REVIEW

Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration

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Received 6 February 2013
Revised 4 June 2013
Accepted 7 June 2013
Published Online First 6 July 2013

To cite: O'Callaghan C, Bertoux M, Hornberger M. *J Neurol Neurosurg Psychiatry* 2014;**85**: 371–378.

ABSTRACT

Investigations of cognitive and behavioural changes in neurodegeneration have been mostly focussed on how cortical changes can explain these symptoms. In the proposed review, we will argue that the striatum has been overlooked as a critical nexus in understanding the generation of such symptoms. Although the striatum is historically more associated with motor dysfunction, there is increasing evidence from functional neuroimaging studies in the healthy that striatal regions modulate behaviour and cognition. This should not be surprising, as the striatum has strong anatomical connections to many cortical regions including the frontal, temporal and insula lobes, as well as some subcortical regions (amygdala, hippocampus). To date, however, it is largely unclear to what extent striatal regions are affected in many neurodegenerative conditions—and if so, how striatal dysfunction can potentially influence cognition and behaviour. The proposed review will examine the existing evidence of striatal changes across selected neurodegenerative conditions (Parkinson's disease, progressive supranuclear palsy, Huntington's disease, motor neuron disease, frontotemporal dementia and Alzheimer's disease), and will document their link with the cognitive and behavioural impairments observed. Thus, by reviewing the varying degrees of cortical and striatal changes in these conditions, we can start outlining the contributions of the striatal nexus to cognitive and behavioural symptoms. In turn, this knowledge will inform future studies investigating corticostriatal networks and also diagnostic strategies, disease management and future therapeutics of neurodegenerative conditions.

INTRODUCTION

Impairment of the striatum (caudate, putamen, nucleus accumbens) in neurodegenerative conditions has long been recognised. Striatal dysfunction in motor disorders, including Parkinson's disease (PD) and Huntington's disease (HD), has uncovered the crucial role this region has in the organisation and production of voluntary movements. However, these same disorders can also present with substantial behavioural and cognitive symptoms, especially in volition, executive dysfunction and reward processing.

The role of the striatum in a diverse range of processes is supported by its anatomical positioning as a central hub in several cortico-subcortical loops, projecting to, and receiving input from many cortical areas. Figure 1, adapted from Alexander and colleagues,[1] shows a simplified version of the main corticostriatal connections (please note that interconnectivity between striatal regions is not taken into account in the figure). There is a high degree of spatial topography in the organisation of the striatum, which corresponds to functional divisions that follow a dorsal-ventral gradient whereby the dorsolateral region of the striatum (ie, putamen) is engaged in sensorimotor functions, the dorsomedial striatum (ie, caudate) in associative functions, and the ventral striatum (ie, nucleus accumbens) in motivational and emotional function.[2 3] In terms of connectivity, the putamen is primarily connected to sensory and motor cortices, the caudate with frontal and parietal association cortices, and the nucleus accumbens has substantial connections to limbic structures (amygdala, hippocampus) as well as the ventromedial prefrontal cortex[4] (figure 1). These extensive cortico-subcortical loops explain why a constellation of motor, cognitive and behavioural symptoms can result from striatal dysfunction.

Functional brain imaging in healthy subjects has highlighted the role of the striatum in complex cognitive functions, including working memory, abstract rule learning and attentional control.[5] Human and animal literature further confirm that the dorsal striatum has a role in forming action-outcome associations and in action selection, which contribute to high-level cognition and goal-directed behaviour.[6] The striatum has also been implicated in reward-related cognition, with human imaging studies associating the ventral striatum with representation of subjective value, reward expectation and reward magnitude.[7 8] Animal lesion and neuronal recording studies indicate that key processes underpinning reward-related cognition, namely prediction error, incentive salience and valence coding, are directly associated with the ventral striatum, and are critical for reward learning, attaching motivational values to stimuli and processing its hedonic value. Further, lesions in discrete ventral striatal regions have been associated with various forms of behavioural dysregulation (eg, impulsivity).[9] Animal models of anhedonia, motivational deficits and anxiety also confirm a crucial role for the striatum (particularly ventral striatum) in these processes.[10] Nevertheless, despite these robust associations between the striatum and a range of cognitive and psychiatric processes, the extent to which the striatum plays a causal or modulatory role, and by what mechanisms, is still debated.[5]

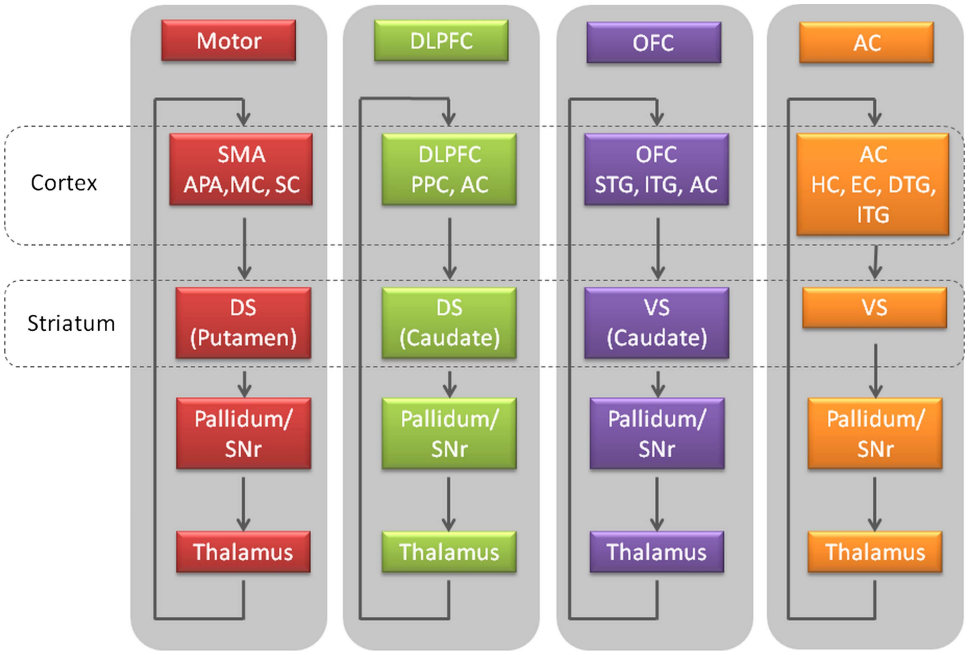

Figure 1 Simplified representation of basal ganglia-thalamocortical circuits, adapted from Alexander *et al*.[1] Each circuit engages specific regions of the cerebral cortex and striatum. Note, the figure does not take into account interconnectivity between striatal regions. AC, anterior cingulate area; APA, arcuate premotor area; DS, dorsal striatum; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; HC, hippocampal cortex; ITG, inferior temporal gyrus; OFC, orbitofrontal cortex; MC, motor cortex; PPC, posterior parietal cortex; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra; STG, superior temporal gyrus; VS, ventral striatum.

The role of the striatum in non-motor symptoms has clear relevance for neurodegenerative conditions, with patients manifesting a variety of symptoms among which the diagnosis of behavioural/cognitive changes can be particularly challenging. Increased understanding of how striatal dysfunction gives rise to motor symptoms in neurodegenerative diseases has led to vast improvements in diagnostic techniques and in pharmacological and surgical therapies; however, the same cannot be said for the cognitive and behavioural symptoms in neurodegenerative disease where the focus has typically been on how cortical dysfunction modulates these impairments. Many neurodegenerative diseases present with both cortical and striatal changes, and thus a delineation of these regions and their contribution to the generation of behavioural/cognitive deficits would improve diagnostic procedures and also lead to disease-modifying therapies.

The current review aims to address this issue by reviewing striatal integrity and its relation to behavioural/cognitive symptoms in some of the most common neurodegenerative conditions. We start the review with conditions that have well described striatal damage: PD, progressive supranuclear palsy (PSP) and HD, before reviewing three other major neurodegenerative conditions: motor neurone disease, frontotemporal dementia (FTD) and Alzheimer's disease (AD), for which striatal damage has been less investigated to date. We have focussed on the early and even preclinical stages across the diseases to avoid findings being confounded by disease progression effects. Further, of the synucleinopathies with known cognitive/behavioural deficits, we have limited our discussion to PD as there has been the most extensive research into how these symptoms reflect striatal dysfunction (for these reasons we have not included sections on PD dementia, dementia with Lewy bodies or multiple-system atrophy). We deliberately excluded corticobasal degeneration (CBD) in the review, because of its current diagnostic uncertainty[11]; thus, any CBD studies are prone to the inclusion of an admixture of pathologies and behavioural syndromes, making it difficult to delineate specific striatal dysfunction in this condition.

DISORDERS WITH WELL DESCRIBED STRIATAL DYSFUNCTION

Parkinson's disease

PD, which is characterised by hallmark motor disturbances (bradykinesia, tremor, rigidity and postural instability), has its primary neuropathology within the nigrostriatal pathway. The resultant effect is severe dopamine depletion in the dorsal striatum, while the ventral striatum is relatively preserved in the early stages of the disease.[12] With disease progression, more extensive distribution of pathology (especially Lewy body pathology) is found throughout the brainstem and neocortex. On a macroscopic level, putaminal volumes have been shown to be significantly reduced in early PD,[13] and further atrophy of both caudate and putamen occurs with progression of the disease,[14] however, volumetric reductions in the striatum have not been consistently documented in de novo PD.[15]

Cognitive decline is common in early PD, with mild impairments evident in 15–20% of de novo, untreated patients.[16] Decline in executive abilities represents the dominant pattern of cognitive impairment in non-demented PD and dysfunction in the dorsal striatum (particularly the dorsolateral caudate head) has been directly linked to this dysexecutive profile, given its strong connectivity with the dorsolateral prefrontal cortex.[17] Imaging studies in very early PD suggest a dopaminergic basis to these deficits, with under-recruitment of the dorsal striatum apparent during aspects of working memory, set shifting and planning.[18] Dopamine replacement therapy can alleviate executive deficits arising from dysfunction in the associative loop[19] and normalise functional connectivity in these regions.[20] Nevertheless, cognitive impairment in non-demented PD is heterogeneous, and studies have identified other impairments, namely memory or visuospatial dysfunction, as being the most prominent initial deficits.[21] Widespread deficits may suggest more diffuse distribution of striatal and cortical Lewy bodies and an additional burden of non-PD pathology (eg, amyloid); indeed, striatal amyloid has been documented in PD dementia[15] and even more consistently in Lewy body dementia.[22 23] In their in vivo study Edison *et al*[23] found non-demented PD patients to have mildly increased amyloid load in the striatum

but not in the cortical regions, suggesting that the striatum may be an early site of amyloid deposition in synucleinopathies—with amyloid burden recently being linked to accelerated cognitive decline over time in non-demented PD.[24]

Damage to the dorsal striatum impairs the ability to form habits, resulting in an over-reliance on slower and more effortful goal-directed modes of action at the expense of the faster and less demanding parallel processing involved in automatic behaviours.[3] PD patients have difficulty expressing automatic actions from the early stages of the disease, affecting habitual movements such as gait, arm-swing and facial expression. Additional impairment in automatic processes ensues when patients are required to simultaneously perform a concurrent cognitive or motor task.[25] Difficulty managing cognitive load and an over-reliance on goal-directed behaviour impedes multitasking and interferes with patient's ability to carry out everyday cognitive and motor tasks. Improving this via cognitive training in mild patients represents an important avenue of non-pharmacological treatment in PD.

A different set of cognitive functions are mediated by the ventral striatum, including reward-related learning, response inhibition and value-based decision making. Given the relative preservation of ventral striatum integrity in the early stages of PD, it is unsurprising to find that de novo patients perform similarly to controls on reward-based decision making and reversal learning tasks.[26] However, impairment in these ventrally mediated functions can arise with the progression of the disease and with dopamine replacement therapy. In particular, dopamine replacement therapy—titrated to replenish severely depleted dopamine levels in the dorsal striatum and improve motor symptoms—can cause impaired reversal learning and reward-based decision making in PD patients.[27] Clinically, dopamine replacement therapy can lead to impulse control disorders (ICDs) in a portion of patients. ICDs include pathological gambling, hyper sexuality, compulsive shopping and binge eating, and can be considered to reflect deficient reward-valuation and impulse control due to dysfunction in the ventral striatum.

PD is associated with a range of behavioural/neuropsychiatric disturbances, which can even predate motor symptoms. Apathy, depression and anxiety are most common among these disturbances, and clinically significant symptoms are present in over 25% of de novo, untreated patients.[28] Prevalence rates of up to 70% of patients experiencing these symptoms during the course of the disease have been reported, with apathy having the highest incidence.[29] The early manifestation of these neuropsychiatric symptoms suggests a role for striatal dopamine dysfunction, and some improvement can result from dopamine therapy. However, it is likely that early and preclinical affective disturbances result from a complex interaction of dopaminergic, serotonergic and noradrenergic imbalances in the striatum and brain stem, and further studies with de novo patients may shed more light on this. There is some clearer evidence for dissociable roles of the striatum in mild and more advanced PD. In mild PD, apathy symptoms correlate with reduced binding of dopamine in the ventral striatum.[30] Depression and anxiety have been related to reduced anterior putamen dopamine uptake in mild PD,[31] and more extensive dopaminergic dysfunction throughout the dorsal striatum in advanced PD.[32]

Progressive supranuclear palsy

PSP shares some motor features with PD (eg, bradykinesia, rigidity), although PSP is associated with more pronounced postural instability, eye movement abnormalities and pseudobulbar features, with its pathological hallmark including accumulation of tau protein and neuropil threads throughout the basal ganglia and brainstem.[33 34] Motor abnormalities are usually the presenting feature in PSP, though cognitive impairment (most prominently executive dysfunction), cognitive slowing and behavioural change often emerge early in the disease course.[35] Frontal neuropsychiatric features are prevalent, in particular apathy and disinhibition which have a higher incidence and greater severity than in PD.[36] When present, such neuropsychiatric symptoms can be as severe as those seen in FTD.[37]

In vivo volumetric studies have consistently shown dorsal striatum atrophy, with significantly smaller striatal volumes found in PSP patients (ie, putaminal volumes 10% smaller and caudate volumes 17% smaller than in age-matched controls).[38] Striatal pathology occurs in concert with more significant atrophy of the thalamus and midbrain—regions that exert major regulatory effects on movement, cognition and behaviour process via projections through the caudate. Importantly, PSP patients also exhibit some degree of cortical atrophy, with a predilection for prefrontal areas.[39–41] Both cortical and subcortical grey matter atrophy, as well as degeneration of the connective white matter tracts, is already apparent in mild patients.[42] A recent resting state study complements these findings by showing significant connectivity disruptions within large-scale networks involving the brainstem, basal ganglia and cortex.[43]

Studies exploring regional atropy correlates of cognitive/behavioural dysfunction in PSP are comparatively limited and have been inconclusive with respect to whether subcortical or frontal pathology are driving these deficits. While evidence has linked basal ganglia dysfunction to executive deficits in this patient group,[44] there is also evidence implicating prefrontal atrophy.[40] More interestingly, some behavioural symptoms, in particular apathy, have been shown to correlate with volume loss in both frontal and striatal regions (primarily posterior frontal lobe and putamen).[45] Still, given the scarcity of these investigations these findings require future corroboration.

Huntington's disease

Similar to PD, research into HD has been strongly focussed on striatal damage. This is not surprising, as caudate and putamen changes are one of the hallmarks of HD,[46] with preferential involvement of the basal ganglia 'indirect' pathway causing the early prominence of choeric movements.[47] Nevertheless, other cortical and subcortical regions can also be affected in HD, leading to an overall brain weight loss of greater than 40% at the end of the disease. Microscopic pathology usually begins in the dorsal caudate head and progresses to the ventrolateral striatum, and is characterised by neuronal intranuclear inclusions and severe loss of projection spine neurons.[46]

In vivo neuroimaging reveals substantial macroscopic changes, with caudate and putamen both showing marked volume loss over time,[48–50] and volume loss being related to age of onset and length of trinucleotide (CAG) repeat.[51] Positron emission tomography (PET) and MRI findings indicate that caudate loss is already apparent in presymptomatic HD gene carriers[48] and is thus considered to be an excellent anatomical outcome measure for HD clinical trials. In terms of cortical changes, premotor and sensorimotor cortices are particularly affected and longer disease duration has been associated with more widespread cortical changes.[49 52] These findings suggest that corticostriatal circuits are systematically affected in HD.

Indeed, diffusion tensor imaging investigating white matter integrity in HD has identified widespread changes in the cortex and striatum, even in presymptomatic cases.[53] Recent white matter tractography investigation of specific corticostriatal

motor pathways corroborate this notion by showing that caudate and putamen white matter connections to motor and sensorimotor cortical regions are most severely affected.[54] Further functional neuroimaging findings have shown corticostriatal changes, with functional connectivity between caudate and motor cortex being particularly affected from the prodromal stages.[55]

The above findings suggest that the motor system is mostly affected in HD, however, cognitive and mood/behavioural changes are well recognised, and deficits across the three domains represent the classic triad of HD symptomatology. There is significant variability in the time course of when symptoms emerge, with some patients eluding mood/cognitive symptoms until well into the course of their motor dysfunction and others manifesting these symptoms at onset or preclinically.

Early and preclinical emergence of cognitive and behavioural disturbance in HD suggests striatal dysfunction plays a critical role, as this is the initial primary site of pathology. Executive function deficits have been consistently described in early and preclinical HD[56] and have been linked to striatal damage, in particular measures of planning, attention and rule learning have been strongly associated with caudate atrophy.[57] Still, cortical atrophy in combination with striatal atrophy has also been linked to cognitive symptoms in HD.[58] Similarly, corticosubcortical white matter tract changes have been associated with those deficits.[59] Finally, functional imaging studies of cognitive changes in HD have consistently found cortical and striatal activation alterations compared with healthy controls in relation to cognitive load, planning, attention[60] and more specifically, ventral striatal regions being related to reward processes.[61] Of particular relevance are studies that show alterations of cortical and striatal functional connectivity between HD patients and healthy controls,[60] indicating that cortical and striatal regions, and also their interaction, are explicitly affected during these cognitive processes.

HD is associated with an array of behavioural/neuropsychiatric disturbances. These include apathy, anxiety, irritability, aggression or disinhibition and are experienced, to varying degrees, by nearly all patients.[62] The natural progression of neuropsychiatric symptoms in HD is not well known and likely reflects interplay between disease-specific neurodegeneration, genetic and reactive factors. Subtle affective and behavioural disturbances are reported in presymptomatic individuals, even decades prior to diagnosis. Depression is common in this preclinical group[63] in addition to apathy and disinhibition which have been associated with smaller striatal volume in presymptomatic individuals.[64] Interestingly, although a variety of neuropsychiatric disturbances can emerge within the course of HD, they do not typically show stepwise evolution with disease severity (by contrast with cognitive symptoms, which tend to worsen with disease progression).[47] One exception is the progression of apathy, which is strongly related to disease stage and motor symptom severity[65]; this is presumed to reflect progressive impairment of the more ventral areas as neuronal loss in the striatum progresses along a dorsal-ventral gradient.

DISORDERS WITH LESS DESCRIBED STRIATAL DYSFUNCTION

Motor neuron disease

By contrast with PD, PSP and HD, motor neuron disease (MND), also referred to as amyotrophic lateral sclerosis (ALS), had been classically regarded as a progressive motor systems disorder causing muscle weakness.[66] It is now increasingly recognised that the central nervous system can be also affected in MND patients even at an early disease stage, and that those patients presenting with more pronounced cortical changes can exhibit cognitive impairments as well.[67] The combination of motor and cognitive symptoms in MND suggests that striatal regions might also be affected in this disorder, in particular in those patients with additional marked behavioural/cognitive impairment (MND with FTD symptoms: MND-FTD). Additionally, striatal dysfunction has been shown in a rare levodopa-responsive PD-ALS variant (Brait–Fahn–Schwartz disease),[68 69] and can be associated with a dementia syndrome, though not necessarily one that is characteristic of FTD,[70] suggesting that this PD-ALS variant may represent a distinct nosological entity.

Neuropathological investigations have commonly observed microscopic striatal changes in MND patients with extrapyramidal features.[71] In particular, MND-FTD patients have been regularly reported to have striatal pathologic changes.[72 73] Accordingly, those striatal changes consisted of ubiquitin inclusions in MND-FTD, and also moderate to severe cell loss and gliosis.[72] Interestingly, these pathological changes were much less severe or even absent in MND patients without extrapyramidal symptoms.[73]

Similarly, on a macroscopic level, there has been little evidence of striatal changes in MND without extrapyramidal changes,[74] but white matter intensity changes in the caudate have been identified in MND patients with cognitive FTD-like symptoms.[75] These convergent microscopic and macroscopic striatal findings in MND suggest that the striatum is intact in MND patients without extrapyramidal changes. By contrast, MND patients presenting with extrapyramidal features and FTD-like behavioural/cognitive symptoms show striatal changes, although it is currently unclear which parts of the striatum are affected. Still, few studies have investigated the striatum in MND and, thus, further investigations are needed, in particular those contrasting MND patients with and without behavioural/cognitive symptoms directly.

Frontotemporal dementia

FTD has the most significant behavioural and cognitive changes of all the reviewed neurodegenerative conditions. Three clinical syndromes of FTD exist: behavioural variant FTD (bvFTD), primary progressive aphasia—semantic variant (PPA-sem) and primary progressive aphasia—non-fluent variant (PPA-nfv), all with varying degrees of frontal, temporal and insula atrophy. This cortical atrophy has long been identified and associated with prototypical cognitive and behavioural symptoms in FTD. Specifically, prefrontal cortex atrophy in bvFTD has been consistently associated with severe behavioural changes, and the memory and language deficits in FTD have been mostly associated with frontotemporal-insula atrophy.[76]

Only recently has the focus in FTD shifted towards the striatum, which neuropathological and perfusion imaging studies have shown to be affected significantly and from the early disease stages, particularly in the bvFTD subtype.[77] This was further corroborated by structural neuroimaging studies that identified striatal atrophy in FTD, again with the most severe changes seen in bvFTD.[78 79] In both bvFTD and PPA-nfv, atrophy has been shown in the caudate and putamen, as well as nucleus accumbens, with putaminal atrophy in bvFTD being more right lateralised and less severe than caudate atrophy.[78 79] By contrast, in PPA-sem the caudate nucleus appears to be relatively spared, while there have been inconsistent results for putamen integrity.[78–80] These structural findings are

complimented by resting-state fMRI findings that show striatal dysfunction in FTD.[81]

Among studies that have directly investigated the subcortical correlates of cognitive and behavioural functions in FTD, striatal atrophy has been shown to covary with poorer general cognition,[80] disinhibition[82] and binge eating.[83] These findings are further supported by a case study of a patient with striatal infarcts who developed behavioural and cognitive changes mimicking bvFTD.[84] Interestingly, there is an apparent lateralisation of striatal contributions to behavioural/cognitive disturbances in FTD, with the right striatum being more often linked with behavioural disturbances, including eating disorders, apathy, reduced empathy and aberrant motor behaviour.[82 85] By contrast, the left striatum appears to have greater involvement in cognitive functions and has been linked to executive, language and psychomotor dysfunction in FTD.[79]

Overall, there is growing evidence that FTD behavioural and cognitive symptomatology is highly related to striatal impairments. Still, how the cortical and striatal dysfunctions interact to cause the symptoms remains to be explored.

Alzheimer's disease

Finally, AD is clinically characterised by a progressive decline of cognitive functions, among which episodic memory impairment is typically the earliest and most prominent. Structural cortical changes of the medial temporal lobe and hippocampus are characteristically observed, as well as hypoperfusion or hypometabolism in temporoparietal areas.[86]

Voxel-based morphometry studies investigating striatal integrity in AD patients reported either no change[80] or only subtle atrophy of the caudate in more severe cases,[87] which is taken to be proportional to the whole brain atrophy seen in the later stages of the disease. This is further confirmed by neuropathological findings that show a moderate to severe presence of amyloid deposition in the striatum at late-stage AD.[88] More importantly, recent neuropathological findings suggest that microstructural damage in the striatum can occur independently of macrostructural changes during the late stages of AD.[89] Studies quantifying caudate volume loss in AD compared with age-matched control have found reductions of 6–7%, with prodromal AD patients in the form of mild cognitive impairment only showing 3.5% reduction.[90] By comparison, bvFTD patients have been reported to show a 25% caudate volume reduction compared with age-matched controls.[91] Similarly, the nucleus accumbens and putamen appeared to be relatively spared in AD,[78 80] although some studies have reported putaminal volume loss, in particular for the left putamen.[92]

There have been few investigations into whether these relatively subtle striatal changes contribute to cognitive or behavioural symptoms in AD. Selected findings show that overall general cognitive functioning covaries with caudate[90] and putamen[92] volumes. An important direction for future research would be to explore striatal dysfunction in the atypically presenting frontal variant of AD. Given the overlap in cognitive/behavioural symptoms across frontal-variant AD and bvFTD, it may be the case that there is also more significant striatal dysfunction, which would provide further insight into the pathophysiology of this atypical AD variant.

SUMMARY

The above review clearly shows that striatal dysfunction is a crucial factor in the generation of cognitive and behavioural symptoms in neurodegenerative disease. In the reviewed conditions, striatal damage has been most strongly linked with executive dysfunction, impaired reward/punishment processing, and affective and motivational disturbances, with PD, PSP, HD and FTD showing structural and functional changes throughout the course of disease, while in MND and AD striatal involvement appears to depend on extrapyramidal signs and disease stage, respectively (table 1). Nevertheless, review of the literature to date highlights that there is still much scope to better delineate cortical versus striatal contributions to cognitive and behavioural symptoms via a more targeted assessment approach. In the following section, we propose future directions to address this issue and identify areas where further delineation of these contributions would have important implications for improving diagnostic and therapeutic strategies.

In terms of assessing striatal function, cognitive tests that tap executive abilities, such as attention, working memory and set shifting are already in routine clinical usage as part of brief screening tools (eg, The Montreal Cognitive Assessment[93]; Addenbroke's Cognitive Examination—Revised[94]), however, though the dorsal striatum is implicated in these processes, existing screening measures may lack the sensitivity to detect early striatal dysfunction. A possible candidate may be cognitive tests that include more demanding measures of working memory, as caudate activation has been uniquely found during the *manipulation* phase in working memory tasks[95]—a finding that fits well

Table 1 Striatal dysfunction and the associated cognitive and behavioural impairments across the neurodegenerative conditions at diagnosis

	Striatal dysfunction			
	DS	VS	Cognitive symptoms	Behavioural symptoms
PD	++	+	Working memory, planning, set-shifting, cognitive load	VS—apathy; DS—depression/anxiety
PSP	+	+	Executive dysfunction, cognitive slowing	Apathy, disinhibition
HD	+++	++	Planning, attention, rule learning, reward processing	VS—apathy; Depression, anxiety, disinhibition, irritability
MND				
+EPS	+	+	FTD-like cognitive syndrome	FTD-like behavioural syndrome
−EPS	–	–	–	–
FTD	++	++	Executive, language and psychomotor dysfunction	Apathy, binge eating, reduced empathy, aberrant motor behaviours
AD	–	–	–	–

Note: Striatal dysfunction incorporates both atrophic and functionally mediated changes; see text for further detail of the relative contributions of these across the different conditions.
– Not impaired + Mild ++ Moderate +++ Severe.
AD, Alzheimer's disease; DS, dorsal striatum; EPS, extrapyramidal symptoms; FTD, frontotemporal dementia; HD, Huntington's disease; PD, Parkinson's disease; PSP, progressive supranuclear palsy; VS, ventral striatum.

with computational models, whereby the balance of excitatory and inhibitory striatal activity triggers updates in working memory representations in the prefrontal cortex.[96]

By contrast, few clinical screening tools incorporate measures of ventromedial prefrontal cortex/ventral striatum cognitive functions, and mostly these are assessed by very involved gambling, probabilistic learning or reward-valuation tasks, which are not always feasible in a clinical setting. As such, assessment and monitoring of these functions does not often form part of routine clinical practice. A useful starting point would be to adapt these decision-making/reward-valuation tasks into briefer screening tools. A further strategy is to use established executive measures, and instead of focussing on overall achievement scores, focus on error scores, which have been found to be sensitive to inhibitory and self-monitoring processes that relate to ventral striatum function.[97]

Contrasting across diseases may be a valuable way of exploring the interaction between striatal and cortical contributions to symptoms. In this regard, contrasting PD and FTD patients could be of great interest, as early PD patients show mainly striatal dysfunction, while FTD patients, in particular bvFTD, show both cortical and striatal changes. Behavioural and cognitive symptoms in FTD have been mostly ascribed to cortical changes, but contrasts with PD patients 'on' and 'off' dopamine replacement would offer insight into dorsal and ventral striatal contributions to those symptoms. To our knowledge, only one study to date has taken such an approach and shown that FTD and PD share cortical and striatal contributions to inhibitory dysfunction, with FTD having more severe symptoms and significantly more ventromedial prefrontal cortex atrophy associated with these symptoms.[98] These findings suggest that ventral striatal regions make a contribution to inhibitory dysfunction in both diseases, but that the prefrontal cortex changes are predominant in causing the disinhibition. Delineation of those striatal and cortical contributions seems, therefore, very informative, as striatal damage might increase or even mimic cortical symptoms.

Regarding neuropsychiatric symptoms, apathy is consistently related to striatal dysfunction in the reviewed conditions. Although apathy is primarily associated with ventral striatum dysfunction, that is not always clear as it can be a prominent feature early in the disease courses of PD, HD and PSP when the dorsal striatum is typically more affected. Similarly, other symptoms, such as depression and anxiety, can emerge at varying time courses in the reviewed conditions and have been associated with both ventral and dorsal striatum dysfunction. In this respect, it might be useful if future studies incorporated the framework suggested by Levy and Dubois[99] to describe apathy. They suggest three distinct manifestations of apathy: (1) an emotional/affective type related to disruption of the ventral striatum-orbitofrontal cortex (limbic territory) causing deficits in the ability to link emotional and affective signals with the required ongoing behaviour; (2) a cognitive type, related to disruptions to dorsal striatum-dorsolateral prefrontal cortex (associative territory), whereby there is a deficit in elaboration/planning of actions necessary for ongoing or forthcoming behaviour and finally (3) an autoactivation deficit relating to more diffuse prefrontal and striatal dysfunction, causing marked difficulties in self-activating thoughts and actions. Such a framework may explain why apathy can originate from different regions of striatal dysfunction, and it offers testable predictions for possible qualitative differences in the types of apathy exhibited in neurodegenerative conditions. Such differences could be probed by more targeted measures, such as exploring other symptoms that correlate with the types of apathy (eg, would expect greater executive dysfunction to accompany cognitively driven apathy). By the same methods of validation, it could be further explored whether anxiety and depressive features are mediated by discrete emotion, affective, or cognitive processes.

There are several areas where diagnostic strategies could be improved by applying more sensitive striatal measures and by better delineating cortical versus striatal contributions to symptoms. Tasks that are sensitive and specific to dorsal striatum function could be extremely useful as outcome measures in clinical trials, for example, in HD where traditional measures employed have lacked the sensitivity to tap striatal dysfunction in those prodromal patients who are now identifiable by genetic testing and available for clinical trials.[56 97] Specific ventral striatum tools may have important utility in improving patient management in PD, where dopaminergic therapies can cause ventral striatal dysfunction with associated behavioural/cognitive changes. More sensitive screening tools that could detect ventral striatal pathology may better inform clinicians as to which patients may be more susceptible to dopaminergic overdose with the initiation of treatment.

By contrast with PD and HD, the initial diagnosis of FTD is still challenging, and to date only a neuropathological FTD diagnosis is seen as definite. Incorrect diagnosis in FTD is not uncommon, and sensitive and specific biomarkers are urgently needed. This is especially the case for bvFTD patients who can present with symptoms that overlap with AD, such as amnesia.[100] Recent research has endeavoured to find more specific atrophy and behavioural profiles for bvFTD, with particularly ventromedial prefrontal cortex dysfunction emerging as a prominent candidate,[101] although a small percentage of atypical AD patients can also show deficits in this brain region.[102] The above review highlights that the striatum is virtually intact in AD while it is impaired in FTD. Substantial striatal changes in FTD have only been recently described, which is likely due to prevailing cortical atrophy masking the subcortical changes seen in these patients, and this raises the question as to whether striatal integrity could be employed as a diagnostic marker in FTD. In combination with the well-known ventromedial prefrontal cortex atrophy, striatal changes could potentially distinguish bvFTD and AD to a very high degree. Similarly, tasks or screening tests tapping into striatal dysfunction in FTD would be important. One obvious task type would be probabilistic learning, and a recent study highlights that FTD patients are impaired on this measure, and that the performance is dependent on prefrontal and striatal integrity.[103]

Striatal integrity might also be an important diagnostic factor in the classification of MND-FTD patients. The reviewed studies suggest that MND patients with FTD symptoms can show significant striatal changes, while in MND patients without extrapyramidal symptoms, the striatum appears virtually intact. This finding is of great diagnostic potential, as currently a diagnosis of MND-FTD is based mostly on clinical and neuropsychological assessment, while the neural correlates of this group are still being established.[104] Thus, identification of striatal atrophy may be a promising avenue to identify MND-FTD patients even very early on in the disease course. Again, striatal screening tests would be vital for the diagnostic procedures of this patient group as well.

CONCLUSION

Taken together, there is increasing evidence that the striatum is affected across many neurodegenerative conditions, even if they do not present with motor symptoms. In concert with animal

and healthy neuroimaging findings, this supports that the striatum, in conjunction with the cortex, plays an important role in behavioural regulation and cognition. There is an urgent need to further delineate the functions of striatum and cortical regions to determine the genesis of behavioural and cognitive symptoms. In turn, this will allow the development of novel striatal screening tests, which will increase diagnostic accuracy, as well as informing disease modifying therapies in many neurodegenerative conditions.

Acknowledgements We would like to thank Eneida Mioshi for proof-reading the manuscript.

Contributors All authors made a significant contribution to compiling and reviewing the manuscript.

Funding CO is supported by an Alzheimer's Australia Dementia Research Foundation PhD scholarship. MH is supported by an Australian Research Council Research Fellowship (DP110104202). MB has no financial disclosures to make.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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