Apathy in Huntington’s Disease: A Review of the Current Conceptualization

Marta Camacho1, Roger A Barker1,2 and Sarah L Mason*1,2
1John Van Geest Centre for Brain Repair, University of Cambridge, UK
2Department of Clinical Neuroscience, University of Cambridge, UK

Abstract

Apathy is one of the most common psychiatric symptoms experienced by patients with Huntington’s disease (HD). It appears early, progresses with the disease course and has been shown to contribute significantly to caregiver burden. However, what is understood by apathy in HD is not clearly defined nor the underlying mechanisms responsible for it. In this review, we discuss the concept of apathy in the context of HD and propose that a consensus regarding its conceptualisation and subsequently its diagnostic criteria would significantly benefit the field.

In order to undertake this work, we began by reviewing the existing literature on the definition and assessment of apathy in HD, its underlying neurobiological basis and its relationship to other related features such as abulia, anhedonia and alexithymia.

In the context of HD, apathy could be described by a loss of or diminished motivation, emotion and goal-directed behaviour that is not best explained by motor or social constraints of the disease. However, there is an urgent need to better understand the characteristics of apathy specifically in HD, how they evolve across the disease course and how they relate to central dopaminergic pathways. Only by undertaking such work can we hope to better understand this early and disabling aspect of HD.

Keywords: Huntington’s disease; Apathy; Reward; Abolition; Anhedonia; Basal ganglia

Introduction

Huntington’s disease is a rare autosomal-dominant neurodegenerative disorder caused by the expansion of a CAG triplet in the huntingtin gene, affecting approximately 2.71 people per 100,000 worldwide [1]. It is a fatal condition that typically develops between the ages of 30 and 50 years old [2,3] and progresses over a 20 year period [4]. During this time, patients experience a range of problems including a movement disorder [5], cognitive dysfunction and neuropsychiatric symptoms [6]. The exact profile of these features varies between patients but the typical non motor features include executive dysfunction [7,8], memory problems [9], irritability and disinhibition [10], depression [11], anxiety [12] and apathy [13]. For some people, these symptoms can appear before the motor abnormalities and are the strongest predictors of loss of independence and the need for residential care [14].

Within the psychiatric domain, apathy is thought to be one of the most common features of HD. Studies suggest that between 11% [13] and 64% [15] of premanifest and 47% to 76% [15-19] of manifest HD patients (Table 1) experience some degree of apathy at some point during their disease and that apathetic symptoms are associated with cognitive, motor and functional decline [20,21]. Nonetheless, not all patients experience apathy. Van Duijn et al. [13] reported that 52% of mutation carriers experienced no apathy and those who did were more likely to be male, with lower functional capacity scores and have a history of depressive episodes (and a previous suicide attempt), obsessive-compulsive symptoms and benzodiazepines or antipsychotics use. This work both confirmed and added to this group’s previous study [22] which found that, in comparison to non-apathetic mutation carriers, apathetic participants were more often older and showed worse global and executive cognitive function. Interestingly though, unlike other psychiatric features, apathy did not seem to be inheritable [23].

Importantly, apathy is considered a significant problem by patients and caregivers alike who both rank it as one of the three most impactful features of the disease [19]. This is apparent from clinical observation and empirical evidence where apathy is negatively associated with patient’s quality of life [24]. Furthermore, caregiver burden in HD is driven by feelings of isolation and the sense that they are putting their lives on hold whilst caring for the patient [25]. If a patient socializes and interacts less and stops engaging in hobbies and activities due to their level of apathy these feelings are likely to be amplified, although this has never been formally assessed in the context of HD. Thus, the impact of apathy is clear as is the potential to improve the quality of life of both patients and their caregivers and to delay the need for costly residential care through treating it.

Cross-sectional cohorts studies have shown that apathy maps closely to disease progression [7,15,22,26,27]. Given how many patients are affected by apathy and the impact it has on disease, it has been suggested that apathy should be considered a core trait of the HD15 and as such, should be treated as a priority in the clinical care of patients. However, it is currently understudied in HD and not enough is known about its etiology or pathophysiology to be able to treat it effectively. This is in part due to the poverty of validated assessment tools available for use in HD and the lack of methodological consistency in the literature. But it may also be due to the overlap between similar conditions, such as depression, abulia, alexithymia and other disorders of motivation which also occur in HD, making it difficult for clinicians to recognize
What is Apathy?

Definitions of apathy

Classically, apathy is defined as a flattening of affect, in which a patient exhibits an abnormal lack of feeling, interest or concern and regarded as a state of non-reactivity [28]. Marin, in 1990, was the first to consider apathy as more than a symptom but as a distinct psychiatric syndrome and described it as a state of primary motivational impairment not attributable to diminished levels of consciousness, cognitive deficits or emotional distress [29]. Through the use of scales such as the Apathy Evaluation Scale (AES) [30] most HD research conducted to date has adopted Marin's definition of apathy. Yet, reducing apathy simply to an impaired motivational state makes it difficult to objectively assess and fails to take into consideration the other well reported symptoms such as lack of initiative and poverty of self-generated actions that seem to be core features of it. In addition, Marin's conceptualization excludes apathy in the context of cognitive dysfunction but evidence suggests these are dissociable phenomena, as while apathy can occur in the absence of cognitive dysfunction [28], it is also commonly reported in conditions that are also associated with cognitive dysfunction such as Parkinson's disease [31], Frontal temporal dementia [32], Alzheimer's disease [33], traumatic brain injury [34] and stroke [35]. Furthermore, some studies have found strong positive correlations between apathy and cognitive impairment [35,36], suggesting that while Marin's exclusion criterion of cognitive deficits may be appropriate when looking at apathy in a healthy population, it is too strict for clinical studies.

Levy and Dubois took the alternative viewpoint and proposed a fully operational account of apathy, describing it as "a quantitative reduction in self-generated or purposeful behaviour" [37]. Consequently, apathy can be identified by a simple quantification of the number of activities that HD patients initiate and engage in. However, this approach has several limitations: firstly, there are many reasons why a patient with HD displays a reduction in their "self-generated and purposeful behaviours", not least because they find these activities harder to do due to their emerging movement disorder. Secondly, a quantifiable reduction in behaviours only happens at a relatively advanced stage of apathy. Prior to this the changes may be subtle and easy to miss or may be better reflected by the amount of additional effort a patient has to undertake in order to maintain their regular levels of activity. Either way, Levy & Dubois's definition is poorly equipped to measure the very early changes that are common in the prodromal and early phases of HD. Finally, its broad scope makes it difficult to differentiate apathy from other psychopathological concepts of abnormal drive and motivation such as abulia or anhedonia.

More recently, Starkstein and Leentjens [28] has built upon Marin's definition by extending it to include a temporal element and formulating it into diagnostic criteria (Table 2). Their work was further refined by an international task force in 2008 to provide the consensus criteria for the diagnosis of apathy in Alzheimer's disease and other neuropsychiatric disorders [38]. The aim of these consensus criteria was to facilitate the accurate identification, description and treatment of apathy in both clinical and research settings. It has achieved this by broadening the scope of behaviour that is considered supportive of a diagnosis of apathy whilst accepting that this behavior does not necessarily occur in all domains (e.g. goal-directed behavior, goal-directed cognition and emotion). Consequently, although Marin's description of apathy has been the one most widely adopted in the literature, going forward we feel that there is a clear rationale for utilizing the criteria identified by the International Task Force as the most appropriate and useful definition of apathy in the context of HD. Of note, the Statistical Manual of Mental Disorders (DSM-V) [39] and the International Classification of Diseases (ICD-10) [40] do not recognize apathy as a syndrome and consider it as a supporting symptom for several psychiatric diseases, including HD, warranting no definition or criteria. But importantly, considering apathy as either a symptom (of, for example, depression) or as a syndrome does not need to be mutually exclusive [28] and indeed may represent a number of related but separable states [41].

| Study                      | Sample Size | Disease Stage                 | Assessment Tool | Used Cuff-off | Prevalence |
|----------------------------|-------------|--------------------------------|-----------------|--------------|------------|
| van Duijn, et al. [13]     | 1993        | Mutation carriers from premanifest to late HD | UHDRS          | scale score of ≥ 2 | 47.4%      |
| Martinez-Horta et al. [15] | 34          | Premanifest individuals far-from motor-based HD onset | Short PBA-HD    | scale score of ≥ 2 | 23%        |
| Martinez-Horta et al. [15] | 25          | Premanifest individuals close-to motor-based HD onset | Short PBA-HD    | scale score of ≥ 2 | 64%        |
| Martinez-Horta et al. [15] | 70          | Patients with Early manifest HD | Short PBA-HD    | scale score of ≥ 2 | 63%        |
| Martinez-Horta et al. [15] | 101         | (Not applicable) Controls | Short PBA-HD    | scale score of ≥ 2 | 2%         |
| Simpson et al. [19]        | 556         | HD Manifest patients | Customized Survey on HD symptoms | Not clear | 46.3%      |
| Naarding et al. [17]       | 34          | HD Manifest patients | AES             | score of ≥ 40 | 52%        |
| Paulsen et al. [16]        | 52          | HD Manifest patients | NPI             | scale score >1 | 55.8%      |
| Craufurd et al. [56]       | 134         | HD Manifest patients | PBA-HD          | scale score of ≥ 2 | 76%        |

Table 1: Summary of apathy prevalence rates in samples of patients with HD and controls when applicable.

Overlapping conditions
The symptoms of apathy share many features with other conditions that affect the motivational spectrum. Differentiating between depressed mood, apathy, abulia, alexithymia and anhedonia can be difficult because of the similarity of their clinical features [44]. There are many more clinical conditions that, if present, may confound the accurate diagnosis of apathy in HD, such as anergia, hopelessness and others on the negative affect and akinetic spectrum. Understanding the boundaries that each of these conditions shares with apathy may inform our knowledge of how to better define and manage them all in HD.

**Abulia:** Abulia is usually defined as a lack of will or motivation [45]. From a conceptual standpoint, abulia and apathy are on a continuum of motivational and emotional deficit and it has been proposed that abulia represents the more severe part of the continuum [28], which at its most extreme leads to akinetic mutism [46]. However, this is a conceptual framework that is not strongly based on empirical research but rather on the clinical understanding that apathy tends to produce abulia in more severe neurological conditions [29]. For example, in a review of 240 cases from the literature, Bhatia and Marsden reported that abulia was recorded in approximately 28% of patients with a focal lesion to the caudate [47]. Interestingly, a Delphi survey involving 35 neurologists and 30 psychiatrists showed that there was no consensus about whether abulia and apathy represent distinct phenomena and if and how, they differed in terms of severity [48], highlighting the need for more precise differential definitions and diagnostic criteria. To our knowledge, abulia has never been formally assessed in HD.

**Anhedonia:** Anhedonia is described as the ‘difficulty to anticipate or experience pleasure’ [49]. Generally, anhedonia is not considered a syndrome in its own right but rather a symptom of different psychopathologies such as depression and schizophrenia [39]. It may also be part of the apathy syndrome following the criteria of Marin and subsequent revisions. According to the DSM-V, a patient experiencing anhedonia reports less pleasure from daily activities (the focus here is on the subjective emotional experience of the patient) or loss of interest in those activities (slightly more focused on interpersonal behavioral aspects). The apparent overlap with apathy is striking, particularly considering the recent efforts in operationalizing both apathy and anhedonia within the context of disrupted reward processing systems and the role of dopaminergic frontostriatal circuits in both constructs.

In HD, anhedonia has been studied in the context of hedonic

### Table 2

| Authors | Temporal dimension | Inclusion Criteria | Exclusion criteria |
|---------|--------------------|-------------------|-------------------|
| Marin [29] | None | State of primary motivational impairment. (Marin’s conceptualization of apathy was done as a description and not as diagnostic criteria.) | ‘Lack of motivation is not attributable to a diminished level of consciousness, an intellectual deficit or emotional distresses’. |
| Starkstein and Leentjens [28] | At least 4 weeks during most of the day | Diminished goal directed behaviour 1. Lack of effort or energy to perform everyday activities. 2. Dependency on prompts from others to structure everyday activities. Diminished goal directed cognition 1. Lack of interest in learning new things, or in new experiences. 2. Lack of concern about one’s personal problems. Diminished concomitants of goal directed behaviour 1. Unchanging or flat affect 2. Lack of emotional responsiveness to positive or negative events. C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. | D. The symptoms are not due to diminished level of consciousness or the direct physiological effects of a substance. |
| International task force [38] | At least 4 weeks during most of the time | A. Loss of or diminished motivation in comparison to the patient’s previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others. B. Presence of at least 1 symptom in at least 2 of the 3 following domains for a period of at least 4 weeks and present most of the time B1. Loss of or diminished, goal-directed behaviour as evidenced by at least 1 of the following: - Loss of self-initiated behaviour (e.g. starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices) - Loss of environment-stimulated behaviour (e.g. responding to conversation, participating in social activities) B2. Loss of or diminished, goal-directed cognitive activity as evidenced by at least 1 of the following: - Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/ family and social affairs). - Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighbourhood or community) B3. Loss of or diminished, emotion as evidenced by at least 1 of the following: - Loss of spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect) - Loss of emotional responsiveness to positive or negative stimuli or events (e.g., observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news) C. These symptoms (A-B) cause clinically significant impairment in personal, social, occupational or other important areas of functioning. | D. The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication). |
olfaction. In a very small study, 15 patients at various stages of HD had lower hedonic ratings compared to controls as well as a narrower hedonic rating range [50]. Currently there is an ongoing study that aims to assess hedonic olfaction in HD has the potential to differentiate anhedonia and apathy from depression [51]. This study has been designed to compare the hedonic perception of odours between patients with HD and matched controls and correlate hedonic olfaction with questionnaire-based assessments of depression, apathy and anhedonia. A further discussion awaits publication of the results from this ongoing study.

**Alexithymia:** Alexithymia is defined as a dysfunction in the cognitive processing of emotion that results in the diminished subjective feeling of these states [52]. Like apathy, it has been described as a symptom in several psychiatric disorders such as depression, post-traumatic stress disorder (PTSD) and progressive supranuclear palsy among others [53] as well as a personality trait [52]. The two constructs (namely alexithymia and apathy) also share a common neurobiological basis as it is believed that alexithymia may also be a consequence of dopamine depletion and alterations in front temporal brain structures and the anterior cingulate cortex [37,53,54].

In a study of 353 patients with PTSD, apathy was found to be highly correlated with alexithymia, depression and emotional blunting but all were identified as distinct conditions that could be assessed independently. Interestingly, the only study analyzing the relationship between apathy and alexithymia in HD, found no correlation between the two. However, the study sample consisted of only 13 patients with HD and so no robust conclusions can be drawn from this. Thus, while the constructs of apathy and alexithymia appear to overlap and are frequently co-morbid [53], their relationship to one another, particularly in HD, is still unknown.

**Assessment of Apathy in Huntington’s Disease**

Apathy is usually assessed using psychometric tools. These are used to provide objective measures of symptom severity, their change over time and to evaluate the effectiveness of treatments and so are of critical importance for the clinic and research settings. However, to date, no such tool has been properly validated for use in patients with HD. Nevertheless, several rating scales are currently available and the most commonly used in HD are reviewed below.

**Clinician lead, semi-structured interviews**

The unified Huntington’s disease rating scale (UHDRS)-behavioural scale [55]: The UHDRS is a clinical rating scale used to rate four domains in HD: motor function, cognitive function, behavioural abnormalities and functional capacity. The behavioural assessment is composed of 10 items that refer to symptoms in the last 6 months, scored between 0 and 4, in progressive severity. Only one item pertains to apathy (‘inability to enjoy anything’) and is included in the general category of Mood.

The problem behaviour assessment for Huntington's disease (PBA-HD) [56]: A semi-structured clinical interview modelled after the behavioural section of the UHDRS. The scale comprises 40 items covering an extensive range of neuropsychiatric symptoms including apathy. The items pertain to the last 4 weeks and are scored separately for frequency and severity between 0 and 5, in progressive order. In the study of Craufurd et al. [56] apathy was considered present if a severity score of 2 or higher was obtained. Naarding et al. [17], in a sample of patients with HD, found apathy scores on the PBA to be significantly correlated with total Apathy Evaluation Scale scores (AES, described in section 3.2.1.). This factor structure was also corroborated in a shorter version of the PBA, the PBA-s [57].

**Neuropsychiatric Inventory (NPI) [58]:** An informant-based interview originally developed to assess neuropsychiatric symptoms in dementia. It entails one item dedicated to apathy in the last 4 weeks (‘Does he/she seem less interested in his/her usual activities or in the activities of others?’). If the answer is affirmative, informants are asked to assess this behaviour in terms of severity and frequency. Several studies have used the NPI to assess apathy symptoms in HD [16,59].

**Structured Clinical Interview for Apathy [60]:** Designed to screen for symptoms of apathy as operationalized by Starkstein and colleagues, in patients with Alzheimer’s disease. This interview includes questions referring to lack of motivation relative to the individual’s previous level of functioning, lack of effort to perform every day activities, lack of interest in learning new things or in new experiences, lack of self-concern, flat affect and lack of emotional response. Additional follow up questions are used to rate the severity of symptoms, the approximate date of onset, the pattern of progression and discrepancies in the information provided by patient and caregiver. Apathy is diagnosed if a patient scores 3 on criterion A and on at least three B criteria and a score of 1 on criteria C and D. This interview, along with AES and UHDRS, was used as an outcome measure in the first drug trial for apathy in HD [61].

All these instruments are clinician lead, semi-structured interviews with the patient and/or their companion. Only the Structured Clinical Interview for Apathy does not look at apathy as part of a composite of many other behavioural features of HD. These assessments are time consuming to administer (approximately 30 min each) and their accuracy is highly dependent upon the skill and training of the clinician administering it which limits the utility of the scales in many settings. Additionally, while these interviews provide data about apathy at the global level they are insensitive to the finer details. For example, patients whose apathy is mild in severity but occurs frequently may have the same total domain score as a patient with occasionally severe episodes of apathy. Thus, using such tools can make it difficult to detect subtle changes that may occur as a result of any therapeutic intervention. Therefore, in such circumstances it may be relevant to consider severity and frequency independently.

**Rating scales**

There is an extensive list of psychometric scales published to assess apathy [46,62,63], however, for the purpose of this review we have focused on those which have been published using HD patients.

**Apathy evaluation scale (AES):**30 is based upon Marin’s conceptualization of apathy. There are three versions of the AES: Clinician (AES-C), informant (AES-I) and self-rated (AES-S) versions. Administration time is approximately 5 min. All versions include the same core 18 items presented in a 4 point likert scale, with a higher score indicating a greater severity of apathy. Several cut-off score have been proposed, according to different studies and clinical samples [30,64,65]. In samples of patients with HD, cut-offs of 4017 and 4165 have been used to differentiate patients with clinically significant apathy in patient rated AES. For the companion rated AES, a cut-off of 39 has been used to be indicative of apathy in HD [65].

**The apathy scale (AS):** [66]: Is a short modified version of the Apathy Evaluation scale. It comprises of 14 items distributed in a 4 point likert scale that is administered by a clinician.
The AES has proven to have satisfactory psychometric properties in healthy controls [30] and in several clinical samples [30,67,68]. However, no proper validation of the AES has been performed in a population of patients with HD and appropriate cut-offs are still lacking. Several threshold values have been proposed for clinically significant apathy (ranging from 30 to 41.5) and there is no clear consensus on which one to use making cross study comparisons difficult [69]. Furthermore, the widespread use of the AES across different clinical populations, whilst making it useful for cross-cohort comparisons, can lead to the assumption that different etiologies result in the same apathetic phenotype which is a preconception that has not been empirically verified. Further research is needed to ascertain whether the AES can detect differences in apathy profile between different neurodegenerative disorders.

Irritability-apathy scale [70]: It is an informant questionnaire developed for use in patients with Alzheimer's Disease (AD) and HD. The companion of the patient is asked to rate the presence of 5 symptoms of apathy since the onset of their disease on a 5 item likert scale. Apathy is considered as clinically significant if a patient obtains a score of ≥ 4 on items 1 and 3 and a score of ≥ 3 on items 2, 4 and 5. Because the Irritability-Apathy Scale asks the companion to compare symptoms before and after a diagnosis, it is not suitable for studies with premanifest HD patients. Apart from the validation study, to the best of our knowledge, this scale has not been used in any HD studies.

Frontal system behavioral scale (FrSBE) [62]: FrSBE is a 46-item self-report symptom inventory designed to assess behavioral disturbances associated with damage to the frontal-subcortical (brain) circuits. Symptoms are scored on a 5 item likert scale for frequency and distress of a given symptom before and after a specific illness or injury. Because the FrSBE refers to symptoms before and after the diagnosis, it is not suitable for studies with premanifest HD patients. Three subscales can be derived: Apathy, Disinhibition and Executive Dysfunction. The apathy subscale has 14 items referring to difficulties in initiation, spontaneity, loss of interest and decreased concern about self-care. This scale is also known in the HD literature as frontal lobe personality scale (FLOPS) [21].

The Huntington's disease-behavioural questionnaire (HD-BQ) [71]: It is a quick screening tool for common behavioural changes in HD. It consists of 30 items that cover apathy, depression, irritability, anxiety and disinhibition. Items are rated on a 3-point likert scale with higher scores indicating more behavioural changes. A maximum score of 90 is possible and the assessment takes about 5 min to complete. The full paper on this instrument is yet to be published, therefore details on the specific assessment of apathy are not available. To our knowledge this scale has not yet been used outside of the validation studies.

None of the psychometric instruments described above have been validated against external criteria due to the lack of established diagnostic standards [46]. Furthermore, they are all based on slightly different definitions of apathy, so the scores obtained may not be directly comparable [72]. Furthermore, it is important to remember that when evaluating apathy in HD using subjective psychometric tools, it is crucial to consider potential confounding factors such as comorbid depression [17], adverse effects of concomitant medication [22] and lack of insight [61]. While there is a tendency to believe that patients with apathy rate their symptoms of apathy as significantly less severe than the caregivers or clinicians, the literature seems to be conflicting. Mason and Barker [65] found a strong correlation between self-rated and companion-rated AES scores. However, the degree of agreement varied across disease stage, so despite there being a high degree of agreement in early disease, when cognitive performance is preserved, patients tend to rate their levels of apathy higher than their companions in later disease stages. Additionally, the reliance on a companion report can be problematic when designing a clinical trial, as it restricts the cohort of eligible patients to those who have a reliable companion willing to accompany them for study visits. This also has the potential to create an additional potential recruitment bias, as patients with a good support network tend to fare better psychiatrically than those without [65].

Novel assessment techniques

Despite psychometric scales being the only currently available tools to assess apathy in HD, their use poses several limitations. Firstly, interviews are time consuming and require extensive training to be completed accurately which puts practical limitations on the number of patients who can be assessed using this method. Secondly, questionnaires are of limited use in the later stages of the disease due to increasing cognitive impairment and decreasing insight which make the responses unreliable. Furthermore, all self-report measures are subject to cultural and personality biases which may confound the data. Finally, reliance upon these current assessment tools limits the potential to translate between patients and non-human models of apathy which can provide a more mechanistic understanding of the neurobiological mechanisms that underlie this condition. Thus, more objective measures of apathy are needed.

Psychophysiological measures: David et al. [73] assessed daytime motor activity with wrist actigraphs in patients with AD as a surrogate marker of apathy. They found that those patients who had symptoms of apathy (as measured by the NPI) had significantly lower daytime mean motor activity compared with patients without apathy, while there was no difference in mean night-time motor activity between the two groups. Furthermore, in a sample of patients with traumatic brain injury, Andersson et al. [74] found that apathy (as measured by the AES) was significantly correlated with heart rate reactivity but not with electrodermal reactivity. However, to our knowledge, neither skin conductance nor heart rate reactivity have been used in the context of apathy research in HD. Furthermore, whilst these measures provide interesting support to the subjective assessments, they have limitations especially in HD where motor and autonomic abnormalities form part of the disease process.

Cognitive measures: Recently, there has been a move towards using effort-based and reward-based decision-making tasks [42] as an objective measure of apathy. In the HD literature, McLaughlan et al. [75] designed a battery of tasks that measured reward, sensitivity to negative stimuli and decision-making to encompass the different dimensions of apathy and looked at the association between performance on these tasks and scores on the PBA and AES in 53 mutation carrier individuals. They found that performance on both scales correlated with impaired sensitivity to negative stimuli and deficits in decision making but not to measures of effort, reward or learning. It was concluded that apathy was a result of inertia due to an impaired ability to formulate and enact a plan to change current behaviour. At present their work is published as a conference poster and therefore a more complete discussion awaits the full publication of their data.

Neurobiology of Apathy

Apathy is most commonly associated with lesions in and dysfunction of, the prefrontal cortex (PFC) and basal ganglia (BG) [37].
However, the neurobiological substrates driving apathy in the context of HD are currently not well understood. This is further complicated by the realization that they may vary according to disease stage and the exact “type” of apathy being described.

**Neuroimaging changes**

Classical neuropathological studies in HD have shown that the striatum is the major site of early pathology becoming evident in the premanifest stage, after which the pathology becomes more widespread [76]. Given that apathy also appears early in the disease and gets progressively worse, it seems logical to explore the relationship between striatal pathology and apathy in HD. In the only study to do this, Duff and colleagues reported that higher scores on both the patient and companion versions of the FrSBe apathy subscale correlated with smaller striatal volumes in 558 premanifest HD gene carriers [77].

It is well known that the early striatal degeneration in HD compromises the functional integrity of the cortico–basal ganglia networks [78,79]. In particular, it is the role of the so called “limbic loop” [80] that may be particularly relevant to the understanding of apathy in HD. The limbic loop involves the ventral striatum and receives projections from the cingulate, orbital and prefrontal cortices [81]. These regions are linked to emotional processing, mood and affect and overlap with the areas proposed by Levy & Dubois to be involved with apathy [37].

In support of this Martinez-Horta et al. [82] performed an 18-FDG PET/CT scan in a sample of 11 premanifest HD patients in whom they had assessed apathy and depression severity. Apathy scores (measured by the short version of PBA) significantly correlated with hypometabolism in the dorsolateral PFC, right frontopolar PFC and left posterior insula, while depressive scores were associated with hypometabolism in parietal-temporal regions.

Furthermore, Delmaire et al. [78] observed white matter changes in the gyrus rectus bilaterally of 27 patients with HD which correlated negatively with apathy scores, as measured by the Problem Behaviours Assessment (PBA). They did not, however, find a correlation between abnormalities in the ventral striatum and apathy scores. In contrast, Gregory et al. [83] investigated the relationship between apathy and white matter microstructure in a larger group of 38 premanifest and 43 manifest patients and found no relationship between PBA apathy scores and fractional anisotropy (FA), even when the effect of medications was controlled for. It is likely that these contradictory results come from methodological differences, including different measures of apathy. For example, Gregory had a larger sample size but used a group of premanifest patients as their control group, whereas Delmaire used a healthy control group and a more advanced group of manifest patients. Also, while both studies used the PBA with mean scores that did not differ between the clinical groups, the DTI technique was slightly different and Gregory collated imaging data from multiple centres. Gregory et al. [83] also advanced other plausible reasons for the lack of association between apathy and white matter integrity, namely, an inherent bias of HD patients with more severe apathy are less likely to participate and the participants who do participate do not have marked white matter microstructural changes. While this bias is an important confounding effect of all apathy studies, the participants in Gregory’s study had a mean apathy score that was well above the PBA clinical cut-off of 2 and is therefore unlikely to be the sole factor for the absence of an association. The authors propose that apathy in HD is related not to white matter microstructural changes but instead to that of grey matter. While this association has been found in studies with PD patients [84] we are not aware of any published data on the relationship between whole brain grey matter density and apathy in HD. Future research on grey and white matter density and apathy severity could prove to be useful to delineate potential intervention targets in treating this aspect of HD.

**Neurotransmitters**

Surprisingly, to the best of our knowledge, no study has focused on the role of dopamine (DA), serotonin or other neurotransmitters on apathy severity in HD. The lack of treatments for apathy accentuates the little knowledge we have of its neurobiological basis. Yet, untangling this aspect of the condition would allow for the development of effective treatments. Consequently, the evidence reported here has mostly been extrapolated from other neurodegenerative diseases or derived from the current knowledge of neurotransmitter dysfunction in HD.

**Dopamine:** Dopaminergic abnormalities in the CNS have been widely described in HD (for a comprehensive review see Schwab et al. [85]). Moreover, the dopaminergic system has been implicated in different component processes of reward, mainly mediating anticipatory phases, reinforcement processes and hedonic response [86,87]. Hence, dopamine could be a key neurotransmitter in the development and/or management of apathy in HD.

Although currently non-existent, studies regarding the effect of dopaminergic medication on apathy in HD could provide important insight into the role of this neurotransmitter. PD, AD and lesion studies suggest that dopaminergic receptor agonists improve apathy symptoms, hypothesizing that this is a result of improved dopaminergic input to the basal ganglia and frontal lobes [88,89]. The complete withdrawal of dopaminergic medication following deep brain stimulation for PD has also been shown to markedly increase apathy scores resulting in the need to restart these medications in some cases [90,91].

In HD patients, Mason and Barker [65] examined the impact of dopamine blocking drugs (e.g., sulphiride, amisulpiride, olanzapine, tetrabenazine and haloperidol) on apathy severity, as measured by the Apathy Evaluation scale. They found no difference in apathy scores, as assessed by the patient or their companion, between HD patients on antidopaminergic medication and HD patients who were not. Martinez-Horta et al. [15] in a large cohort of premanifest individuals and patients with early HD, did (in contrast) find a significant correlation between apathy scores and use of antidepressants and neuroleptics. However, these are observational studies and therefore cannot provide any information about causality.

Although it is currently unclear whether these drugs are contributing to the changes in affect seen in patients in HD, clinicians are recommended to exclude iatrogenic causes of apathy when managing patients and to consider a reduction of neuroleptics in HD apathetic patients if motor symptoms allow it [22,92].

It is also important to acknowledge that neurotransmitters do not act in isolation, for example, serotonergic innervation of the anterior striatum may exert a facilitatory influence on DA release [93].

**Serotonin:** The serotonergic system has of late been implicated in the mediation of reward and in motivation but the literature is currently somewhat inconsistent. Both a reduction in activation elicited by rewarding stimuli in the ventral striatum and orbitofrontal cortex following administration of Selective Serotonin Reuptake Inhibitors (SSRIs) [94] and an increase in activation of reward on brain structures such as the ventral tegmental area have been shown [95]. Furthermore,
some studies have documented improvements in apathy scores after administration of SSRIs [44,96]. Still, this evidence consists of case reports and it is not clear whether an adequate differential diagnosis between depression and apathy was achieved in these cases. Therefore, there is likely that the serotonergic system is involved in apathy but the exact nature of its role is currently unclear.

In the HD literature, little had been done to solve the relationship between apathy and the serotonergic system. While no study has directly looked at this, some reports exist that speak to it. Mason and Barker [65] examined the impact of SSRIs on apathy and found that apathy scores did not differ significantly as a function of antidepressant use, when depression symptoms were controlled for. On the other hand, Naarding et al. [17] found a positive correlation between antidepressant use and apathy score on the PBA and in a previously described study, Martinez-Horta et al. [15] also showed a significant correlation between apathy scores and use of antidepressants. However, neither study looked specifically at SSRIs.

Other neurotransmitters: There is evidence favouring the participation of several other neurotransmitters in the pathogenesis of apathy, including the GABAergic, cholinergic and glutamatergic systems [46]. However, while none of these neurotransmitters have been studied in the context of apathy in HD, it does highlight that the successful treatment of apathy may involve drugs affecting more than one neurotransmitter system.

Future Research Directions

Throughout the course of this review the poverty of research into apathy in HD has become apparent (Table 3). Currently it is not possible to present an empirically validated holistic synopsis of what apathy looks like in HD, nor how it impacts patients or what causes it. This is partially due to the methodological differences in the few existing studies, specifically in the classification of the stages of disease as well as the assessment tools they used to measure apathy, but also due to the overall scarcity of literature on the subject. Given the importance of apathy to both patients with HD and their families who are trying to care for them, this needs to be rectified.

Simple changes, such as adopting a consistent approach to defining and measuring apathy could have a meaningful and important impact to better understand this aspect of HD. For example, by using the consensus criteria identified by the International Task Force [38] as a framework for all future research, it would be possible to compare across studies in a meaningful way. Also, given the increased scope of this definition, it would allow for a true appreciation of the full breadth of apathetic symptoms experienced by patients.

### Table 3: Summary of apathy rating scales used in HD.

| Instrument | Versions | Temporal window | Number of total items | Average time for completion | Comments |
|------------|-----------|-----------------|-----------------------|----------------------------|----------|
| AES [30]   | Self-rated, informant and clinician. | Past 4 weeks | 18 | 5 min | No proper validation of the AES or AS has been performed in a population of patients with HD and appropriate cut-offs are still lacking. |
| AS [66]    | Clinician | Present time | 14 | Less than 5 min | Because the Irritability-Apathy Scale and the FrSBE refer to a comparison of symptoms before and after a diagnosis, it is not suitable for studies with premanifest HD patients. |
| FrSBE [82] | Informant | Comparison before and after illness, not recent past | 14 items in total, 5 items on apathy | 5 min | Validation study of this rating scale has not been published. |
| HD-BQ [71] | Self-rated and informant | Unknown | 30 items, number of items specifically referring to apathy unknown | 5 min | |

### Conclusion

Given this, a primary focus of future work should be to clearly define the specific characteristics of apathy in HD and how it evolves across the disease course. Attention should be paid as to whether this profile of symptoms is universal across all patients or if subgroups can be identified that reflect people who either have a more aggressive or more benign phenotype. Doing so will allow for a more focused approach to identifying the underlying etiology of apathy in HD which in turn could lead to more effective treatments, for this most disabling of clinical features.

### Acknowledgment

The authors highly appreciate the contribution of all HD patients and their families that participate in our research efforts at the John Van Geest Centre for Brain Repair and motivate us to better understand the disease. This work was supported by the NIHR funded Cambridge BRC.

### References

1. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, et al. (2012) The incidence and prevalence of Huntington’s disease: A systematic review and meta-analysis. Mov Disord 27: 1083-1091.

2. Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RA, Durr A, et al. (2009) Biological and clinical manifestations of Huntington’s disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. Lancet Neurol 8: 791-801.

3. Roos RA (2010) Huntington’s disease: A clinical review. Orphanet J Rare Dis 5: 40.

4. Lanska DJ, Levine L, Lanska MJ, Schoenwies BS (1988) Huntington’s disease mortality in the United States. Neurology 38: 769-772.

5. Reilmann R, Leavitt BR, Ross CA (2014) Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 29: 1335-1341.

6. Crawford D, Snowden J (2014) In Huntington’s disease. Oxford University Press.

7. Tabrizi SJ, Stahlhut RI, Owen G, Durr A, Leavitt BR, et al. (2013) Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington’s disease in the TRACK-HD study: Analysis of 36-month observational data. Lancet Neurol 12: 637-649.

8. Mörkl S, Blesil AC, Wurm TW, Hoff A, Painold A (2016) Inconsistent decline of executive functions in patients with early and late Huntington’s disease. European Psychiatry 33: S371.

9. Begel F, Schwab LC, Mason SL, Barker RA (2016) Hippocampal dysfunction defines disease onset in Huntington’s disease. J Neurol Neurosurg Psychiatry 87: 975-981.

10. Mendez MF (1994) Huntington’s disease: Update and review of neuropsychiatric aspects. Int J Psychiatry Med 24: 189-208.

11. Paulsen JS, Niel C, Hoeh KF, Kanz JE, Benjamin M, et al. (2005) Depression and stages of Huntington’s disease. J Neuropsychiatry Clin Neurosci 17: 496-502.
12. Dale M, van Dulijn E (2015) Anxiety in Huntington’s disease. J Neuropsychiatry Clin Neurosci 27: 262-271.
13. van Dulijn E, Craufurd D, Hubers AA, Giltay EJ, Bonelli R, et al. (2014) Neuropsychiatric symptoms in a European Huntington’s disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry 85: 1411-1418.
14. Dawson S, Kristjansson LJ, Toye CM, Flett P (2004) Living with Huntington’s disease: Need for supportive care. Nurs Health Sci 6: 123-130.
15. Martínez-Horta S, Perez-Perez J, van Dulijn E, Fernandez-Bobadilla R, Carceller M, et al. (2016) Neuropsychiatric symptoms are very common in premanifest and early stage Huntington’s disease. Parkinsonism Relat Disord 25: 58-64.
16. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL (2001) Neuropsychiatric aspects of Huntington’s disease. J Neurol Neurosurg Psychiatry 71: 310-314.
17. Naarding P, Janzing JG, Eling P, van der Wart S, Kremer B (2009) Apathy is not depression in Huntington’s disease. J Neuropsychiatry Clin Neurosci 21: 266-270.
18. van Dulijn E, Kingma EM, van der Mast RC (2007) Psychopathology in verified Huntington’s disease gene carriers. J Neuropsychiatry Clin Neurosci 19: 441-448.
19. Simpson JA, Lovecky D, Kogan J, Vetter LA, Yohrling GJ (2016) Survey of the Huntington’s disease patient and caregiver community reveals most impactful symptoms and treatment needs. J Huntington’s Dis 5: 395-403.
20. Thompson JC, Snowden JS, Craufurd D, Neary D (2002) Behaviour in Huntington’s disease: dissociating cognition-based and mood-based changes. J Neuropsychiatry Clin Neurosci 14: 37-43.
21. Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, et al. (2003) Behavioural abnormalities contribute to functional decline in Huntington’s disease. J Neurol Neurosurg Psychiatry 74: 120-122.
22. van Dulijn E, Reederer N, Giltay EJ, Roos RA, van der Mast RC (2010) Correlates of apathy in Huntington’s disease. J Neuropsychiatry Clin Neurosci 22: 287-294.
23. De Souza J, Gordon-Smith K, Jones L, Rickards H (2014) H07 The familiality of psychiatric symptoms in Huntington’s disease. J Neurol Neurosurg Psychiatry 85: A54.
24. Ready RE, Mathews M, Leserman A, Paulsen JS (2008) Patient and caregiver quality of life in Huntington’s disease. Mov Disord 23: 721-726.
25. Rathsing M, Malterud K, Frich JC (2015) Balancing needs as a family caregiver in Huntington’s disease: A qualitative interview study. Health Soc Care Community 23: 569-576.
26. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, et al. (2012) Longitudinal evaluation of neuropsychiatric symptoms in Huntington’s disease. J Neuropsychiatry Clin Neurosci 24: 53-60.
27. Kingma EM, van Dulijn E, Timman R, van der Mast RC, Roos RA (2008) Behavioural problems in Huntington’s disease using the problem behaviours assessment. Gerontol Psychiatry 30: 155-161.
28. Starkstein SE, Leentjens AF (2008) The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry 79: 1088-1092.
29. Marin RS (1990) Differential diagnosis and classification of apathy. Am J Psychiatry 147: 22-30.
30. Marin RS, Biedrzycki RC, Frincucigullari S (1991) Reliability and validity of the apathy evaluation scale. Psychiatry Res 38: 143-162.
31. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P (2015) Apathy in Parkinson’s disease: Clinical features, neural substrates, diagnosis and treatment. Lancet Neurol 14: 518-531.
32. Zamboni G, Huey ED, Krueger F, Nichelli PF, Graffam J (2008) Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. Neurology 71: 736-742.
33. Landes AM, Sperry SD, Strauss ME, Geldmacher DS (2001) Apathy in Alzheimer’s disease. J Am Geriatr Soc 49: 1700-1707.
34. Starkstein SE, Pahissa S (2014) Apathy following traumatic brain injury. Psychiatr Clin North Am 37: 103-112.
35. Jorge RE, Starkstein SE, Robinson RG (2010) Apathy following stroke. Can J Psychiatry 55: 350-354.
36. Baudic S, Maisin P, Dolbeau G, Boissé MF, Bartolomeo P, et al. (2006) Cognitive impairment related to apathy in early Huntington’s disease. Dement Geriatr Cogn Disord 21: 316-321.
37. Levy R, Dubois B (2006) Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 16: 916-928.
38. Robert P, Onyike CJU, Leentjens AF, Dujardin K, Aalton P, et al. (2009) Proposed diagnostic criteria for apathy in Alzheimer’s disease and other neuropsychiatric disorders. Eur Psychiatry 24: 98-104.
39. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders DSM-5. (Fifth Edition).
40. World Health Organisation (1993) The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research.
41. Board JC (2000) Neuropsychology of Emotion. Oxford University Press.
42. Bonnelle V, Veromann KR, Burnett Hayes S, Lo Sterzo E, Manohar S, et al. (2015) Characterization of reward and effort mechanisms in apathy. J Physiol Paris 109: 16-26.
43. Brodaty H, Attendorf A, Withall A, Sachdev P (2010) Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. Int Psychogeriatrics 22: 426-438.
44. Marin RS, Fogel BS, Hawkins J, Duffy J, Kruiss P (1995) Apathy: A treatable syndrome. J Neuropsychiatry Clin Neurosci 7: 23-30.
45. Berrios GE, Gill M (1995) Abulia and impulsiveness revisited: A conceptual history. Acta Psychiatr Scand 92: 161-167.
46. Chase TN (2011) Apathy in neuropsychiatric disease: Diagnosis, pathophysiology and treatment. Neurotox Res 19: 266-278.
47. Bhata KP, Marsden CD (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117: 859-876.
48. Vijayaraghavan L, Krishnamoorthy ES, Brown RG, Trimble MR (2002) Abulia: A delphi survey of british neuroleogists and psychiatrists. Mov Disord 17: 1052-1057.
49. Ritsner (2014) Anhedonia: A comprehensive handbook volume I: Conceptual issues and neurobiological advances.
50. Hayes CJ, Stevenson RJ, Coltheart M (2007) Disgust and Huntington’s disease. Neuropsychologia 45: 1135-1151.
51. Maxreiter F, Mrochen A, Kozay C, Regensburger M, Klucken J, et al. (2016) G3 Hedonic olfaction in Huntington’s disease. J Neurol Neurosurgery Psychiatry 87: A55.
52. Taylor GJ, Bagby RM, Parker JD (1991) The alexithymia construct: A potential paradigm for psychosomatic medicine. Psychosomatics 32: 153-164.
53. Sturm VE, Levenson RW (2011) Alexithymia in neurodegenerative disease. Neurocase 17: 242-250.
54. Bogdanova Y, Cronin-Golomb A (2013) Alexithymia and apathy in Parkinson’s disease: Neurocognitive correlates. Behav. Neurol 27: 535-545.
55. (1996) Unified Huntington’s disease rating scale: Reliability and consistency. Huntington Study Group. Mov Disord 11: 136-142.
56. Craufurd D, Thompson JC, Snowden JS (2001) Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 14: 219-226.
57. Callaghan J, Stopford C, Arran N, Boisse MF, Coleman A, et al. (2015) Reliability and factor structure of the short problem behaviours assessment for Huntington’s disease (PBA-s) in the TRACK-HD and REGISTRY studies. J Neuropsychiatry Clin Neurosci 27: 59-64.
58. Cummings JL (1997) The neuropsychiatric inventory: Assessing psychopathology in dementia patients. Neurology 48: S10-S16.
59. Kulisevsky J, Litvan I, Berthier ML, Pascual-Sedano B, Paulsen JS, et al. (2001) Neuropsychiatric assessment of Gilles de la Tourette patients: Comparative study with other hyperkinetic and hypokinetic movement disorders. Mov Disord 16: 1098-1104.
60. Starkstein SE, Ingram L, Garau ML, Mizrahi R (2005) On the overlap between apathy and depression in dementia. J Neurol Neurosurg Psychiatry 76: 1070-1074.
61. Gelderblom H, Wüstenberg T, McLean T, Mütze L, Fischer W, et al. (2017) Bupropion for the treatment of apathy in Huntington's disease: A multicenter, controlled, prospective crossover trial. PLoS One 12: 1-17.

62. Carvalho JO, Ready RE, Mallory P, Grace J (2013) Confirmatory factor analysis of the frontal systems behaviour scale (FrSBe). Assessment 20: 632-641.

63. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, et al. (2011) Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res 70: 73-97.

64. Kant R, Duffy JD, Pivovarik A (1998) Prevalence of apathy following head injury. Brain Inj 12: 87-92.

65. Mason S, Barker RA (2015) Rating apathy in Huntington’s disease: Patients and companions agree. J Huntington Dis 4: 49-59.

66. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, et al. (1992) Reliability, validity and clinical correlates of apathy in Parkinson’s disease. J Neuropsychiatry Clin Neurosci 4: 134-139.

67. Kirsch-Darrow L, Fernandez HH, Marisike M, Okun MS, Bowers D (2006) Dissociating apathy and depression in Parkinson disease. Neurology 67: 33-38.

68. Marin RS, Finincigullari S, Biedrzycki RC (1994) Group differences in the relationship between apathy and depression. J Nerv Ment Dis 182: 235-239.

69. Weiser M, Garibaldi G (2015) The relationship between apathy and depression in Huntington disease. J Psychopharmacol 18: 133-135.

70. Corcoran C, Wong ML, O'Keane V (2004) Bupropion in the management of apathy. J Psychiatr Res 38: 591-599.

71. Weiser M, Garibaldi G (2015) Quantifying motivational deficits and apathy: A review of the literature. Eur Neuropsychopharmacol 25: 1050-1081.

72. Burns A, Folstein S, Brandt J, Folstein M (1990) Clinical assessment of cognitive impairment: The mini-mental state examination. J Psychiatr Res 24: 107-113.

73. Agronin ME, Rabins PV, Jeste DV (2001) The effect of apathy on the quality of life of Alzheimer’s disease patients and their caregivers. J Neurosci Nurs 33: 165-176.

74. An actigraphic study. Am J Geriatr Psychiatry 20: 806-814.

75. Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: Hedonic impact, reward learning or incentive salience? Brain Res Brain Res Rev 28: 309-369.

76. Wise RA (2004) Dopamine, learning and motivation. Nat Rev Neurosci 5: 483-494.

77. Blundo C, Gerace C (2015) Dopamine agonists can improve pure apathy associated with lesions of the prefrontal-basal ganglia functional system. Neuro Sci 36: 1197-1201.

78. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, et al. (2002) Motivation, reward and Parkinson’s disease: Influence of dopatherapy. Neuropsychologia 40: 2257-2267.

79. Thobois S, Arouin C, Lhomée E, Klinger H, Lagrange C, et al. (2010) Nonmotor dopamine withdrawal syndrome after surgery for Parkinson’s disease: Predictors and underlying mesolimbic denervation. Brain 133: 1111-1127.

80. Czernecki V, Schüpbach M, Yaici S, Lévy R, Bardinet E, et al. (2008) Apathy following subthalamic stimulation in Parkinson disease: A dopamine responsive symptom. Mov Disord 23: 964-969.

81. Wyant KJ, Ridder AJ, Dayalu P (2017) Huntington’s disease-update on treatments. Curr Neurol Neurosci Rep 17: 33.

82. Agren H, Mefford IN, Rudorfer MV, Potter WZ (1986) Interacting treatments. Curr Neurol Neurosci Rep 17: 33.

83. McCabe C, Mishor Z, Cowen PJ, Harmer CJ (2010) Apathy following subthalamic stimulation in Parkinson disease: A dopamine responsive symptom. Mov Disord 25: 364-369.

84. Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 20: 91-127.

85. Mehrali NF, Singh-bains MK, Henry J (2016) Cortico-basal ganglia interactions in Huntington’s disease. Ann Neurodegener Disord 1: 1007-1013.

86. Martinez-Horta S, Pérez-Pérez J, Sampedro-Santalo F, Pagonabarraga J, Carceller M, et al. (2014) Brain metabolic correlates of apathy and depression in pre-manifested Huntington’s disease: A 18-fgd Pet Study. J Neurol Neurosurg Psychiatry 85.

87. Gregory S, Scahill RI, Seunarine KK, Stopford C, Zhang H, et al. (2015) Neuropsychiatry and white matter microstructure in Huntington’s disease. J Huntington Dis 4: 239-249.

88. Reijnders JS, Scholliers B, Weber WE, Aalten P, Verhey FR, et al. (2010) Neuroanatomical correlates of apathy in Parkinson’s disease: A magnetic resonance imaging study using voxel-based morphometry. Mov Disord 25: 2318-2325.

89. Schwab LC, Garas SN, Drouin-Ouellet J, Mason SL, Stott SR, et al. (2015) Dopamine and Huntington’s disease. Expert Rev Neurother 15: 445-458.

90. Svenningsson P, Aron R, Beart RW, Brosch N, Conklin DJ, et al. (2003) New dopamine receptor imaging probes for the study of dopaminergic receptor occupancy. J Neurosci 23: 439-445.

91. Wyant KJ, Ridder AJ, Dayalu P (2017) Huntington’s disease-update on treatments. Curr Neurol Neurosci Rep 17: 33.

92. Kranz GS, Kasper S, Lanzenberger R (2010) Dopamine and Huntington’s disease. Expert Rev Neurother 10: 1021-1034.

93. Gregory S, Scahill RI, Seunarine KK, Stopford C, Zhang H, et al. (2015) Neuropsychiatry and white matter microstructure in Huntington’s disease. J Huntington Dis 4: 239-249.

94. Reijnders JS, Scholliers B, Weber WE, Aalten P, Verhey FR, et al. (2010) Neuroanatomical correlates of apathy in Parkinson’s disease: A magnetic resonance imaging study using voxel-based morphometry. Mov Disord 25: 2318-2325.

95. Schwab LC, Garas SN, Drouin-Ouellet J, Mason SL, Stott SR, et al. (2015) Dopamine and Huntington’s disease. Expert Rev Neurother 15: 445-458.

96. Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: Hedonic impact, reward learning or incentive salience? Brain Res Brain Res Rev 28: 309-369.

97. Wise RA (2004) Dopamine, learning and motivation. Nat Rev Neurosci 5: 483-494.

98. Blundo C, Gerace C (2015) Dopamine agonists can improve pure apathy associated with lesions of the prefrontal-basal ganglia functional system. Neuro Sci 36: 1197-1201.

99. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, et al. (2002) Motivation, reward and Parkinson’s disease: Influence of dopatherapy. Neuropsychologia 40: 2257-2267.

100. Thobois S, Arouin C, Lhomée E, Klinger H, Lagrange C, et al. (2010) Nonmotor dopamine withdrawal syndrome after surgery for Parkinson’s disease: Predictors and underlying mesolimbic denervation. Brain 133: 1111-1127.

101. Czernecki V, Schüpbach M, Yaici S, Lévy R, Bardinet E, et al. (2008) Apathy following subthalamic stimulation in Parkinson disease: A dopamine responsive symptom. Mov Disord 23: 964-969.

102. Wyant KJ, Ridder AJ, Dayalu P (2017) Huntington’s disease-update on treatments. Curr Neurol Neurosci Rep 17: 33.

103. Agren H, Mefford IN, Rudorfer MV, Potter WZ (1986) Interacting neurotransmitter approach systems. A non-experimental approach to the 5HTA-HVA correlation in human CSF. J Psychiatr Res 20: 175-193.

104. McCabe C, Mishor Z, Cowen PJ, Harmer CJ (2010) Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. Biol Psychiatry 67: 439-445.

105. Kranz GS, Kasper S, Lanzenberger R (2010) Reward and the serotonergic system. Neuroscience 166: 1023-1035.

106. Corcoran C, Weng ML, O'keane V (2004) Bupropion in the management of apathy. J Psychopharmacol 18: 133-135.