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Multidimensional apathy: evidence from neurodegenerative disease

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Apathy is a demotivation syndrome common in neurodegenerative diseases and is fundamentally multidimensional in nature. Different methodologies have been used to identify and quantify these dimensions, which has resulted in multifarious concepts, ranging in the number and characteristics of apathy subtypes. This has created an ambiguity over the fundamental substructure of apathy. Here we review the multidimensional concepts of apathy and demonstrate that overlapping elements exist, pointing towards commonalities in apathy subtypes. These can be subsumed under a unified Dimensional Apathy Framework: a triadic structure of Initiation, Executive and Emotional apathy. Distinct cognitive processes may underlie these domains, while self-awareness interplays with all subtypes. Evidence from neurodegenerative diseases supports this distinction with differing apathy profiles in amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease.

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Introduction

Apathy is defined as a lack of motivation towards goal-directed behaviour [1], and is a common symptom in neurodegenerative diseases, for review see [2]. Apathy is found in all types of dementia [3], while being prominent in Alzheimer's disease (AD) occurring in up to 92% of patients [4–6] and vascular dementia [7]. In

frontotemporal dementia (FTD) the presence of apathy can be used to support diagnosis [8], with a prevalence of 62% to 89% [9,10]. An apathetic subtype of behavioural variant FTD has been proposed, with defining characteristics of apathy, inertia and avolition [11]. Apathy is also the most common type of behaviour change in amyotrophic lateral sclerosis (ALS) [12], with a prevalence of between 31% and 56% [13-15] and is a key feature of defining ALS with behavioural impairment as part of the ALS-frontotemporal spectrum disorder [16]. Up to 50% of patients with Parkinson's disease (PD) exhibit apathy [17,18] and it is the most frequently reported neuropsychiatric symptom in those with PD dementia [19]. Apathy is also persistent and progressive across all stages of Huntington's disease [20,21], is a feature in progressive supranuclear palsy (PSP) [10,22] and is also relatively common in multiple sclerosis [23]. The prevalence of this symptom in different neurodegenerative diseases provides opportunity to investigate the underlying subarchitecture of apathy.

It is now widely accepted that apathy is syndromic in nature [24**] and is composed of different dimensions/subtypes. As the concept of multidimensional apathy has evolved there has been discord with regards to the number and defining characteristics of these subtypes, with a need for refinement of definition and measurement [24**]. Here we review the past and emerging concepts of apathy in the study of neurodegenerative diseases and present a unified Dimensional Apathy Framework.

Evolution of multidimensional apathy

The evolution of models of apathy has been influenced by different research methodologies. Most have come from a psychometric approach, wherein subtypes are based on different descriptors and measurements of observed behaviour [25–30]. In contrast, others rely on experimental and/or a neurobiological approach, focusing on brain damage or imaging neuroanatomical correlates [31,32]. Table 1 shows a chronological summary of key multidimensional apathy concepts.

Despite varying definitions, most models retain a tripartite structure and many have emerged in parallel with specific measurement scales. The original conceptualisation of the cognitive, behavioural and emotional/affective subtypes [25] was based on observations of patients, prompting development of the initial diagnostic criteria for apathy [1] and also the Apathy Evaluation Scale (AES). This was the gold-standard, one-dimensional

Concepts of multidimensional apathy		
Author	Dimensions/subtypes	Definition, symptoms/deficits
Marin <i>et al.</i> [25]	Behavioural Cognitive	Decreased productivity, effortful actions, perseverance and lack of initiation behaviours. Decreased interest for learning new things, a lack of concern for oneself, inability to contribute value to recreation, social situations
	Affective	or being productive with tasks. Emotional flatness, lack of responsiveness to emotionally charged events (both good and bad) and an emotional blunting with unchanging affect
Cummings et al. [26]	Initiative	Spontaneity is reduced for example does not start conversations or care about doing new things
	Enthusiasm	Enthusiasm for and involvement in activities, interests, and household chores
	Emotion	Reduced affect and emotions when compared to the individual's usual self and reduced interest in family members or friends
Robert et al. [27]	Lack of initiative Lack of interest	Reduced conversation and decision making Reduced interest in hobbies, other people or their family members and their interests
	Emotional blunting	Reduced affection and emotionally expression
Sockeel et al. [28]	Intellectual curiosity Action initiation Self awareness	A lack of novelty seeking, interest and motivation along with a poor social life. Unproductive in day-to-day life and lessened initiative 'Meta-cognitive ability necessary to mediate information from a personal, social past and current history with projections to the future'
	Emotion	Emotional blunting of responses and diminished concern
Starkstein and Leetjens [29]	Goal-directed behaviour	A lack of energy of effort for daily activities and dependence on others for daily structuring
	Goal-directed cognition	A lack of interest in new experiences or in learning new things and concern for one's own well being
	Goal-directed behaviour 'concomitants'	Flat affect and emotional unresponsiveness to positive or negative occurrences
Levy and Dubois [31], Levy [32]	Auto-activation	A lack of activity or initiation of goal-directed thoughts and actions, with a particular focus on self-initiation.
	Cognitive ('Cognitive inertia')	A lack of ability to expand on plans, organization or management of goals
	Emotional affective	Inability to associate behaviours with emotion or affect, which extends to the interpretation of affective content and therefore experience of extreme affect.
Radakovic and Abrahams [30]	Initiation Executive Emotional	Lack of motivation for self-generation of thought Lack of motivation for planning, organisation and attention Lack of emotional motivation, indifference or emotional neutrality

instrument with a three factor substructure which when interpreted post hoc (through examination of face validity) were akin to cognitive, behavioural and emotional/ affective dimensions. Research using the AES and the Apathy Scale (an abridged version of the AES) has shown a three factor substructure, albeit with variable characteristics (e.g. [33–35]). Other scales were developed including the Neuropsychiatric Inventory (NPI)—a behavioural screen for dementia which included a subscale to assess apathy [26], and The Apathy Inventory (AI) [27]. The latter signified a conceptual shift to the specific assessment of multidimensional apathy. The introduction of the Lille Apathy Rating Scale (LARS) [28], highlighted this further, albeit with four apathy domains instead of three. Starkstein and Leentjens [29] placed more of a focus on goal-directed elements of behaviour and cognition, and their view of emotional aspects of apathy acknowledged a conceptual distinction between a disorder of emotion or expression of emotions (affect) or a motivational disorder affecting emotional reactivity (flat affect and emotional unresponsiveness).

Levy and Dubois [31,32], similarly focused on motivation towards goal-directed behaviour but here they shifted to focus on the neuroanatomy of apathy. Different apathy subtypes were related to specific prefrontal-basal ganglia pathways. Damage to the medial prefrontal cortex, cognitive and limbic territories of the basal ganglia results in Auto-Activation apathy. Emotional-affective apathy is characterised by lesions to the orbito-medial prefrontal

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