specific tools for assessing apathy, originally used in research on Alzheimer's disease (AD), was the Apathy Evaluation Scale, developed by R. Marin *(*AES, Marin et al., 1991), and based on his diagnostic criteria. Currently used in studies of patients belonging to different clinical populations, it is still very popular in English-speaking countries (Lee et al., 2020). Other frequently mentioned and easily accessible online tools are, among others, the AES-based Apathy Scale (Starkstein et al., 1992) and the Apathy Inventory (Robert et al., 2002). In research on dementia syndromes, a multidimensional Neuropsychiatric Inventory (NPI) is often used, a tool that assesses several other domains of functioning in addition to drive and motivational aspects (Cummings et al., 1994). Intensive development of diagnostic methods is observed especially in studies of patients with AD and Parkinson's disease (PD), both due to the large size of these populations and high prevalence of apathy in these diseases. In PD, the proposed methods of detailed assessment (e.g. Lille Apathy Rating Scale, LARS, Sockeel et al., 2006) consider the specificity of this disease symptoms, including motor deficits, which may wrongly suggest a diagnosis of apathy (e.g. slowness, hypomimia). In diseases associated with high prevalence of apathy, global neurological scales often consider this

aspect of patient's functioning, at least in screening (e.g. Unified HD Rating Scale, UHDRS; Unified PD Rating Scale, UPDRS). It is worth noting that there are still only a few available tools that provide assessment of different dimensions or subtypes of apathy, as opposed to providing only a general verification of its presence and severity. An example of a more detailed diagnostic method is the above-mentioned LARS scale, a structured interview covering nine domains of functioning, and the Apathy-Motivation Index (AMI, Ang et al., 2017) developed on its basis. The Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014) also belongs to this group of tools. It is based on the framework of three apathy dimensions (initiating, executive and emotional). DAS studies have shown significant differences not only in the severity but also in the apathy profiles in various neurodegenerative diseases (Radakovic et al., 2018).

Many of the tools mentioned above have their self-report and proxy versions for a relative and/or clinician – using both of them is a practice recommended by experts since it increases the sensitivity of evaluation and assesses the patient's insight into their symptoms – according to research, self-awareness of apathy symptoms can be significantly limited (Leśniak et al., 2022; Mele et al., 2020).

Distinguishing Apathy From Depression

Decreased drive and motivation is an important feature in the clinical picture of mood disorders, often present even in their mild forms, such as dysthymia, especially in the elderly (Steffens et al., 2022). It is most typical of severe depressive episodes, in which the prevalence of apathetic symptoms can reach up to 53% (Ishizaki & Mimura, 2011). Despite the partial overlap in symptoms, much attention has been paid in the literature to differentiate between isolated apathy and depression, especially in individuals with brain injuries (Levy et al., 1998). Depression is thought to be primarily an "emotional disorder," while apathy is primarily considered a "motivational disorder" (Ishizaki & Mimura, 2011). Apathy and depressive disorders have been shown to be distinct both in terms of clinical picture and hypothetical pathomechanism (Jaracz, 2008). The decline in frontal lobe metabolism reported in depressed patients may also be associated with apathy syndrome, but during a depressive episode, in other parts of the limbic system metabolism increases in proportion to severity of mood disorders. These regions include, among others, amygdala, ventrolateral part of prefrontal cortex, and subgenual anterior cingulate gyrus (Drevets et al., 1992, 1999, 2002). In the clinical picture of apathy syndrome, affective symptoms typical of a depressive syndrome (such as sadness, anxiety, negative thoughts, pessimism, and guilt) or significant sleep and appetite disorders are not present. On the other hand, in an isolated depressive syndrome (especially of mild/moderate severity) there is a lack of significant features of indifference and a decrease in emotional reactivity typical for apathy – the main characteristic of depression being relative predominance of negative emotions and focus on negative stimuli, without a significant quantitative reduction in

overall level of reactivity – it is secondarily reduced only in relation to reward signals (McFarland & Klein, 2009).

Apathy in Focal Brain Injury

Apathy is a common consequence of stroke and traumatic brain injury (TBI). In a pioneering study by Starkstein et al. (1993), it was diagnosed in 23% of 80 patients with vascular disease – half of them, however, showed co-occurring symptoms of depression. In another study, 28% of participants showed apathy syndrome without accompanying depressed mood (Andersson et al., 1999), in further studies this percentage ranged between 20–25% (Jorge et al., 2010). The results indicate, among others, a higher prevalence of apathy in the chronic phase of the disease (6–12 months), the absence of a significant association with the severity of motor disability (Angelelli et al., 2004), older age, functional dependence on the caregiver, and more severe cognitive deficits in patients with post-stroke apathy (Brodaty et al., 2005; Santa et al., 2008), as well as lower rates of improvement in daily functioning (Hama et al., 2007; Santa et al., 2008). Some studies have not confirmed the relationship between stroke location and apathy at all (Angelelli et al., 2004), others indicate a higher prevalence of damage to anterior region of right hemisphere of the brain (Bearded et al., 2005), bilateral damage to basal ganglia (Bhatia & Mardsen, 1994; Carnes-Vendrell et al., 2019; Hama et al., 2007), bilateral lesions of medial parts of thalamus (Carrera & Bogousslavsky, 2006) or frontal lobes – in the latter location, apathy is considered a typical element of the clinical picture (Carnes-Vendrell et al., 2019). Damage to internal capsule, resulting in disruption of neuronal connections of globus pallidus and substantia nigra with thalamus, also seems to correlate with this syndrome (Starkstein & Manes, 2000).

Studies suggest that apathy can be a chronic deficit even in relatively mild vascular brain injury: Carnes-Vendrell et al. (2019) found that it was still present in 34.1% of patients one year after a mild stroke or even only an episode of transient ischemic attack (TIA). A link between apathy and post-stroke cognitive impairment has been noted (mainly in auditory-verbal learning, delayed recall, semantic fluency, abstract reasoning, and attention), which, according to researchers, may signal a functional interdependence of neuronal networks regulating these functions and motivational aspects of goal-directed behavior (Tay et al., 2021).

In the case of traumatic brain injury (TBI), apathy is also a common consequence (45–50% of patients: Arnould et al., 2015), associated with poorer rehabilitation outcomes (Brett et al., 2017), increased caregiver stress (Bayen et al., 2013) and difficulties in social reintegration of patients (Arnould et al., 2015). It seems that apathy in TBI disorders may be as persistent as in the case of post-stroke apathy – in longitudinal studies they have been described in more than half of patients even 8 years after the onset of the disease (Monsalve et al., 2012). Not surprisingly, prefrontal cortex is indicated as the most common

lesion location associated with the onset of apathy after TBI (Da Costa et al., 2013). A study of 60 patients with TBI revealed an association between reduced medial prefrontal cortex volume and a higher severity of apathy symptoms (Guild & Levine, 2015). However, there are fewer publications analysing the neuroanatomical correlates of apathy in TBI than in stroke (Le Heron et al., 2018).

Apathy is also indicated as a significant problem for patients with brain tumors: in one study, it was found in 63.6% of patients with frontomedial localisation of meningiomas, and in 25% of patients with tumors located in ventral part of frontal lobes (Peng et al., 2022). Infrequently, apathy may be the first isolated signal of tumor growth, which poses a particular diagnostic challenge (Zarandy et al., 2023). A review of available studies suggests that it is not possible to predict the location of the lesion in such cases (Madhusoodanan et al., 2015). Apathy may also occur after surgical tumor removal – it is often observed in the postoperative period as a consequence of frontal lobe glioma resection, correlating, among others, with high grade tumor type, a left-sided location of the lesion, involvement of anterior cingulate gyrus, dorsolateral and/or orbital prefrontal cortex, as well as a decreased score in the phonemic verbal fluency test: a low result obtained in the examination during awake brain mapping is indicated as possible predictor of post-operative apathy (Motomura et al., 2023).

Apathy in Diseases With Basal Ganglia Involvement

In Parkinson's disease (PD), apathy often co-occurs with depression, but it can be an isolated syndrome as well as the first clinically noticeable sign of the disease (Pont-Sunyer et al., 2014). At the stage of PD diagnosis, apathy is diagnosed in 20–36% of patients, after the introduction of dopaminergic medication it tends to subside, but after 5–10 years of the disease its frequency increases again, reaching 40% in patients without dementia to even 70% in patients with PD dementia (Mele et al., 2020; Pagonabarraga et al., 2015; Starkstein et al., 2009). A significant problem accompanies the therapeutic use of *subthalamic nucleus deep brain stimulation (*STN-DBS) in PD – it has been shown that it may be associated with the onset or worsening of apathy (Zoon et al., 2021). It has been suggested that in PD, apathy is a direct consequence of brain disease rather than a psychological response to acquired disability (Pluck & Brown, 2002), and in the case of selected genetic mutations (especially in the glucocerebrosidase gene), symptoms of apathy may precede any motor symptoms (Pachi et al., 2021). Apathy in PD is associated with executive dysfunctions, which may indicate a common pathomechanism of some symptoms (dysfunction of corticobasal ganglia circuits, Pagonabarraga et al., 2015). This, in turn, is the so-called *executive apathy* that correlates most strongly with a decline in quality of life of PD patients and their ability to perform everyday activities (D'Iorio et al., 2017; Radakovic & Abrahams, 2018). The presence of apathy in PD is also associated with poorer outcomes of movement disorders treatment and is sometimes

indicated as the symptom causing the greatest burden on caregivers (Mele et al., 2020).

In Huntington's disease (HD), apathy may affect as many as 55–90% of patients (Krishnamoorthy & Craufurd, 2011; Thompson et al., 2012). It strongly correlates with disease duration, being an inevitable consequence of its progression; it has even been indicated as a marker of severity of the neurodegeneration process in HD (De Paepe et al., 2019). The main deficit of auto-activation may manifest itself long before the first motor symptoms: patients studied by De Paepe et al. (2019) initially emphasized that they needed external encouragement to act, other aspects of apathy emerged and increased as the disease progressed. The main localization of cerebral pathology, associated with clinical manifestations, was thalamus, but in a two-year follow-up in 171 patients, no association between atrophy of other subcortical structures and worsening of apathy was demonstrated (Baake et al., 2018). As in PD, apathy in HD is closely related to executive dysfunction, and it is strongly reducing quality of life of patients and their caregivers (Ready et al., 2008).

In the neurological form of Wilson's disease (WD), preliminary reports indicate, among others, the incidence of apathy in about 27% of patients, its independence from depressed mood, co-occurrence with executive dysfunctions and low patient insight into symptoms (Leśniak et al., 2022), this issue, however, requires further research.

Apathy in Dementia

It is estimated that apathy occurs in 20–25% of patients with Alzheimer's disease (AD) in its early stages, in 80% it develops over time and can occur without accompanying mood disorders (Nobis & Husain, 2018; Starkstein, 2001). Apathy in AD correlates with decreased glucose metabolism in orbitofrontal cortex and ventral striatum, while hypometabolism in ventral tegmental area is associated with apathy in other types of dementia as well (Le Heron et al., 2018; Theleritis et al., 2017).

Studies indicate a high prevalence of apathy in Lewy body dementia (DLB) – it affects about 50% of patients and is more strongly associated with executive dysfunctions than in AD (Bjoerke-Bertheussen et al., 2012; Breitve et al., 2018).

Prevalence of apathy is estimated to be even higher in neurodegenerative diseases with more pronounced involvement of prefrontal cortex and caudate nuclei, such as progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) (Litvan et al., 1996). In these diseases, apathy is particularly often one of the first neuropsychiatric symptoms to be revealed, and even a prodromal sign of illness. According to many authors, it may be even more clearly distinguished from depression than in PD (Bathgate et al., 2001; Litvan et al., 1996; Naarding et al., 2009). It has been shown that severity of apathy in PSP and FTD is higher than in AD, while severity of depression it is lower

(Derouesné et al., 2012; Litvan et al., 1996). In PSP, major depression is rare, in contrast to impulsivity, executive dysfunction, and apathy, affecting an average of 58.3% of patients (Flavell & Nestor, 2022; Millar et al., 2006). The latter correlates primarily with cortical atrophy of frontomedial regions and insular area (Stanton et al., 2013).

In FTD, apathy is the hallmark symptom of the behavioral variant (up to 100% of patients – Merrilees et al., 2013). Predominance of apathy symptoms in the emotional domain is indicated, in comparison with decreased intellectual curiosity and limited initiation of activity, which are slightly more common in patients with AD (Fernández-Matarrubia et al., 2017). Apathy is also observed in most patients with semantic dementia (SD), but its severity is usually lower than in the behavioral variant of FTD (Merrilees et al., 2013).

Apathy is also indicated as an important clinical feature in amyotrophic lateral sclerosis *(*ALS), although this neurodegenerative disease is usually considered a model example of isolated motor pathology (cognitive and behavioral disorders are found in about half of patients, although dementia is rare – cf. Abramzon et al., 2020; Giordana et al., 2010). Prevalence of apathy in ALS reported in the literature ranges between 31 and 56% (Lillo et al., 2011), studies suggest a leading role for initiation disorders occurring regardless of both the degree of motor disability and other dimensions of apathy (Radakovic et al., 2016).

In the case of dementia, it is noted that the presence of apathy not only significantly increases the level of stress and burden on the caregivers of affected patients (Diehl-Schmid et al., 2013; Merrilees et al., 2013), but is also associated with faster disease progression and earlier need for institutional care (Breitve et al., 2018).

In patients with mild cognitive impairment (MCI), the presence of apathy doubles the risk of developing dementia, regardless of the impact of depression (Ma, 2020), while in small vessel disease (SVD), frequent screening for apathy is postulated, since it is considered an early signal of dementia with greater prognostic significance than depression, as well as a sensitive clinical indicator of white matter circuits damage (Tay et al., 2020).

Brain Mechanisms Underlying Apathy

An analysis based on the concept of functional neuronal circuits may help explain the variety of brain damage locations that lead to apathy. Especially in the case of focal lesions, in which dysfunction of a given circuit is caused not only by focal damage to specific brain structures, but also by dynamic changes resulting from diaschism and/or secondary neurodegeneration, which may have additional impact on worsening or remission of apathy symptoms over time (Tay et al., 2021).

Motivated, goal-directed behaviors are regulated by a complex network of interconnected brain regions, primarily involving medial frontal cortex as well as caudate nucleus, putamen, dorsal anterior cingulate cortex, ventral tegmental area, and ventral pallidum (Le Heron et al., 2018). However, it has been

suggested that different clinical manifestations of apathy (or its subtypes) may be due to partly separate brain mechanisms (De Paepe et al., 2019; Pagonabarraga et al., 2015; Stanton et al., 2013).

According to research, both the intentional (auto-activation), emotional and cognitive aspects of apathy involve basal ganglia, dorsolateral prefrontal cortex, and their connections with caudate nucleus. However, the key symptoms of apathy in the emotional domain seem to be mainly due to orbitofrontal cortex and subgenual cingulate disfunction, while dysfunction of dorsolateral prefrontal cortex and functionally connected posterior parietal regions is associated with apathy revealed primarily in the cognitive domain (Pagonabarraga et al., 2015). Generalized dysfunctions of basal ganglia, prefrontal medial cortex, and especially supplementary motor area (SMA) are most often described in apathy with a leading deficit of auto-activation (Bonnelle et al., 2016).

According to Levy (2012), dysfunctions of limbic regions of frontal lobes (orbitomedial prefrontal cortex) and basal ganglia (especially ventral striatum) lead to apathy mainly due to difficulties in assigning affective value to a specific context of behavior. On the other hand, dysfunctions of frontal associative regions ("cognitive" – mainly dorsolateral) and basal ganglia (primarily caudate nucleus) lead to a quantitative reduction of goal-directed behavior secondary to disruption of strategies necessary for implementation of its program. Overlapping of both mechanisms or more generalized bilateral disruptions of prefrontal-basal ganglia circuits can result in the most severe disorders of auto-activation.

White matter tractography studies of the brain (*diffusion tensor imaging*, DTI) seem to suggest a tendency towards hemispheric asymmetries in the discussed processes: higher level of auto-activation deficit has been shown to be associated with dysfunction of right uncinate fasciculus, while apathy in the cognitive domain – with disruption of right hemisphere frontostriatal tract and left dorsolateral prefrontal cortex to caudate nucleus pathway (De Paepe et al., 2019). Depending on the disease, apathy may be associated with different patterns of changes in functional neuroimaging, e.g. in patients with the behavioural variant of FTD, hypometabolism has been described, among others of left lateral, medial, orbitofrontal cortex and anterior cingulate, while in AD changes in anterior cingulate were right-sided (Fernández-Matarrubia et al., 2017). Another study of patients with AD and apathy has shown bilateral hypometabolism in insula and orbital prefrontal cortex, while left-sided hypometabolism was revealed in putamen, thalamus, and nucleus accumbens (Jeong et al., 2018).

Summary

In current literature, various concepts of apathy syndrome still coexist, but its syndromic character is widely accepted, as well as the assumption that several variants/subtypes of apathy can be distinguished (Lanctôt et al., 2017; Lázaro-Perlado, 2019). Studies indicate high prevalence of apathy in neurological diseases, especially those associated with damage to prefrontal cortex and/or

basal ganglia. Unfortunately, the results are not easy to generalize, mostly due to the diversity of both apathy criteria and tools used for assessment (e.g. uni- vs. multidimensional), heterogenity of the studied clinical groups and possible mechanisms of disorders. Efforts to unify criteria for recognizing apathy and standardize diagnostic methods are an important direction of expert activity in this field. Unfortunately, in the latest diagnostic manuals (International Classification of Diseases, Eleventh Revision, ICD-11; Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5), apathy is still considered only as one of the symptoms of other disorders and not as a separate syndrome. It may hinder and reduce its diagnosing in the field of brain disease. (Tay et al., 2021).

References

Abramzon, Y. A., Fratta, P., Traynor, B. J., & Chia, R. (2020). The Overlapping Genetics of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. *Frontiers in Neuroscience*, *14*, article 42. https://doi.org/10.3389/fnins.2020.00042

Andersson, S., & Bergedalen, A. M. (2002). Cognitive correlates of apathy in traumatic brain injury. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*, *15*, 184–191.

Andersson, S., Krogstad, J. M., & Finset, A. (1999). Apathy and depressed mood in acquired brain damage: relationship to lesion localization and psychophysiological reactivity. *Psychological Medicine*, *29*, 447–456. https://doi.org/10.1017/s003329179-8008046

Ang, Y. S., Lockwood, P., Apps, M. A., Muhammed, K., & Husain, M. (2017). Distinct Subtypes of Apathy Revealed by the Apathy Motivation Index. *Plos One*, *12*(1), https://doi.org/10.1037/t77043-000

Angelelli, P., Paolucci, S., Bivona, U., Piccardi, L., Ciurli, P., Cantagallo, A., Antonucci, G., Fasotti, L., Di Santantonio, A., Grasso, M. G., & Pizzamiglio, L. (2004). Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. *Acta Psychiatrica Scandinavica*, *110*(1), 55–63. https://doi.org/10.1111/j.1600-0447.2004.00297.x

Arnould, A., Rochat, L., Azouvi, P., & Van der Linden, M. (2015). Apathetic symptom presentations in patients with severe traumatic brain injury: Assessment, heterogeneity and relationships with psychosocial functioning and caregivers' burden. *Brain Injury*, *29*(13–14), 1597–1603. https://doi.org/10.3109/02699052.2015.1075156

Baake, V., Coppen, E. M., van Duijn, E., Dumas, E. M., van den Bogaard, S., Scahill, R. I., Johnson, H., Leavitt, B., Durr, A., Tabrizi, S. J., Craufurd, D., & Roos, R. (2018). Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study. *NeuroImage: Clinical*, *19*, 66–70. https://doi.org/doi:10.1016/j.nicl.2018.03.033

Bathgate, D., Snowden, J. S., Varma, A., Blackshaw, A., & Neary, D. (2001). Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurologica Scandinavica*, *103*, 367–378. https://doi.org/10.1034/j.1600-0404.2001.2000236.x

Bayen, E., Pradat-Diehl, P., Jourdan, C., Ghout, I., Bosserelle, V., Azerad, S., Weiss, J., Joël, M., Aegerter, P., & Azouvi, P. (2013). Predictors of informal care burden 1 year after a severe traumatic brain injury: results from the PariS-TBI study. *Journal of Head Trauma Rehabil*itation, *28*(6), 408–418. https://doi.org/10.1097/htr.0b013e31825413cf

Benoit, M., Clairet, S., Koulibaly, P. M., Darcourt, J., & Robert, P. H. (2004). Brain perfusion correlates of the apathy inventory dimensions of Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *19*(9), 864–869. https://doi.org/10.1002/gps.1163

Bhatia, K. P., & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain: A Journal of Neurology*, *117*(4), 859–876. https://doi.org/10.1093/brain/117.4.859

Bjoerke-Bertheussen, J., Ehrt, U., Rongve, A., Ballard, C., & Aarsland, D. (2012). Neuropsychiatric symptoms in mild dementia with Lewy bodies and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *34*(1), 1–6. https://doi.org/10.1159/000339590

Bonnelle, V., Manohar, S., Behrens, T., & Husain, M. (2016). Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. *Cerebral Cortex*, *26*(2), 807–819. https://doi.org/10.1093/cercor/bhv247

Breitve, M. H., Brønnick, K., Chwiszczuk, L. J., Hynninen, M. J., Aarsland, D., & Rongve, A. (2018). Apathy is associated with faster global cognitive decline and early nursing home admission in dementia with Lewy bodies. *Alzheimer's Research & Therapy*, *10*(1), article 83. https://doi.org/10.1186/s13195-018-0416-5

Brett, C., Sykes, C., & Pires-Yfantouda, R. (2017). Interventions to increase engagement with rehabilitation in adults with acquired brain injury: A systematic review. *Neuropsychological Rehabilitation*, *27*(6), 959–982. https://doi.org/10.1080/09602011.2015.1090459

Brodaty, H., Sachdev, P., Withall, A., Altendorf, A., Valenzuela, M., & Lorentz, L. (2005). Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. *Psychological Medicine*, *35*(12), 1707–1716. https://doi.org/10.1017/S0033291705006173

Carnes-Vendrell, A., Deus, J., Molina-Seguin, J., Pifarré, J., & Purroy, F. (2019). Depression and Apathy After Transient Ischemic Attack or Minor Stroke: Prevalence, Evolution, and Predictors. *Scientific Reports*, *9*(1), article 16248. https://doi.org/10.1038/s41598-019-52721-5

Carrera, E., & Bogousslavsky, J. (2006). The thalamus and behavior: effects of anatomically distinct strokes. *Neurology*, *66*(12), 1817–1823. https://doi.org/10.1212/01.wnl.0000219679.95223.4c

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308–2314. https://doi.org/10.1212/WNL.44.12.2308

Da Costa, R., Porto, F., & Marrocos, R. (2013). Dissociation of depression from apathy in traumatic brain injury: a case report. *Dementia & Neuropsychologia*, *7*(3), 312–315. https://doi.org/10.1590/s1980-57642013dn70300014

De Paepe, A., Sierpowska, J., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., de Diego-Balaguer, R., & Camara, E. (2019). White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *Neuroimage: Clinical*, *24*, article 101965. https://doi.org/10.1016/j.nicl.2019.101965

Derouesné, C., Lacomblez, L., Fiori, N., Gély-Nargeot, M., & Bungener, C. (2012). L'apathie dans la démence frontemporale et la maladie d'Alzheimer: existe-t-il des profils distincts? [Apathy in frontotemporal dementia and Alzheimer's disease: are there distinct profiles?]. *Geriatrie et Psychologie Neuropsychiatrie du Vieillissement*, *10*(1), 107–115. https://doi.org/10.1684/pnv.2012.0315

De Witte, L., Engelborghs, S., Verhoeven, J., De Deyn, P., & Mariën, P. (2008). Disrupted auto-activation, dysexecutive and confabulating syndrome following bilateral thalamic and right putaminal stroke. *Behavioural Neurology*, *19*(3), 145–151. https://dx.doi.org/10.1155/2008/693671

Diehl-Schmid, J., Schmidt, E-M., & Nunnemann, S. (2013). Caregiver burden and needs in frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology*, *26*(4), 221–229. https://doi.org/10.1177/0891988713498467

D'Iorio, A., Vitale, C., Piscopo, F., Baiano, C., Falanga, A. P., Longo, K., & Santangelo, G. (2017). Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. *Parkinsonism & Related Disorders*, *43*, 114–117. https://doi.org/10.1016/j.parkreldis.2017.08.003

Douven, E., Kohler, S., & Schievink, S. (2017). Temporal associations between fatigue, depression, and apathy after stroke: results of the cognition and affect after stroke, a prospective evaluation of risks study. *Cerebrovascular Diseases*, *44*, 330–337. https://doi.org/10.1159/000481577

Drevets, W. (1999). Prefrontal cortical-amygdalar metabolism in major depression. *Annals of the New York Academy of Sciences*, *877*, 614–637. https://doi.org/10.1111/j.1749- 6632.1999.tb09292.x

Drevets, W., Price, J., Bardgett, M., Reich, T., Todd, R., & Raichle, M. (2002). Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacology Biochemistry and Behaviour*, *71*(3), 431–447. https://doi.org/10.1016/S0091-3057(01)00687-6

Drevets, W., Videen, T., Price, J., Preskorn, S., Carmichael, S., & Raichle, M. (1992). A functional anatomical study of unipolar depression. *The Journal of Neuroscience*, *12*, 3628–3641. https://doi.org/10.1523/JNEUROSCI.12-09-03628.1992

Fernández-Matarrubia, M., Matías-Guiu, J., Cabrera-Martín, M., Moreno-Ramos, T., Valles-Salgado, M., Carreras, J., & Matías-Guiu, J. (2017). Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *33*(1), 141–150. https://doi.org/10.1002/gps.4695

Fisher, C. (1983). Honored guest presentation: abulia minor vs agitated behavior. *Clinical Neurosurgery*, *31*, 9–31. https://doi.org/10.1093/neurosurgery/31.cn_suppl_1.9

Flavell, J., & Nestor, P. (2022). A Systematic Review of Apathy and Depression in Progressive Supranuclear Palsy. *Journal of Geriatric Psychiatry and Neurology*, *35*(3), 280–292. https://doi.org/10.1177/0891988721993545

Giordana, M. T., Ferrero, P., Grifoni, S., Pellerino, A., Naldi, A., & Montuschi, A. (2011). Dementia and cognitive impairment in amyotrophic lateral sclerosis: a review. *Neurological Sciences*, *32*(1), 9–16. https://doi.org/10.1007/s10072-010-0439-6

Guild, E., & Levine, B. (2015). Functional Correlates of Midline Brain Volume Loss in Chronic Traumatic Brain Injury. *Journal of the International Neuropsychological Society, 21*(8), 650–655. https://doi.org/10.1017/s1355617715000600

Habib, M. (2004). Athymhormia and Disorders of Motivation in Basal Ganglia Disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(4), 509–524. https://doi.org/10.1176/JNP.16.4.509

Hama, S., Yamashita, H., Shigenobu, M., Watanabe, A., Hiramoto, K., Kurisu, K., Yamawaki, S., & Kitaoka, T. (2007). Depression or apathy and functional recovery after stroke. *International Journal of Geriatric Psychiatry*, *22*(10), 1046–1051. https://doi.org/10.1002/gps.1866

Ishizaki, J., & Mimura, M. (2011). Dysthymia and apathy: diagnosis and treatment. *Depression Research and Treatment*, article ID 893905, 1–7. https://doi.org/10.1155/2011/893905

Jaracz, J. (2008). Anatomia depresji w świetle wyników badań neuroobrazowych [The anatomy of depression in light of evidence from neuroimaging studies]. *Psychiatria Polska* [*Polish Psychiatry*], *42*(6), 875–888.

Jeong, H., Kang, I., Im, J. J., Park, J. S., Na, S. H., Heo, Y., Yang, Y., Chung, Y. A., & Song, I. U. (2018). Brain Perfusion Correlates of Apathy in Alzheimer's Disease. *Dementia and Neurocognitive Disorders*, *17*(2), 50–56. https://doi.org/10.12779/dnd.2018.17.2.50

Jorge, R., Starkstein, S., & Robinson, R. (2010). Apathy following Stroke. *The Canadian Journal of Psychiatry*, *55*(6), 350–354. https://doi.org/10.1177/070674371005500603

Krishnamoorthy, A., & Craufurd, D. (2011). Treatment of Apathy in Huntington's Disease and Other Movement Disorders. *Current Treatment Options in Neurology*, *13*, 508–519. https://doi.org/10.1007/s11940-011-0140-y

Lanctôt, K. L., Agüera-Ortiz, L., Brodaty, H., Francis, P. T., Geda, Y. E., Ismail, Z., Marshall, G. A., Mortby, M. E., Onyike, C. U., Padala, P. R., Politis, A. M., Rosenberg, P. B., Siegel, E., Sultzer, D. L., & Abraham, E. H. (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimer's & Dementia*, *13*, 84–100. https://doi.org/10.1016/j.jalz.2016.05.008

Laplane, D., Baulac, M., Widlöcher, D., & Dubois, B. (1984). Pure psychic akinesia with bilateral lesions of basal ganglia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *47*(4), 377–385. https://doi.org/10.1136%2Fjnnp.47.4.377

Lázaro-Perlado, F. (2019). Apathy: A Conceptual Review. *Current Psychiatry Research and Reviews*, *15*, 88–104. http://dx.doi.org/10.2174/1573400515666190306150306

Le Heron, C., Apps, M., & Husain, M. (2018). The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia*, *118*(Pt B), 54–67. https://doi.org/10.1016/j.neuropsychologia.2017.07.003

Leśniak, M., Roessler-Górecka, M., Członkowska, A., & Seniów, J. (2022). Clinical significance of self-descriptive apathy assessment in patients with neurological form of Wilson's disease. *Neurological Sciences*, *43*(2), 1385–1394. https://doi.org/10.1007/s10072-021-05366-0

Levy, M. L., Cummings, J. L., Fairbanks, L. A., Masterman, D., Miller, B. L., Craig, A. H., Paulsen, J. S., & Litvan, I. (1998). Apathy is not depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 314–319. https://doi.org/10.1176/jnp.10.3.314

Levy, R. (2012). Apathy: a pathology of goal-directed behaviour. A new concept of the clinic and pathophysiology of apathy. *Revue Neurologique*, *168*(8), 585–597. https://doi.org/10.1016/j.neurol.2012.05.003

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*, *16*(7), 916–928. https://doi.org/10.1093/cercor/bhj043

Lillo, P., Mioshi, E., Zoing, M., Kiernan, M., & Hodges, J. (2011). How common are behavioural changes in amyotrophic lateral sclerosis? *Amyotrophic Lateral Sclerosis*, *12*(1), 45–51. https://doi.org/10.3109/17482968.2011.639376

Litvan, I., Mega, M., Cummings, J., & Fairbanks, L. (1996). Neuropsychiatric aspects of progressive supranuclear palsy. *Neurology*, *47*, 1184–1189. https://doi.org/10.1212/WNL.47.5.1184

Ma, L. (2020). Depression, anxiety, and apathy in mild cognitive impairment: Current perspectives. *Frontiers in Aging Neuroscience*, *12*, article 9. https://doi.org/10.3389/fnagi.2020.00009

Madhusoodanan, S., Ting, M., Farah, T., & Ugur, U. (2015). Psychiatric aspects of brain tumors: A review. *World Journal of Psychiatry*, *5*(3), 273–285. https://doi.org/10.5498/wjp.v5.i3.273

Marin, R. (1990). Differential diagnosis and classification of apathy. *American Journal of Psychiatry*, *147*(1), 22–30. https://doi.org/10.1176/ajp.147.1.22

Marin, R. (1991). Apathy: a neuropsychiatric syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *3*(3), 243–254. https://doi.org/10.1176/jnp.3.3.243

Marin, R., & Wilkosz, P. (2005). Disorders of diminished motivation. *The Journal of Head Trauma Rehabilitation*, *20*(4), 377–388. https://doi.org/10.1097/00001199-200507-000-00009

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-v

McFarland, B., & Klein, D. (2009). Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance. *Depression and Anxiety*, *26*(2), 117–122. https://doi.org/10.1002/da.20513

Mele, B., Van, S., Holroyd-Leduc, J., Ismail, Z., Pringsheim, T., & Goodarzi, Z. (2020). Diagnosis, treatment and management of apathy in Parkinson's disease: a scoping review. *BMJ Open*, *10*(9), https://doi.org/10.1136/bmjopen-2020-037632

Merrilees, J., Dowling, G., Hubbard, E., Mastick, J., Ketelle, R., & Miller, B. (2013). Characterization of apathy in persons with frontotemporal dementia and the impact on family caregivers. *Alzheimer Disease and Associated Disorders*, *27*(1), 62–67. https://doi.org/10.1097/wad.0b013e3182471c54

Millar, D., Griffiths, P., Zermansky, A., & Burn, D. (2006). Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. *Movement Disorders*, *21*(2), 199–207. https://doi.org/10.1002/mds.20707

Miller, D. S., Robert, P., Ereshefsky, L., Adler, L., Bateman, D., Cummings, J., DeKosky, S. T., Fischer, C. E., Husain, M., Ismail, Z., Jaeger, J., Lerner, A. J., Li, A., Lyketsos, C. G., Manera, V., Mintzer, J., Moebius, H. J., Mortby, M., Meulien, D., … Lanctôt, K. L. (2021). Diagnostic criteria for apathy in neurocognitive disorders. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *17*(12), 1892–1904. https://doi.org/10.1002/alz.12358

Monsalve, C., B., Guitart, B. M., López, R., Vilasar, B. A., & Quemada, J. (2012). Perfil psicopatológico de pacientes con traumatismo craneoencefálico evaluados mediante el Inventario Neuropsiquiátrico [Psychopatological evaluation of traumatic brain injury patients with the Neuropsychiatric Inventory]. *Revista de Psiquiatria y Salud Mental*, *5*(3), 160–166.

Motomura, K., Kawamura, A., Ohka, F., Aoki, K., Nishikawa, T., Yamaguchi, J., Kibe, Y., Shimizu, H., Maeda, S., & Saito, R. (2023). Predictive factors of post-operative apathy in patients with diffuse frontal gliomas undergoing awake brain mapping. *Journal of Neuropsychology*, *18*(S1), 73–84. https://doi.org/10.1111/jnp.12345

Naarding, P., Janzing, J., Eling, P., van der Werf, S., & Kremer, B. (2009). Apathy is not depression in Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *21*, 266–270. https://doi.org/10.1176/jnp.2009.21.3.266

Nobis, L., & Husain, M. (2018). Apathy in Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *22*, 7–13. https://doi.org/10.1016/j.cobeha.2017.12.007

Pachi, I., Koros, C., Simitsi, A., Papadimitriou, D., Bougea, A., Prentakis, A., Papagiannakis, N., Bozi, M., Antonelou, R., Angelopoulou, E., Beratis, I., Stamelou, M., Trapali, X., Papageorgiou, S., & Stefanis, L. (2021). Apathy: An underestimated feature in GBA and LRRK2 non-manifesting mutation carriers. *Parkinsonism and Related Disorders*, *91*, 1–8. https://doi.org/10.1016/j.parkreldis.2021.08.008

Pagonabarraga, J., Kulisevsky, J., Strafella, A., & Krack, P. (2015). Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology*, *14*(5), 518–531. https://doi.org/10.1016/s1474-4422(15)00019-8

Peng, Y., Shao, Ch., Gong, Y., Wu, X., Tang, W., & Shi, S. (2015). Relationship between apathy and tumor location, size, and brain edema in patients with intracranial meningioma*, Neuropsychiatric Disease and Treatment*, *11*, 1685–1693. https://doi.org/10.2147/ndt.s85288

Pluck, G., & Brown, R. (2002). Apathy in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *73*, 636–642. https://doi.org/10.1136/jnnp.73.6.636

Pont-Sunyer, C., Hotter, A., Gaig, C., Seppi, K., Compta, Y., Katzenschlager, R., Mas, N., Hofeneder, D., Brücke, T., Bayés, A., Wenzel, K., Infante, J., Zach, H., Pirker, W., Posada, I. J., Álvarez, R., Ispierto, L., De Fàbregues, O., Callén, A., … Tolosa, E.

(2015). The Onset of Nonmotor Symptoms in Parkinson's disease (The ONSET PD Study). *Movement Disorders*, *30*, 229–237. https://doi.org/10.1002/mds.26077

Radakovic, R., & Abrahams, S. (2014). Developing a new apathy measurement scale: Dimensional Apathy Scale. *Psychiatry Research*, *219*(3), 658–663. https://doi.org/10.1016/j.psychres.2014.06.010

Radakovic, R., Davenport, R., Starr, J., & Abrahams, S. (2018). Apathy dimensions in Parkinson's disease. *International Journal of Geriatric Psychiatry*, *33*(1), 151–158. https://doi.org/10.1002/gps.4697

Radakovic, R., Stephenson, L., Colville, S., Swingler, R., Chandran, S., & Abrahams, S. (2016). Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(6), 663–669.

Radakovic, R., Stephenson, L., Newton, J., Crockford, C., Swingler, R., Chandran, S., & Abrahams, S. (2017). Multidimensional Apathy and Executive Dysfunction in Amyotrophic Lateral Sclerosis. *Cortex*, *94*, 142–151. https://doi.org/10.1016/j.cortex.2017.06.023

Ready, R., Mathews, M., Leserman, A., & Paulsen, J. (2008). Patient and caregiver quality of life in Huntington's disease. *Movement Disorders*, *23*(5), 721–726. https://doi.org/10.1002/mds.21920

Robert, P., Lanctôt, K., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., Hanon, C., David, R., Dubois, B., Dujardin, K., Husain, M., König, A., Levy, R., Mantua, V., Meulien, D., Miller, D., Moebius, H., Rasmussen, J., Robert, G., … Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, *54*, 71–76. https://doi.org/10.1016/j.eurpsy.2018.07.008

Robert, P., Onyike, C. U., Leentjens, A. F., Dujardin, K., Aalten, P., Starkstein, S., Verhey, F. R., Yessavage, J., Clement, J. P., Drapier, D., Bayle, F., Benoit, M., Boyer, P., Lorca, P. M., Thibaut, F., Gauthier, S., Grossberg, G., Vellas, B., & Byrne, J. (2009). Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *European Psychiatry*, *24*(2), 98–104. https://doi.org/10.1016/j.eurpsy.2008.09.001

Santa, N., Sugimori, H., Kusuda, K., Yamashita, Y., Ibayashi, S., & Iida, M. (2008). Apathy and functional recovery following first-ever stroke. *International Journal of Rehabilitation Research*, *31*(4), 321–326. https://doi.org/10.1097/MRR.0b013e3282fc0f0e

Seniów, J., Komajda, R., & Zaborski, J. (2005). Zespół apatii w konsekwencji uszkodzenia mózgu – trudny problem neurorehabilitacji [Apathy syndrome as a consequence of brain injury – a difficult problem in neurorehabilitation]. *Rehabilitacja Medyczna* [*Medical Rehabilitation*], *9*(2), 15–19.

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*(5), 579–584. https://doi.org/10.1136/jnnp.2005.075929

Stanton, B., Leigh, P., Howard, R., Barker, G., & Brown, R. (2013). Behavioural and emotional symptoms of apathy are associated with distinct patterns of brain atrophy in

neurodegenerative disorders. *Journal of Neurology*, *260*(10), 2481–2490. https://doi.org/10.1007/s00415-013-6989-9

Starkstein, S., Fedoroff, J., Price, T., Leiguarda, R., & Robinson, R. (1993). Apathy following cerebrovascular lesions. *Stroke*, *24*(11), 1625–1630. https://doi.org/10.1161/01.str.24.11.1625

Starkstein, S., & Manes, F. (2000). Apathy and depression following stroke. *CNS Spectrums*, *5*(3), 43–50. https://doi.org/10.1017/s1092852900012955

Starkstein, S., Mayberg, H., Preziosi, T., Andrezejewski, P., Leiguarda, R., & Robinson, R. (1992). Reliability, validity, and clinical correlates of apathy in Parkinsons disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *4*(2), 134–139. https://doi.org/10.1176/jnp.4.2.134

Starkstein, S., Merello, M., Jorge, R., Brockman, S., Bruce, D., & Power, B. (2009). The syndromal validity and nosological position of apathy in Parkinson's disease. *Movement Disorders*, *24*(8), 1211–1216. https://doi.org/10.1002/mds.22577

Starkstein, S., & Pahissa, J. (2014). Apathy following traumatic brain injury. *The Psychiatric clinics of North America*, *37*(1), 103–112. https://doi.org/10.1016/j.psc.2013.10.002

Starkstein, S., Petracca, G., Chemerinski, E., & Kremer, J. (2001). Syndromic validity of apathy in Alzheimer's disease. *The American Journal of Psychiatry*, *158*(6), 872–877. https://doi.org/10.1176/appi.ajp.158.6.872

Steffens, D. C., Fahed, M., Manning, K. J., & Wang, L. (2022). The neurobiology of apathy in depression and neurocognitive impairment in older adults: a review of epidemiological, clinical, neuropsychological and biological research. *Translational Psychiatry*, *12*(1), https://doi.org/10.1038/s41398-022-02292-3

Stuss, D. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the International Neuropsychological Society*, *17*(5), 759–765. https://psycnet.apa.org/doi/10.1017/S1355617711000695

Stuss, D., & Benson, F. (1986). *The Frontal Lobes*. Raven Press.

Stuss, D., van Reekum, R., & Murphy, K. (2000). Differentiaton of states and causes of apathy. In J. Borod (Ed.), *The neuropsychology of emotion* (pp. 340–352). Oxford University Press.

Tay, J., Morris, R., & Markus, H. (2021). Apathy after stroke: Diagnosis, mechanisms, consequences, and treatment. *International Journal of Stroke*, *16*(5), 510–518. https://doi.org/10.1177/1747493021990906

Tay, J., Morris, R., Tuladhar, A., Husain, M., de Leeuw, F., & Markus, H. (2020). Apathy, but not depression, predicts all-cause dementia in cerebral small vessel disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *91*(9), 953–959. https://doi.org/10.1136/jnnp-2020-323092

Theleritis, C. (2017). Pharmacological and Nonpharmacological Treatment for Apathy in Alzheimer Disease: A systematic review across modalities. *The Journal of Geriatric Psychiatry and Neurology*, *30*(1), 26–49. https://doi.org/10.1177/0891988716678684

Thompson, J., Harris, J., & Sollom, A. (2012). Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *24*, 53–60. https://doi.org/10.1176/appi.neuropsych.11030057

Zarandy, J., Yoon, S., Saravanan, S., Das, S., & Thomas, S. (2023). Differential Diagnostic Considerations in a Patient With New Onset Apathy: A Case Study on Frontal Lobe Glioblastoma Multiforme. *The Journal of Integrated Primary Care*, *1*(1), article 3. https://digitalcommons.pcom.edu/jipc/vol1/iss1/3

Zoon, T., van Rooijen, G., Balm, G., Bergfeld, I., Daams, J., Krack, P., Denys, D., & de Bie, R. (2021). Apathy Induced by Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Meta-Analysis. *Movement Disorders*, *36*(2), 317–326. https://doi.org/10.1002/mds.28390

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