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# Apathy: from the underlying pathophysiological mechanisms to future assessments and therapeutic strategies.

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## **Abstract**

This chapter details a viewpoint in which apathy is described from its behavioural manifestations and its multidimensional mechanisms. We propose a model for the psychological mechanisms and neural bases of apathy. We provide evidence that apathy results from dysfunctions of prefrontal cortex-basal ganglia system causing impairments of the key components of goal-directed behaviours: 1. motivation; 2. planning and execution; 3. auto-activation. We present clinical aspects of apathy with a critical analysis of its assessment, relying so far on subjective report. After describing current treatments and their limits, we show how an ecological approach may help to develop new therapeutic interventions.

**Keywords:** apathy; goal-directed behaviour; executive functions; motivation; auto-activation deficit; self-initiation; prefrontal cortex; basal ganglia; striatum; behavioural signature; ecological context

## **1. Definition of apathy**

Apathy is traditionally considered by clinicians as a syndrome due to an “absence of feeling, emotion, interest or concern” and it has long been defined as a “lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress” (Marin, 1991). However, clinicians may find it difficult to use this definition in their practice because it requires a psychological subjective interpretation of the origin of the observed decrease of spontaneous activity reported by patients or their relatives. In accordance with the recent international consensus (Robert et al., 2018), we define apathy from the clinically observed status rather than from its presumed cause. Following the apathy diagnostic criteria of 2018, the main criterion characterizing apathy is: “A quantitative reduction of goal-directed activity either in behavioural, cognitive, emotional or social dimensions in comparison to the patient’s previous level of functioning in these areas.” This definition takes into account the evidenced multidimensional nature of apathy but from a strictly behaviourist point of view, we suggest to narrow the definition of apathy to the quantitative reduction of goal-directed behaviours (GDBs). Thus, we can distinguish the clinically observable behavioural aspect defining apathy from its underlying emotional and cognitive mechanisms. We consider the case of patients with “auto-activation” deficit (AAD) (Laplane and Dubois, 2001) as a good model for the description of apathy. In this severe form of the syndrome, despite the loss of self-driven behaviours, the ability to execute externally-driven behaviour is relatively spared and unwanted automatic behaviours (such as stereotypies or compulsions) can be observed. It is therefore necessary to precise that the reduction of GDBs in apathy typically regards self-generated voluntary and purposeful behaviours (Levy, 2012; Levy and Czernecki, 2006; Levy and Dubois, 2006).

## 2. Mechanisms and neural bases of apathy

### 2.1. Key components of goal-directed behaviours and mechanisms of apathy

We propose that apathy is the observable clinical output resulting from different underlying mechanisms, more precisely from impairments in different functions in the process of elaboration of GDBs (Brown and Pluck, 2000; Levy, 2012). Several theoretical processes are indeed required to achieve a GDB. Imagine someone is entering a room that he/she has never seen before and in which he/she knows he/she will have to stay for a rather long period of time. This room has been equipped to offer opportunities to make oneself at home: there is a comfortable sofa, a table, chairs and after exploring a bit, one can find foods, drinks, games, magazines, books, etc... In this situation, he/she has many potential goals to reach (e.g., making a coffee, reading an article in a magazine, succeeding a Sudoku game...) but to do so, he/she has to: 1. evaluate the external context (physical contingencies, social constraints) as well as his/her own personal current desire according to his/her values, beliefs and internal homeostatic state (e.g., make the decision to make a coffee); 2. elaborate a plan of concrete actions and execute them to actually reach the chosen objective (e.g., program and execute the set of actions to make a coffee with the available material). Moreover, these two functions need to be coupled and added since they actually occur in parallel all along the process of goal achievement: at each moment of the plan of actions, the incentive towards the goal has to be updated and it has to remain strong enough to make one initiate each necessary action (e.g., if someone enters the room and provides with a warm cup of tea, then he/she may decide to abort the plan of actions to make a coffee because his/her motivation for coffee has decreased). Thus, we suggest that apathy, or reduction of GDBs, is the result of an impairment of one of these three broad psychological functions (which are not exclusive): 1. assessing the environmental context and tagging it with one's own motivational value to define an objective to reach; 2. planning and execution of actions towards this objective ; 3. auto-activation of each action towards the objective according to its assessed motivational value (which may evolve). The different theoretical mechanisms of apathy corresponding to impairments of these broad functions are detailed hereafter.

- Assessment of the context and attribution of a motivational value

Apathy can firstly be due to an inability to attribute a correct value to stimuli according to their relative capacity to generate reward or to avoid punishment in a given context. Indeed such a deficiency

may lead to the reduction of GDBs by reducing the motivation to perform and maintain actions until their completion. We thus label this first mechanism of apathy: "loss of motivation".

- Planning and execution of goal-directed thoughts/actions

Apathy can also occur in case of impaired executive functioning (i.e., the ability to organize programs of actions or thoughts in relation to internal goals) or self-regulation (i.e., self-corrective adjustments requiring feedback control to stay on track for the purpose being served), leading to concrete difficulties in reaching goals and thus reducing the capacity to show GDBs. In this case, apathy would be the consequence of a "purely" cognitive mechanism that we may name "cognitive inertia".

- Auto-activation of goal-directed thoughts/actions

Finally, apathy may appear because of a failure to auto-activate the correct sequence of thoughts/actions towards proper goals. Several sub-mechanisms may theoretically support an impaired auto-activation. A first possibility is that due to a disconnection between the systems of motivational evaluation and executive functioning, incentives identified by the motivation system fail to trigger the initiation of proper thoughts or actions towards the objective (Schmidt et al., 2015). We call this mechanism "invigoration deficit". A second sub-mechanism explaining auto-activation deficit is that motivational evaluation, executive functioning and their coupling are all deficient because of a general failure to amplify the signals of interest for goal-directed thoughts/actions. This alternative possibility probably occurs in association with the subjective report of "empty mind", an impression described by some patients that may correspond to a global significant decrease in all signal transmission potentially triggering the initiation of goal-directed thoughts/actions. A third theoretical sub-mechanism that we call "loss of focalisation" is related to difficulties to extract the relevant signals, corresponding to specific goal-directed thoughts/actions, from noise. Due to the loss of temporal and/or spatial focalisation of the relevant signal blended with non relevant ones, this mechanism leads to delayed or aborted initiation of goal-directed thoughts/actions.

Clinical observations of patients with neurodegenerative diseases suggest that these different mechanisms may be somewhat dissociable (Massimo et al., 2015) although not necessarily exclusive. For example, some patients may initiate actions and be able to complete a plan of actions even though they show no motivation to perform these actions. Other patients who have impairments in executive abilities may initiate simple actions (on their own initiative) and show an intact capacity to associate an affective value to stimuli. Finally, some patients may be incapable of initiating the

proper actions to reach goals according to their preserved motivational assessments even though their capacity to plan and execute actions is maintained.

This last situation has been evidenced in a particular form of apathy termed “auto-activation deficit” (AAD) (or psychic self-activation deficit or athymhormia) (Laplane and Dubois, 2001). We consider AAD as the most severe form of apathy and as a clinical model to describe key features of this syndrome. AAD consists in a severe reduction in self-initiated actions contrasting with the sparing of externally-driven ones under strong solicitations and the presence of automatic stereotypic behaviour. Unconscious messages such as adaptive neurovegetative signals or those triggering automatic actions are present and lead to normal behavioral responses, but thoughts and actions requiring higher level of consciousness are not spontaneously performed (although the general cognitive efficiency seems to be intact). Schmidt et al. (2008) showed that this severe form of apathy is likely to result from a disconnection between motivational and executive functions. In this study, participants had to complete two tasks: an externally-driven task in which they were instructed to produce different levels of force by squeezing a hand grip and a self-driven task in which they could win different incentive amounts of money (1, 10 or 50 euros) by squeezing the same hand grip. Through this behavioural paradigm, AAD patients firstly showed their capacity to execute external instructions: in the externally-driven task, they produced levels of force which were similar to those of healthy control participants. However, in the self-driven task, ADD patients did not react like healthy controls did: despite their preserved emotional reaction to monetary incentives (as evidenced by their skin conductance), they did not present a proportional increase of their force level according to the incentive. In other words, this study evidenced an inability to translate an expected reward into the appropriate behavioural activation in ADD patients.

## 2.2. Neural bases

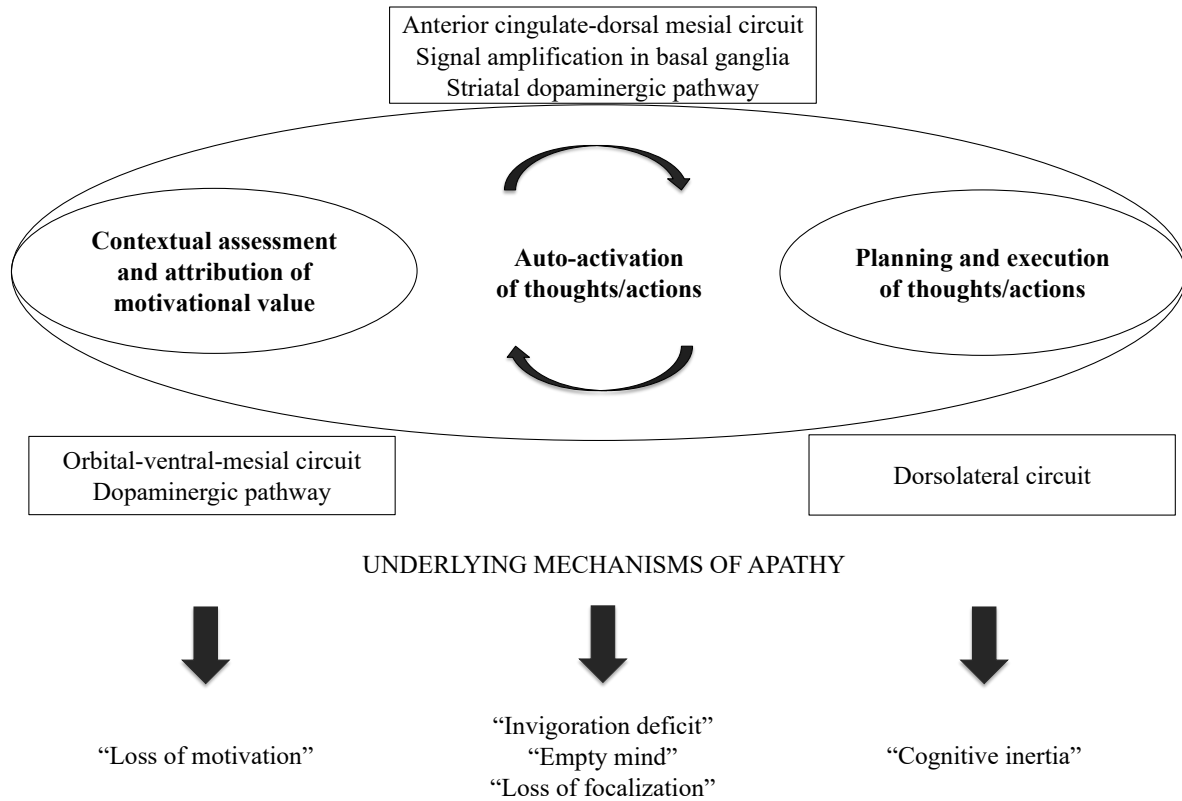
Results of clinical studies localizing brain regions associated with apathy have provided a remarkably consistent pattern in spite of their heterogeneity in terms of patient selection criteria, coexisting brain disorders and methodology of data acquisition and analysis. Indeed most neuropathological and neuroimaging investigations link apathy to abnormalities in specific regions of the frontal lobe and basal ganglia, thus supporting the idea that dysfunctions of prefrontal cortex-basal ganglia system are responsible for the emergence of apathy in patients (Chase, 2011; Levy, 2012).

The strong connectivity between PFC and basal ganglia has been shown in the monkey (Middleton and Strick, 2002) and also in humans using MR diffusion tensor fiber tracking (Lehéricy et al., 2004). Prefrontal cortex (PFC) which represents nearly one third of human brain volume, can be divided anatomically and functionally into several subregions (Thiebaut de Schotten et al., 2016; Volle et al., 2008). Accordingly, as detailed in a review of studies on cortical-striatal pathways in primates (Haber, 2003), the PFC-basal ganglia system is composed of several relatively segregated anatomical and functional circuits. In particular, we assume the existence of three theoretical circuits that could be related to the three key components of GDB and therefore to the corresponding mechanisms of apathy (described in subsection 2.1): (i) the “orbital-ventral-mesial circuit” grossly linking the orbital and ventral-mesial PFC to the ventral regions of the basal ganglia; (ii) the “dorsolateral circuit” linking the dorsolateral PFC to the dorsal regions of the basal ganglia, and (iii) The “anterior cingulate-dorsal mesial circuit” linking the mesial wall of the PFC (mostly the dorsal anterior cingulate cortex and supplementary motor area) to basal ganglia portions located between the dorsal and ventral regions.

The theoretical model of GDB key functions, with corresponding neural bases and mechanisms of apathy is summarized in Figure 1 (see below).

## THEORETICAL MODEL OF GOAL-DIRECTED BEHAVIORS

### Key components, neural bases and mechanisms of apathy



- Assessment of the context and attribution of a motivational value

We suggest that the brain system in charge of evaluating stimuli for GDB and underlying the “loss of motivation” mechanism of apathy belongs to the “limbic system”: it corresponds more precisely to its paleocortical division in charge of the implicit integration of affect, drives, and object associations (Mega et al., 1997). Among the three theoretical circuits of GDB, this is the orbital-ventral-mesial circuit. Neuropathological, neurophysiological and neuroimaging studies provide arguments to justify this assumption. First, defaults in the valuation function have been observed in bvFTD patients with atrophy in ventral-mesial regions (Massimo et al., 2015) as well as in primates (humans and animals) with ventral-mesial focal lesions (Manohar and Husain, 2016; Schneider and Koenigs, 2017). Besides studies focusing on damages to the ventral striatum showed a significant

impact on the capacity to evaluate one's emotional status (e.g., Calder et al., 2004). Neuronal activity recording in monkeys also demonstrated the important role of orbital-ventral-mesial PFC (Padoa-Schioppa, 2009; Schultz et al., 2000) and ventral striatum (Hollerman et al., 1998) in providing the contextual value of a reward. Finally, neuroimaging studies in humans support this same hypothesis of an involvement of orbital-ventral-mesial PFC in value-based decision-making (Elliott et al., 2003; Knutson et al., 2003; Rolls, 2000).

We also assume that dopamine plays a major role in the evaluation function of GDB and thus in the "loss of motivation" form of apathy. Indeed, dopaminergic neurotransmission has multiple actions at each level of the reward pathway and although the role of dopamine in the reward process was classically associated with the ability to experience pleasure, more recent data insist on its motivational role (Bressan and Crippa, 2005). Dopamine signal is involved in reward-based learning processes and may in particular code the discrepancies between predicted and experienced reward (Tobler et al., 2003) as well as reward probability and uncertainty (Fiorillo et al., 2003).

- Planning and execution of thoughts/actions

We postulate that the impairments of executive function leading to the "cognitive inertia" mechanism of apathy are related to abnormalities in the dorsolateral prefrontal-basal ganglia circuit. All the experimental approaches including neurophysiological, neurobiological, neuroimaging, and computational studies support the hypothesis that the dorsolateral PFC is a central node for the basic executive functions of working memory, inhibitory control and cognitive flexibility (Miller and Cohen, 2001). Dorsolateral PFC indeed plays a global and flexible role in executive control, regardless of any distinctions in terms of processing or domain (Volle et al., 2008). Moreover cerebral activity in the dorsal striatum (head of the caudate nucleus) has been related to the performance on working memory and planning tasks in both primates (Levy et al., 1997) and humans (Owen et al., 1996).

- Auto-activation of thoughts/actions

Evidence suggests that a third circuit (i.e., the "anterior cingulate-dorsal mesial" circuit) may be in charge of triggering the self-initiation of thoughts/actions towards goals through motivation/execution coupling. We assume that damages within this circuit could represent the pathophysiological basis for the apathy mechanism of "invigoration deficit". Both lesion reports and neuroimaging studies focusing on mesial PFC in humans are in agreement with this assumption. For

instance, extensive bilateral lesions of the mesial PFC following stroke have been associated with a clinical state called “akinetetic mutism” in which patients do not speak or move on their own initiative even though they are still able to speak and to feel motivation for speaking (Nagaratnam et al., 2004). Besides, studies using PET (Jenkins et al., 2000) and fMRI (Wiese et al., 2004) compared cerebral activity during self-initiated vs externally triggered movements and observed a significantly enhanced activity in mesial frontal cortex (in particular, supplementary motor area and anterior cingulate cortex) for self-driven motor actions requiring motivation-execution coupling. We also know that basal ganglia are involved in motivation / execution coupling, thanks to the observations made in patients with auto-activation deficit due to bilateral basal ganglia lesions (Schmidt et al., 2008). We lack clinical evidence proving that the intermediary part of basal ganglia (between ventral and dorsal parts) is specifically responsible for motivation-execution coupling. However we argue that this anatomical position with interdigitated connections from both motivational and executive systems can have a functional importance: it may indeed facilitate the communication and thus coupling between the two circuits.

More generally, the auto-activation of adaptive GDBs through motivation, execution and coupling systems relies on the performance of the three PFC-basal ganglia loops. Any problem in the transmission of relevant signals between basal ganglia and PFC may thus impact all of the three systems allowing the self-generation of GDBs. We suggest that the specific architecture of basal ganglia (combining the succession of distinct parallel anatomical circuits and a gradient of concentration of fibers increasing from striatum to thalamus) may contribute to select, amplify and transmit to PFC the relevant signal, allowing to activate thoughts/actions towards goals. Moreover, several studies in primates (Tremblay, Filion and Bédart, 1989; Kimura et al., 2003) confirm the role of striatum within cortico-basal ganglia loops for the selection of goal-specific neuronal activation. In case of focal and bilateral damage within basal ganglia such as seen in the auto-activation deficit, this centralized system of signal selection and amplification may thus fail to transfer proper goal-directed thought/action signals to PFC, potentially leading to “empty mind” (i.e., a major decrease in the signal to noise ratio in the PFC).

As suggested by Tremblay, Filion and Bédart (1989), striatal dopamine depletion observed in Parkinson’s disease (PD) can also lead to problems in the process of signal transmission between basal ganglia and PFC thus impacting the auto-activation of GDBs. Spatial and temporal focalisation of signals going through the striatum is indeed impaired in monkeys rendered parkinsonian, which may be the neural substrate of the “loss of focalisation” mechanism. Besides, several neuroimaging

studies support that apathy in patients with PD appears as a result of a dysfunction of dopaminergic transmission in the PFC-basal ganglia system. For instance, a PET study (Thobois et al., 2010) using an antagonist of dopamine D2 and D3 receptor has demonstrated differences in dopaminergic binding and transmission through the comparison of patients with PD with and without apathy. In patients with apathy (compared to those without apathy), the antagonist binding potential was increased in several regions of the PFC-basal ganglia system, implying either a reactive increase in dopamine receptor expression or a reduced endogenous synaptic dopamine, or both. Observations after the introduction of methylphenidate (which inhibits the recapture of dopamine) provided evidence of a reduced capacity for endogenous dopamine release in patients with apathy: indeed there was a smaller decrease in the antagonist binding potential in patients with apathy compared to those without apathy. Another PET study in patients with PD (Remy et al., 2005) used a ligand with affinity for both dopamine and noradrenaline transporters and showed that the severity of apathy was inversely correlated with the ligand binding potential in the ventral striatum. This study therefore suggests a reduced dopamine and/or noradrenaline binding capacity within ventral striatum in apathetic PD patients. Even though primary dopaminergic deficit is an important cause of apathy in PD (Le Heron et al., 2018), other neurotransmission systems may be involved in the emergence of apathy: other monoaminergic pathways such as noradrenergic (Remy et al., 2005) and serotonergic (Barber et al., 2018) systems but also cholinergic, glutamatergic, and GABAergic systems (Chase, 2011).

### **3. Clinical aspects of apathy**

#### **3.1. Assessment**

In current clinical practice, apathy is assessed either through validated questionnaires. These assessment tools are either multi-item scales focused on apathy or instruments quantifying broader concepts and containing a subscale or a single item related to apathy. With three available versions (clinician, informant, and self-rated), the Apathy Evaluation Scale (AES, 18 items) is the most used instrument for the evaluation of apathy (Marin, 1991). The Starkstein Apathy Scale (SAS) is another commonly used instrument resembling the 18-item AES, with 14 items scored by the patient's relative or caregiver (Starkstein et al., 1992). The Apathy Inventory (AI) is a reliable tool for assessing the emotional, behavioural and cognitive dimensions of the apathy syndrome, and also the subject's awareness of these symptoms (Robert et al., 2002). The Lille Apathy Rating Scale (LARS) also yields

subscores for different domains of apathy (cognitive, behavioural, affective, self awareness) through a relatively lengthy (33 items) semi-structured patient interview (Sockeel, 2006). The 24-item Dimensional Apathy Scale (DAS) is another scale developed more recently for the assessment of 3 dimensions of apathy: Executive, Emotional and Behavioural/Cognitive Initiation (Radakovic and Abrahams, 2014). Aside from these scales specifically dedicated to apathy, other broader instruments such as the Frontal Systems Behaviour Scale (FrSBe) or the Neuropsychiatric Inventory (NPI) can be used for its assessment. The 46-item FrSBe is intended to measure the behavioural effects of frontal brain damage and includes a 14-item subscale measuring apathy (Stout et al., 2003). The NPI is a structured interview which is very often used to evaluate behavioural dysfunction including apathy in patients with dementia (Cummings et al., 1994).

All these clinical scales, however, present one major drawback for the precise evaluation of apathy syndrome: they are only subjective measures relying on questions about patient's internal state of mind, thoughts and past activities. These evaluations are therefore biased by the specific perspective of the reporter (patient, caregiver or clinician) and more objective methods should be used as complements to make the assessment of apathy more accurate (Levy, 2012).

### 3.2. Prevalence, morbidity and functional consequences

Apathy is a pervasive neuropsychiatric symptom of most neurocognitive, neurodegenerative, and psychiatric disorders (Robert et al., 2018). It may also be a consequence of normal ageing and therefore not necessarily arises from a pathological status (Brodaty et al., 2010). Regarding neurological conditions, dementia is the most common source of clinically significant apathy although this syndrome is probably still underestimated in dementias with anosognosia. In association with dementia, apathy is generally quite persistent and difficult to treat (Brodaty and Burns, 2012). Apathy is recognised as one of the most prevalent neuropsychiatric symptoms in various neurodegenerative diseases (Pagonabarraga et al., 2015). At early stage of Alzheimer Disease (AD), apathy is present in only 20-25% of patients but about 80% of them develop apathy in the course of the disease (Starkstein et al., 2006). Apathy is also a core feature of Lewy-bodies disease: it is observed in nearly 60% of these patients (Borroni et al., 2008). The prevalence of apathy is even higher in neurodegenerative diseases mostly involving prefrontal cortex and basal ganglia (Pagonabarraga et al., 2015): it is present in 60–90% of patients with progressive supranuclear palsy, 75–95% of patients with frontotemporal dementia, and 55–90% of patients with Huntington's disease. In PD, apathy can be hard to disentangle from motor dysfunction but globally

its reported frequency ranges from 15 to 70% (Pagonabarraga et al., 2015). Aside from neurodegenerative diseases, apathy can also appear in other conditions with neurological impacts such as stroke, cerebral small vessel disease (CSVD), human immunodeficiency virus infection (HIV) or traumatic brain injury (Le Heron et al., 2018; Levy, 2012). Regarding psychiatric conditions, apathy is often observed in schizophrenia with negative signs and in adults with attention deficit-hyperactivity disorders (Levy, 2012). Moreover, apathy is not a clinical criterion of depression but can be one of the clinical expressions of a depressed state (Marin et al., 1994), which sometimes implies major diagnostic challenges. In demented individuals, a significant relationship between apathy and depression has been observed in those with the greatest cognitive deficits, but apathy in the absence of depression is not infrequent and indeed, in most neurological diseases apathy is not the consequence of depression (Chase, 2011; Levy, 2012).

Although few studies have addressed directly the issue of the course of apathy in the natural history of a given disease, it has been found to worsen during the time course of most neurodegenerative diseases. Longitudinal studies showed that apathy scores increased as the disease evolves in particular in PD (Funkiewiez et al., 2004), Lewy body disease (Borroni et al., 2008) and AD (Aalten et al., 2005). More generally within neurological conditions, apathy is considered as a major source of morbidity predicting bad prognosis (Levy, 2012). For instance in dementia of AD, apathy is associated with earlier institutionalisation, higher risk of developing parkinsonism and faster cognitive decline. Besides several studies demonstrated its negative impact on the quality of life of both patients and their caregivers (Hurt et al., 2008). Apathy is indeed associated with a higher level of global functional impairment and loss of autonomy in activities of daily living (Lechowski et al., 2009; Wadsworth et al., 2012). Considering the globally high prevalence of apathy and the extent of its debilitating consequences, it is of high importance to progress in its treatment.

### 3.3 Treatments

#### 3.2.1. Pharmacological treatments

Because apathy reflects dysfunction of PFC-basal ganglia circuits relying on specific neurotransmitters pathways, pharmacotherapeutic interventions targeting these pathways should help to reduce apathetic behaviour. Pharmacological treatments which are most often administered to patients with apathy include: acetylcholinesterase inhibitors, dopaminergic agents, antidepressants, antipsychotics and psychostimulants (Berman et al., 2012; Chase, 2011; Harrison et al., 2016; Pagonabarraga et al., 2015). Pharmacological treatments of apathy have been mostly

tested for AD and PD. In AD, apathy seems to slightly benefit from cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine (Rodda et al., 2009). However, a recent review on pharmacological treatments of apathy in dementia (Harrison et al., 2016) indicates that previously reported benefits of cholinesterase inhibitors failed to be replicated. In PD, treatment of coexisting apathy with dopaminergic drugs (including methylphenidate) has reportedly been successful (Pagonabarraga et al., 2015). Recent evidence (Harrison et al., 2016) tend to show that antidepressants globally have mixed results on apathy with positive effects only for agomelatine. Antipsychotics are only useful in combination with nonpharmacological interventions while psychostimulants do not seem to be effective.

Altogether, results mostly support the use of cholinesterase inhibitors and dopaminergic drugs. One possible approach suggests that apathy treatment strategy should be adapted according to its underlying mechanism and neural substrate: in this view, cholinesterase inhibitors should be preferred to treat executive function deficiencies whereas dopaminergic drugs could be used in case of motivational assessment trouble or auto-activation deficit (Pagonabarraga et al., 2015). Nonetheless, most studies on pharmaceutical treatments of apathy did not specifically focus on apathy as primary outcome and were designed to assess effects on other parameters, which complicates the interpretation of positive effects (Chase, 2011; Harrison et al., 2016). Besides, no study has ever dissected outcomes for the different underlying mechanisms of apathy (Harrison et al., 2016). Improved experimental designs and analyses on distinct apathy forms are therefore required in order to better assess the effect of apathy pharmacological treatments.

### 3.2.2. Non-pharmacological treatments

Non-pharmacological treatments are mostly studied in dementia-related apathy. These interventions are based on very diverse theories and disciplines but interestingly, four studies assessing the impact of music therapy (alone or combined with other intervention elements) in institutionalized patients with dementia demonstrated a significant decrease in apathy (Ferrero-Arias et al., 2011; Fischer-Terworth and Probst, 2011; Raglio et al., 2010, 2008). Although interventions were not identical for the four studies, they all included music therapy for at least 10 sessions of a minimum of 30 minutes. The underlying mechanism explaining this effect of music therapy still has to be investigated. A review on non-pharmacological treatments of dementia-related apathy (Goris et al., 2016) concludes that among all sorts of interventions, music therapy is the one supported by the strongest evidence. More generally, this review suggests that positive

sources of interest and intellectual stimulation should be incorporated into care to target apathy. However, like for the evaluation of pharmacological interventions, the authors underline the lack of focus on apathy as the primary outcome of interventions as well as the need to adapt non-pharmacologic interventions to the aetiologic mechanism of apathy.

#### **4. Perspectives for novel strategies of apathy assessment and therapy**

Limitations of current assessment methods of apathy open the way towards the development of new tools to evaluate this syndrome more precisely and objectively. Improving the characterization of the behavioural signature of apathy is the first step to complete in order to further develop therapeutic strategies targeting this syndrome. Making the clinical diagnosis of apathy more reliable is indeed crucial to be sure to administer the adapted treatment. Moreover identifying the accurate behavioural expression (both qualitatively and quantitatively) of different pathophysiological mechanisms of apathy would be very helpful for the development of new personalized treatments.

##### **4.1. Towards an improved assessment of apathy**

One of the main limitation of traditional clinical scales used to assess apathy is their lack of objectivity. Current information and communication technologies (ICTs) can be used for the development of objective assessments of apathy (König et al., 2014). The 2018 international consensus group of experts has indeed acknowledged that new ICTs could provide clinicians with valuable additional information in terms of assessment, and therefore more accurate diagnosis of apathy (Robert et al., 2018).

ICTs include computerized reaction time in behavioral tasks such as the Iowa Gambling Task which assesses decision-making depending upon cost-benefit ratio. Performance on this task has already been related to apathy and could thus contribute to the objective measurement of this syndrome (Njomboro et al., 2012). The Philadelphia Apathy Computerized Test, developed specifically for the evaluation of three assumed key components of GDB (i.e., motivation, planning and initiation), is another potential source of objective apathy assessment (Massimo et al., 2015). Techniques of indirect measures based on voice analysis, video analysis, serious games, and robots, are also currently being developed and could have interesting applications for apathy evaluation.

Although these methods allow an observer-independent evaluation, they are employed only in research settings and the measures they provide are not necessarily representative of behavior under natural context. The majority of clinical assessment is still carried out under these laboratory-like conditions due to the difficulties in capturing precise human behaviours while performing varied tasks in natural, uncontrolled and non-standardized settings. However several limitations are inherent to this type of evaluation: in particular, 1. the problem of test awareness which may bias subject's behavior, 2. the lack of ecological validity which limits the transfer of measures to more general settings and 3. the impossibility to obtain continuous or frequent measures for monitoring purpose (Korman et al., 2016). An "ecological" approach to apathy assessment would offer a way to overcome these limitations. A key facilitating factor in the feasibility of applying such an approach is the rapid surge over the past decade in sensing and monitoring devices that enable the direct and accurate capture of real-world functioning.

To date, only actigraphy which uses a sensor measuring acceleration on three orthogonal directions of space, has been proposed as an observer-independent evaluation of apathy representative of patient's behavior in everyday life. Actigraphy indeed allows to indirectly quantify the reduction of GDBs through the monitoring of motor activity and rest-activity rhythms. Two studies of ambulatory actigraphy in patients with AD (AD) showed that patients' apathy scores on neuropsychiatric assessment scales correlated negatively with mean motor activity measured by the actigraph (David et al., 2012, 2010). Mulin et al. (2011) used ambulatory actigraphy to assess sleep-wake patterns in AD patients. They observed that these patterns were also related to apathy scores on traditional clinical scales. In particular, among all AD patients, those with apathy had significantly lower daytime mean motor activity, higher wake time after sleep onset, and higher total time in bed during the night than those without apathy. Still using ambulatory actigraphy in AD patients, Zeitzer et al. (2013) showed a higher decline in early afternoon motor activity along with an earlier wake and bed time in those with apathy compared to those without apathy. Another study (Valembois et al., 2015) confirmed different activity patterns between dementia patients with and without apathy : those with apathy had a significantly lower level of motor activity between 9 am and 12 am and also between 6 pm and 9 pm. Only one study (Merrilees et al., 2013) using actigraphy has followed patients for a 2 week period but no study has ever investigated a true long-term period of actigraphic monitoring in patients with apathy. Merrilees and colleagues' study also presents another originality: it assesses the level of motor activity in patient-caregiver dyads instead of patients only. Results of this research suggest a link between apathetic patients' and their

caregiver's level of motor activity that should be further investigated through more actigraphic studies in patient-caregiver couples.

An important limitation of actigraphic studies until now is that, while they provide an objective measure of motor activity through the use of scoring algorithms, details on the nature of the associated behaviours still can not be inferred. For example, moments of high activity can be related to a goal-directed behaviour but they may be due to psychomotor agitation as well. Conversely, patients may engage in a purposeful activity which is sedentary, such as talking on the telephone or working on a computer. It is thus necessary to examine additional data along with the analysis of actigraphic records to get further information on the functional consequences of apathy.

#### 4.2. ECOCAPTURE program towards a new therapeutic approach for apathy

Our team (FRONTlab) at the Brain and Spine Institute in Paris has initiated a program of research called "ECOCAPTURE" to improve the characterization and assessment of apathy using multi-modal behavioral measures under ecological conditions. The main objective of ECOCAPTURE is thus to provide a precise behavioral signature of apathy with useful applications for clinicians. By means of a behavioral sensing system, the protocol tracks each participant's behavior when performing a multiple-phase scenario reproducing a brief real-life situation (45 minutes). The scenario starts with a self-guided phase which consists in discovering a new environment (presented as a waiting room), followed by an externally-guided phase in which the participant has to fill out a questionnaire. We can thus test participant's capacity to generate GDBs under different conditions. The behavioral sensing system comprises 6 cameras, a 3D-accelerometer and eye-tracking glasses (Batrancourt et al., 2019). First results of this protocol allowed to show that exploration deficits may be one of the behavioral markers of apathy in patients with the behavioral variant of fronto-temporal dementia (bvFTD). In the context of facing a new environment, bvFTD patients are indeed characterized by more inactivity and delayed exploration compared to healthy controls. The final goal of ECOCAPTURE is to facilitate further development of therapeutic strategies targeting apathy. In a near future, we hope to be able to propose efficient personalized interventions implemented within patients' everyday life.

#### 5. General conclusion

To conclude, defining apathy as the reduction of GDBs is a starting point to move ahead in the understanding of its pathophysiology and to make progress in its assessment and treatment. In particular, we suggest the existence of three key components underlying GDBs (contextual motivational assessment, planning and execution, auto-activation) with corresponding underlying mechanisms of apathy. Each mechanism is associated with specific neural bases involving three relatively segregated PFC-basal ganglia circuits and dopaminergic pathways. We finally propose a new rationale to optimize personalized treatment for apathy. This approach relies on the precise measure of the behavioural signature of apathy under ecological context.

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