Review

Cognitive functions and corticostriatal circuits: insights from Huntington's disease

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The basic mechanisms of information processing by corticostriatal circuits are currently a matter of intense debate amongst cognitive scientists. Huntington's disease, an autosomal-dominant neurogenetic disorder characterized clinically by a triad of motor, cognitive, and affective disturbance, is associated with neuronal loss within corticostriatal circuits, and as such provides a valuable model for understanding the role of these circuits in normal behaviour, and their disruption in disease. We review findings from our studies of the breakdown of cognition in Huntington's disease, with a particular emphasis on executive functions and visual recognition memory. We show that Huntington's disease patients exhibit a neuropsychological profile that shows a discernible pattern of progression with advancing disease, and appears to result from a breakdown in the mechanisms of response selection. These findings are consistent with recent computational models that suggest that corticostriatal circuits compute the patterns of sensory input and response output which are of behavioural significance within a particular environmental context.

Interest in the information-processing capabilities of anatomically-defined segregated corticostriatal circuits (see Fig. 1) has spawned a number of conceptual and computational models from workers in a variety of disparate disciplines, ranging from robotics to neuropsychology[1–3]. Insights into the functions of the basal ganglia in human subjects can be achieved through the study of behavioural and cognitive symptoms resulting from neurodegenerative diseases such as Parkinson's disease (PD) and Huntington's disease (HD), which afflict these structures. The striking movement abnormalities caused by PD and HD have supported the view of the basal ganglia as structures important in movement control. However, it is evident that both of these disorders encompass more than simply motor deficits, with impairments in the cognitive and psychiatric domains increasingly becoming major foci of research. PD and HD affect basal ganglia function in very different ways; PD mainly through the degeneration of nigro-striatal dopaminergic circuitry, beginning in the putamen, and HD through the degeneration of the striatum itself, probably beginning in the caudate nucleus. These separate forms of pathology and their associations with distinctive motor symptoms, akinesia in PD and chorea in HD, suggest the possibility of qualitative differences in otherwise overlapping cognitive deficits, that might provide additional clues about the functioning of distinct parts of the striatal circuitry.

The genetic mutation in HD, an unstable, expanded trinucleotide (CAG) repeat in the gene that encodes the protein huntingtin, leads to very characteristic neuropathological changes[4] via mechanisms that are currently unknown. The most striking changes are found within the striatum, with GABA-containing medium-spiny striatal projection neurons bearing the brunt of the pathology. There is a dorsal-to-ventral, anterior-to-posterior, and medial-to-lateral progression of cell death, with the dorsomedial striatum affected earliest and relative sparing of the ventral striatum and nucleus accumbens. Striosomal medium spiny neurons might be affected prior to matrix neurons, although progression of cell death in both compartments appears to be in a dorsal-to-ventral fashion[5]. Although the striatum suffers the greatest damage, other neural regions are affected by HD. Subcortically, the substantia nigra (SN), globus pallidus (GPi and GPe), subthalamic nucleus (STN), amygdala, thalamus and hypothalamus are all affected, to varying degrees. The dopaminergic SN, pars compacta, cholinergic nucleus basalis of Meynert, serotonergic

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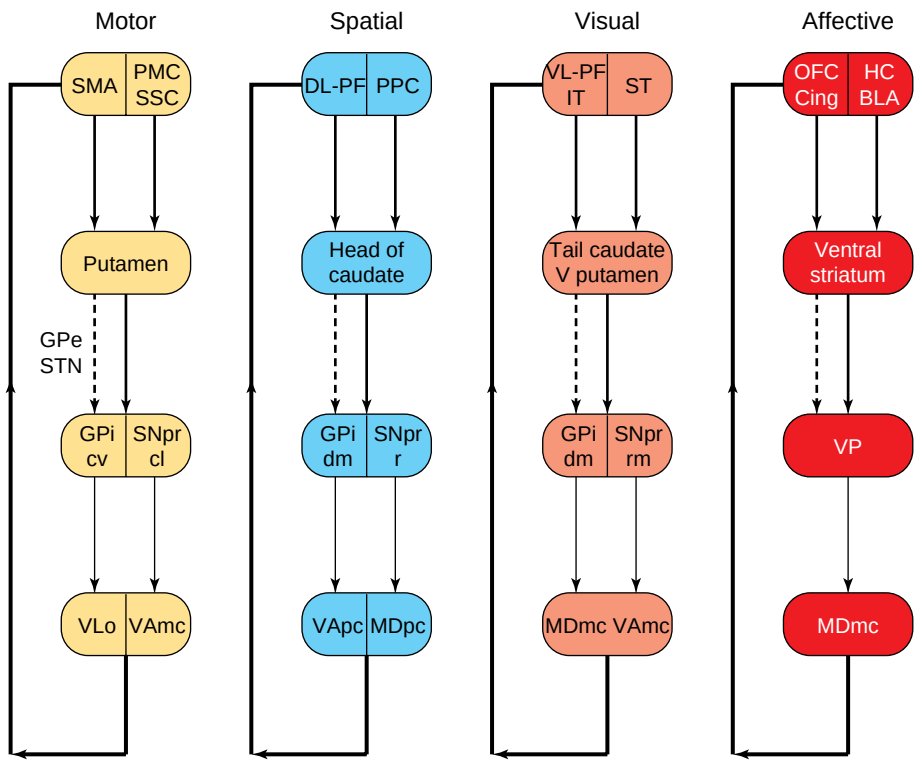

Fig. 1 Corticostriatal loops, modified from the original scheme of Alexander *et al.*[3] Four of the putative segregated, parallel loops are shown with possible functions labelled (Motor etc.). Areas in the left of bisected boxes are those that receive thalamic projections. Abbreviations: SMA, supplementary motor area; PMC, premotor cortex; SSC, somatosensory cortex; DL-PF, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; VL-PF, ventrolateral prefrontal cortex; IT, inferior temporal cortex; ST, superior temporal gyrus; OFC, orbitofrontal cortex; Cing, anterior cingulate; HC, hippocampus; BLA, basolateral amygdala; V putamen, ventral putamen; GPi, internal segment of the globus pallidus; SNpr, substantia nigra, pars reticulata; VP, ventral pallidum; VLo, ventrolateral thalamus; VA, ventral anterior thalamus; MD, mediodorsal thalamus; STN, subthalamic nucleus; GPe, external segment of globus pallidus; o, pars oralis; pc, parvocellularis; mc, magnocellularis; cv, caudo-ventral; cl, caudo-lateral; dm, dorsomedial; r, rostral; rm, rostromedial. Dashed lines indicate net inhibitory influences of the so-called 'indirect' striatal output pathway[2].

dorsal raphé and noradrenergic locus coeruleus afferent projection systems appear to be relatively spared, in contrast to PD (Ref. 4). Cerebral cortical damage or hypoperfusion (see Box 1) has been reported by a number of investigators. Cerebellar, occipital, parietal, temporal, primary motor, cingulate and prefrontal cortices have all been reported to show neuronal loss in HD. Within the cortex, pyramidal projection neurons in layers III, V and VI seem to be most affected[4].

There are thus complications of inferring causal links between cognitive deficits and striatal dysfunction in HD, as changes in cortical function might be the cause of at least some of the cognitive deficits. These alterations in cortical function might themselves stem from lesions in the striatum because of the intimate relationships existing between the cortex and striatum, via corticostriatal circuitry (Fig. 1). On the other hand, there is some evidence that the cortical lesions might be better correlated with some of the cognitive deficits, and even independent of the striatal lesion (see Box 1).

In this review we will focus the discussion on the cognitive pathology in HD. As atrophy and neuropathology of the neocortex become increasingly evident with the progression of HD, special emphasis should perhaps be placed on studying patients early in the course of the disease, as well as longitudinally thereafter. Currently, there is little information available about the precise status of the cortex relative to the striatum in very early, gene-positive, but clinically asymptomatic HD, largely because the brains of few such patients have become available for post-mortem examination. The utilization of neuroimaging techniques allows some examination of the corticostriatal pathology in early HD, but this will be strengthened by a detailed concomitant neuropsychological analysis, ideally in a functional neuroimaging context, that allows precise correlations to be made between cognitive and brain indices. This objective would be facilitated by one of the foci of this review, a detailed cognitive analysis of HD relative to other groups of patients such as those with neurosurgical excisions of the neocortex, or PD.

An alternative strategy is required for making causal inferences about the functions of the striatum within the corticostriatal circuitry. The second aim of this review is to illustrate how specific interventions in experimental animals can be used to investigate the functions of the striatum at a systems level of analysis. It will be shown that the utility of these investigations for human conditions such as HD is enhanced if analogous tests of cognitive function are used for experimental animals and human patients. Finally, we will indicate how such empirical observations can interact with contemporary computational modelling of the striatum, constrained by the available neurobiological evidence concerning its structure and functioning.

The cognitive pathology of HD

Executive functions

Cognitive models of prefrontal cortical function have emphasized its role as a supervisory 'executive', responsible for the control of 'lower-level' routine behaviours[6]. Indeed, the terms 'executive function' and 'frontal function' have often been used synonymously. However, it is important to note that there is not necessarily equivalence between 'executive functions' and 'frontal functions'. We believe that the neural implementation of 'executive functions', defined as the set of processes that serves to optimize performance in complex tasks with many cognitive or behavioural components, cannot be ascribed to a single brain region. Rather, such functioning relies on multiple neural circuits, which code for specialized subprocesses included under the rubric of 'executive functions'.

The notion that HD represents some form of 'dysexecutive syndrome' has some ecological validity, given the findings that many HD patients describe difficulties with organizing their day-to-day activities, and appear behaviourally inflexible[7]. It is somewhat surprising then that the existing

Box 1. Neural correlates of impaired executive function in HD

It is difficult to resolve the issue of the underlying neural substrates for cognitive deficits in HD on the basis of the existing neuropathological[a–d] and neuroimaging[e,f] evidence. Using single photon emission computerized tomography (SPECT), decreases in cortical perfusion were observed prior to evidence of atrophy on magnetic resonance imaging (MRI), suggesting that decreases in neuronal activity precede structural changes. Prefrontal perfusion correlated best with cognitive measures.

Several lines of evidence, however, suggest that executive dysfunction in HD might result from degeneration of the basal ganglia, rather than the frontal cortex. For example, MRI measures of caudate atrophy correlate strongly with impaired 'source monitoring' of memory[g], and SPECT measures of caudate metabolism have been shown to correlate with impaired WCST performance[h]. Furthermore, other SPECT activation studies have shown that HD patients can activate frontal cortex normally when performing the WCST (Ref. i).

Sophisticated correlational analysis of neuropsychological performance of HD patients using both MRI to assess cortical, striatal and thalamic volume, and PET to measure dopamine neurotransmission parameters (DA transporter, D1 and D2 dopamine receptor binding), has shown quite clear relationships between both frontal cortex volume and indices of striatal DA function with most of the cognitive tests employed[j]. In our own studies, we have also examined the relationship between PET measures of striatal neuron loss and cognitive function in clinical HD subjects and presymptomatic HD mutation carriers[k]. Striatal medium spiny neurons express dopamine receptors. Dopamine receptor binding potentials measured with PET provide a direct marker of basal ganglia pathology. We have shown a significant relation between impaired executive functions and dopamine binding potentials (see Fig. for example), suggesting that executive dysfunction in HD is indeed related to striatal neuronal loss. However, from a functional perspective, the basal ganglia should not be viewed in isolation. It makes better sense to attempt to ascribe behavioural functions to entire circuits of interconnected neural structures than to individual structures themselves. The basal ganglia should be viewed as components of circuits organized in parallel and remaining largely segregated from one another[l].

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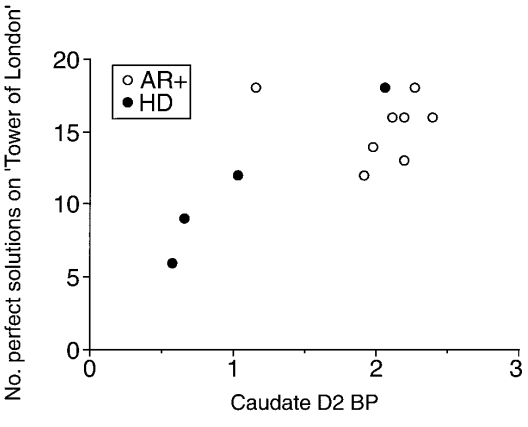

Fig. Relationship between caudate dopamine D2 binding potential and planning performance. Correlation between caudate D2 BP and number of perfect solutions on a 'one-touch' version of the Tower of London task[m] in a group of clinical HD patients (HD) and pre-symptomatic HD mutation carriers (AR+). Rs (Spearman Rank Correlation Coefficient) = 0.61, $P<0.05$. (Data plotted from Ref. k.)

literature on executive functioning in HD is relatively sparse, compared to say, Parkinson's disease. The findings to date can be considered under the headings working memory, planning and attentional set-shifting, which are commonly considered to implicate executive functioning.

Working memory

Working memory is considered by many to be the *sine qua non* of executive function. According to Goldman-Rakic[8] working memory is the ability to hold an item of information 'on-line' in order to guide behaviour. In Goldman-Rakic's model, working memory is a fundamental operation of the frontal cortex, and different areas within prefrontal cortex are specialized according to the different informational domains (spatial, form, etc.). According to this parallel processing model, 'executive control' is considered to be an emergent property of multiple domain-specific processors that operate interactively.

Delayed-choice tasks in primates and span tasks in humans hypothetically tap this 'on-line representational memory'.

Deficits in delayed-choice tasks, such as delayed-response (DR) and delayed-alternation (DALT) have been reported in monkeys following lesions to the principal sulcus region of the prefrontal cortex and the anterodorsal caudate nucleus to which the dorsolateral prefrontal cortex projects[3]. In humans, damage to dorsolateral prefrontal cortex has been reported to impair DR, but not DALT performance possibly because of the propensity of humans to perform a task such as DA in the manner of an automatic routine[13]. Oscar-Berman *et al.*[14] found impaired DALT, but not DR deficits in HD patients, thus suggesting possible striatal rather than frontal involvement. However, there are doubts as to whether these deficits in humans can be so clearly linked to working memory processes, because of the 'procedural' and other, visual elements (see Ref. 12) of the DA task, and because verbal responses could conceivably mediate performance on the DR test in HD patients. Digit span has consistently been found to be impaired in all but the earliest stages of HD (Ref. 7), and sentence span is also reduced[9]. We have reported reduced spatial spans in patients with advanced and asymptomatic HD (Refs 10,11) but there are some doubts about the possible confounding of motor problems with these particular deficits (see Ref. 11).

An additional problem for a straightforward view of working memory processes in HD stems from the fact that Goldman-Rakic's influential view of the neural substrates of working memory has been revised by some authors[17–19]. One such alternative theoretical framework has been advanced by Petrides[18]. According to this 'two-level' hypothesis, the ventral frontal cortex, in conjunction with posterior cortical mechanisms, 'subserves the expression within memory of various first-order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long-term memory'[18]. The mid-dorsolateral cortex, on the other hand, is suggested to be 'a specialized system for the monitoring and manipulation of information within working memory'[18]. Some of the evidence for this position is that short-term spatial memory tasks with subtly different components appear to engage the dorsolateral and ventrolateral prefrontal cortex[19]. For example, spatial span activates ventrolateral, rather than dorsolateral prefrontal regions, whereas a spatial recognition test in which subjects have to recognize the use of spatial locations from a recently-presented sequence produces the opposite pattern[19].

As well as the deficits in spatial span performance, we have found an impairment in both early and advanced HD patients on the test of spatial recognition memory which has previously been shown to be sensitive to frontal but not temporal lobe excisions[15]. Unlike the effects on spatial span, this deficit in spatial recognition was independent of motor slowing, suggesting a true deficit in spatial short-term memory processes in HD, which is consistent with observations of delay-related neuronal activity throughout the corticostriatal circuits[16]. The differences in processing required for the spatial span and spatial recognition tests are that the first involves the passive reproduction of a spatial sequence, whereas the second involves a series of binary decisions about whether a spatial location has previously been used, somewhat independently of the order of the original sequence.

Span tasks do not tap this 'second-order' component of working memory and the delayed response and spatial recognition tests for humans have only minor additional processing requirements. However, more complex 'self-ordered' search tasks which require decisions to be made about the optimal response sequences to be used to maximize reward do appear to activate both the ventrolateral and dorsolateral regions of the prefrontal cortex[19], presumably because of their greater cognitive requirements. In the CANTAB self-ordered spatial working memory task[20,21], subjects are required to search through an array of boxes for 'tokens' which are hidden one at a time. Once a token is found and placed in a 'store', another token is hidden behind a different box, and no box is used twice to hide a token. The subject searches the array of boxes several times in succession, eventually retrieving a token from each box in the array. Two types of error are possible: (1) 'between-search' errors represent a return to a box used to hide a token on a previous trial; (2) 'within-search' errors represent a return to a box already shown not to hide a token within a particular trial. Importantly, successful performance in control subjects entails the use of a search strategy, which involves retracing the route previously employed by the subject in searching through the array, 'editing' each search so as to avoid previously reinforced locations[20,21]. This strategy can be indexed, and is uncontaminated by the overall memory score, yet correlates highly with performance. In frontal lobe excision patients, between-search errors and within-search errors are increased relative to age- and IQ-matched controls, this deficit arising in part from impaired use of such a strategy. In other patient groups with predominantly posterior cortical damage, including early-in-the-course patients with probable Alzheimer's disease[22] and temporal lobe excisions or amygdalo-hippocampectomy[21], considerable performance deficits are observed but, importantly, the subjects still use the above strategy. Thus, mnemonic and monitoring/manipulation components of performance can be dissociated to some extent.

On this self-ordered spatial working memory task, early-stage HD patients made significantly more between-search errors than controls, but were only mildly impaired in their use of an effective search strategy[11], as is also the case in patients with Parkinson's disease who are medicated, with mild to moderate clinical disability[23]. Although patients with frontal lobe lesions show a significant impairment in the use of a search strategy, they also show more within-search errors than controls, which is not the case in early HD patients. These results demonstrate that HD and PD patients are impaired on a task that is sensitive to frontal lobe lesions, but for different reasons. Indeed, the deficits in the early-in-the-course patients are reminiscent of impairments commonly seen in patients with damage to more posterior cortical regions[21].

Patients with more advanced HD exhibit profound impairments on the self-ordered spatial working memory task with a very high degree of perseverative responding which includes repetition of responses within the same search (within-search errors)[10]. Thus, the self-ordered spatial working memory deficit in HD shows a discernible progression in which mechanisms that exert a control over responding

show a graded breakdown. Monitoring responses with respect to previous self-ordered searches is disrupted prior to the monitoring of responses within the same sequence. Analogous deficits in self-ordered searching have also been reported by Rich *et al.*[24] A recent model of the self-ordered task configured for monkeys has shown that excitotoxic lesions of the prefrontal cortex in marmosets can disrupt the performance of a spatial sequence by inducing perseveration within the sequence[25]. It is possible that the deficits in within-search errors in human patients are due at least partly to this loss of inhibitory control over the just-performed response, with frontal involvement.

Overall, it would seem that deficits in both the 'on-line representation' and 'monitoring' components of working memory are present in HD. Such deficits might contribute to the well known impairment of skill learning in HD. Gabrielli *et al.*[9] have shown that HD patients show deficits on 'open-loop' skill learning tasks that place high demands on working memory, and not on closed-loop skill learning that uses visual cues to guide learning. However, working memory connotes a crucial role in planning when response sequences have to be optimized to gain access to a well-specified goal. Indeed, the self-ordered task described above has an important strategic component which might be considered to be analogous to a higher level plan. The next section therefore examines planning ability directly in HD using a task designed expressly for that purpose.

Planning

The planning abilities of patients with HD have typically been studied using various versions of the Tower of Hanoi task. Butters *et al.*[26] failed to find significant deficits in a group of early HD patients using a five-disc version. However, Saint-Cyr *et al.*[27] did find impairments in a small subset (four) of HD patients in a four-disc Tower of Toronto version. However, these methods might not provide a true indication of the ability to plan. Goel and Grafman[28] have cogently argued that completion of these tasks does not necessitate the formulation of a plan because solutions can be 'edited' on-line. The repetitive trial-and-error learning that results is more akin to procedural learning than to 'look ahead' planning. This is especially the case with complex four- and five-disc tasks which place almost intolerable pressure on working memory capacity if the problems are to be solved within a single attempt (akin to solving chess problems that require checkmate in, say, 13 moves!). Thus, subjects are usually allowed multiple attempts to solve the Tower of Hanoi puzzle and recruit procedural memory processes to improve performance (fewer moves) with practice.

Anticipating these problems of interpretation, Shallice and McCarthy designed a simpler three-disc version of the Tower of Hanoi task, which could be solved in a single trial[29]. We have adapted this task for presentation on a computer touch screen[20]. In one variant, after considering the starting and goal configurations of a set of coloured balls on the screen, the subject manoeuvres these balls between the locations simply by touching them and their desired destinations. Although this gets around the problems of working memory capacity alluded to above, it does not quite circumvent the 'on-line' editing problems noted by Goel and Grafman[28], as subjects may stop to think during the performance of the sequence. However, a more recently devised, single choice task, in which the subject estimates how many moves it would take to solve the problem and indicates this by a single touch of the screen, does appear to do so[30]. Goel and Grafman agree that the single trial Tower of London task used in our studies provides a purer measure of this look ahead function in planning and its important working memory component. The importance of this point is shown by the finding that across all problems, early stage HD patients are only impaired on the most stringent index of planning efficiency, the number of 'perfect' solutions, and only made more excess moves than control subjects on the most difficult, five-move problems.

Patients with early HD were also impaired in terms of their initial and subsequent thinking times, after correction for motor slowing. These results are consistent with previous findings of bradyphrenia in HD (Ref. 7). This pattern of results is different from that seen in either cases of frontal lobe excision[20] or in patients with other forms of basal ganglia disorder, such as PD, progressive supranuclear palsy or multiple system atrophy[31]. Early HD patients can thus be seen to show deficits in thinking time consistent with both striatal and frontal lobe dysfunction. These and related deficits are associated with measures of striatal pathology obtained using neuroimaging techniques (see Box 1). In advanced HD patients, there is a far more pronounced deficit, with impairments even at the level of the simplest two- and three-move problems. Thus again, there is a discernible progression in HD, from the high-level selection of the appropriate responses in order to complete quite complicated plan-solution-paths, to the more basic level of selection of responses in routine, easy solutions, consistent with hierarchical neural network models of planning behaviour[32].

Attentional set-shifting

The concept of 'response set' has for a long time been associated with striatal function. Response sets are dispositions or biases and their effect on cognition is one of facilitation, or selection, of specific response options[33]. Robbins and Brown[34] defined response set as 'the prior assignment of probability of selection from the repertoire of available responses'. 'Cognitive set' is defined as 'set to respond according to abstract aspects of input, that is not tied to a particular motor response'[34].

There is some evidence for impaired response set in HD. Patients with HD are not able to engage in the response set necessary to confer a speed advantage to simple reaction time as compared to choice reaction time[35]. Furthermore, HD patients are unable to use a response set for selecting the appropriate response in a task requiring sequential button presses[37]. HD patients also make inappropriate response selections on reinforcement schedules in which behaviour must be paced consistently over time[14], show exaggerated stimulus-response incompatibility effects (i.e. when the response set involves unusual associations between stimuli and responses)[36], and inappropriate response selections on a variety of target detection tasks[38].

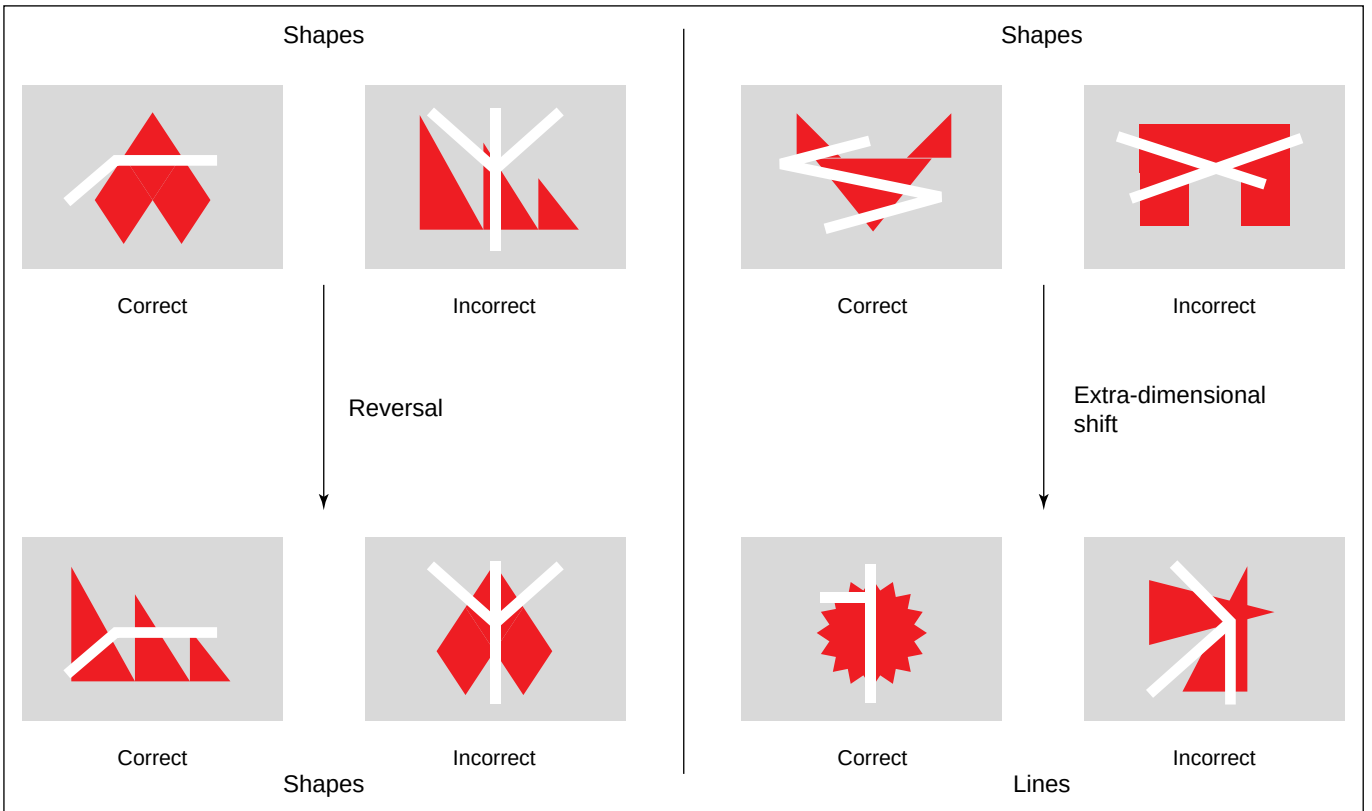

Fig. 2 Stimuli used in the visual discrimination/shifting paradigm. Each stimulus comprises a coloured shape and a white line. Pairs of stimuli are presented on a computer monitor at two of four possible locations[11,23] and the subject chooses one of the stimuli by touching its location on the touch-sensitive screen. Shown in this schematic are the task contingencies for 'Reversal' (where the previously non-rewarded shape now becomes rewarded and *vice versa*) and 'Extra-dimensional shifting' (EDS), where exemplars of the previously rewarded *shape* dimension are no longer rewarded, but *lines* are rewarded instead. In the example shown, the ⅂ line will now be consistently rewarded no matter which shape it occurs in conjunction with. Note the change of exemplar shapes and lines that occurs at the EDS stage.

The Wisconsin Card Sort Test (WCST) is the classical test of cognitive set. Josiassen *et al.*[39] examined the performance of early-stage HD patients on the WCST. They suggested that HD patients were impaired mainly in shifting (as distinct from forming or maintaining) cognitive set, as they made more perseverative than nonperseverative errors (that is, they made more errors resulting from the persistence of a particular response set, when it was no longer appropriate). Imaging studies have shown that deficits in the WCST in HD do not necessarily result from frontal impairment; rather, deficits have been interpreted to result from changes in striatal functioning (Box 1).

The WCST is, however, a deceptively complex task, which can be solved using a number of different strategies. In order to study the formation, maintenance and shifting of cognitive set in a purer form, Roberts *et al.*[40] deconstructed the WCST into its constituent elements (Fig. 2). The WCST involves a series of extra-dimensional shifts, as construed in animal learning theory. In an extra-dimensional shift, attention to compound stimuli is transferred from one perceptual dimension of a complex stimulus to another (e.g. from colour to shape) on the basis of changing reinforcement. In our task, subjects must learn a series of visual discriminations that culminate in an extra-dimensional shift (EDS). Control tests for EDS performance include the ability to alter specific stimulus-reward associations (reversal learning) and the ability to maintain a set and thus successfully shift performance to novel exemplars of the same dimension (intra-dimensional shift). Frontal lobe patients have specific deficits at the EDS stage of the task[41], whereas PD patients have difficulty throughout the task[23], suggesting that frontal lobe patients have a specific deficit in overcoming a bias to respond to a previously reinforced dimension, whereas PD patients have more basic learning deficits.

In our study of early stage HD, the most striking deficit seen was in their performance on the discrimination/shift learning task[11]. Patients were impaired specifically at the EDS stage, with fewer than 20% of patients able to reach the criterion of six consecutive correct responses within 50 trials (Fig. 3). This is a greater impairment than that seen in patients with frontal lobe lesions of a similar age[41] and patients with mild Alzheimer's disease[42]. The deficit in early HD patients was specific to shifting cognitive set at the EDS stage, suggesting that these HD patients do not exhibit the difficulties shown by early stage PD patients in forming cognitive sets[23].

Deficits in shift learning might represent a 'core' cognitive deficit in HD because of its presence in early stage patients. In a recent study[44] of a group of preclinical carriers of the HD mutation we have demonstrated specific deficits at the EDS stage of the discrimination/shift learning task, prior to the onset of any overt clinical movement disorder, and in the absence of any performance deficits on tasks such as the self-ordered spatial search and Tower of London.

The increase in perseverative responding at the EDS stage in preclinical and early stage HD is not observed in the reversal learning phases of this task. However, in advanced

HD, we have shown that patients exhibit dramatic increases in perseveration in the reversal phases of the task, preventing them from reaching the EDS stage (see Ref. 10 and Fig. 3). These deficits are truly perseverative because the patients continue to select the formerly reinforced stimulus to a significant degree. The results are especially striking, as the HD patients perform significantly worse than patients with Alzheimer's disease that have been matched with the HD patients for performance on clinical measures of dementia. Analogous reversal learning deficits in HD were first observed by Oscar-Berman *et al.*[45]

The Huntington's disease deficit in visual discrimination reversal learning is also of considerable theoretical interest because it can be viewed as a difficulty in learning new stimulus-response habits, as recently reported in a probabilistic classification task for HD patients by Knowlton *et al.*[46] This is considered by some (see discussion in Ref. 47) to be characteristic of striatally-mediated, non-declarative, habit-based or stimulus-response reinforcement learning. However, from our own findings the deficit in advanced HD is not so much one of acquiring new visual habits, as of inhibiting previously acquired ones.

The results from the above studies suggest that perseverative behaviour is a cardinal feature of HD, but that its expression varies according to the course of the disease. Neural network models have shown that shift and reversal learning are computationally distinct operations[48], and lesion studies in marmosets have shown that deficits in shift and reversal learning are anatomically doubly-dissociable. Lesions to lateral prefrontal cortex impair shift, but not reversal learning, whilst lesions of ventral prefrontal cortex impair reversal, not shift learning[49]. These regions of the prefrontal cortex probably project to dorsal and ventral portions of the striatum, respectively[49] (see Fig. 1), and so our results are consistent with the known spread of pathology in HD (Ref. 5), with those functions associated with dorsal striatum (shift learning) being impaired prior to those associated with more ventral regions of the striatum (reversal learning).

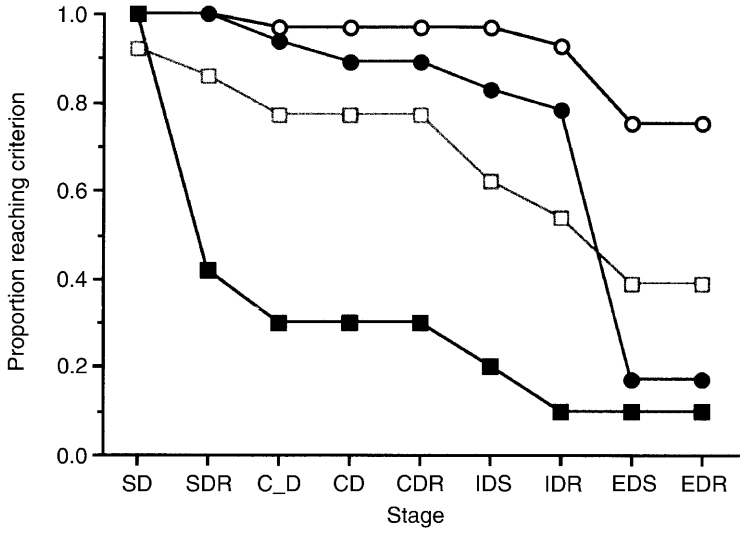

Fig. 3 Summary of data for the attentional-set shifting paradigm in groups of patients with early HD (filled circles) (Ref. 11), advanced HD (filled squares) (Ref. 10), probable dementia of the Alzheimer-type (open squares) (Ref. 42) and age- and IQ-matched controls (open circles). The cumulative failure rate at each stage of the visual discrimination and set-shifting task is shown. Note the marked decline in performance by the advanced HD group at the simple reversal stage, compared with the marked decline by the early HD group at the extra-dimensional shift stage. Abbreviations: SD, simple discrimination (i.e. shapes or lines only); SDR=simple reversal; C_D=compound discrimination (both shapes and lines present); CD=compound discrimination (shapes with lines superimposed); CDR=compound reversal; IDS=intra-dimensional shift; IDR=intra-dimensional reversal; EDS=extra-dimensional shift; EDR=extra-dimensional reversal.

Visual recognition memory

For the most part, frontal areas have been the focus of research on the output targets of the basal ganglia. However, the recent finding that a higher visual area in the temporal lobe (area TE) is also an output target of the striatum[51] (see Fig. 1) has renewed interest in re-evaluating visual functions of the basal ganglia. Although relationships between inferotemporal cortex and ventrocaudal striatum have been well described[51,52], there have been relatively few functional studies of these visual pathways. Recent electrophysiological[53,54] and metabolic[12] studies confirm that they play an important role in visual processing, including short-term visual memory.

HD patients, even relatively early in the disease, can show profound visual recognition impairments. They show deficits in tasks requiring them to memorize complex patterns[7], and show impaired face and facial expression recognition[55], even preclinically (especially the recognition of disgust)[56–59]. In our own studies, we have seen deficits in a test of visual recognition memory in both early and advanced HD patients[10,11], although not preclinically. This test involves yes/no recognition of abstract visual stimuli presented in list-form. Pattern recognition memory impairments have also been observed in patients with temporal lobe lesions or amygdalo-hippocampectomy, but not frontal lobe lesions[15]. We have not observed them in early-in-the-course PD (Ref. 60), possibly because the relevant portions of the striatum (e.g. tail of caudate) are probably among the last to be affected in the striatum in PD (Ref. 61). However, the possibility also exists that this deficit in visual stimulus processing is not dependent upon striatal, or even frontal cortical function, given the recent finding of reduced dopamine D1-receptor density in the temporal lobes of HD patients measured *in vivo* using PET (Ref. 62). This might also apply to the deficits in recognition of facial expressions alluded to above[56–59].

Implications for theories of corticostriatal information processing

From the results described it is evident that HD involves deficits that can be attributed to disruptions of processing associated with a number of different corticostriatal loops. Thus, as is evident from Fig. 1, deficits in spatial working memory and planning would be associated with that loop especially associated with spatial processing (although interactions of this loop with the temporal lobe might also be involved); reversal learning implicates the affective loop; the exact corticostriatal substrates of extra-dimensional shifting are still to be established, but a recent functional imaging study (R.D. Rogers, T. Andrews, P.J. Grasby, D.J. Brooks, T.W. Robbins, unpublished results) suggests that they might implicate aspects of the visual processing loop, as well as the frontal pole. The apparent deficits in visual recognition are

Box 2. Computational models of the striatum

Perhaps the most fully specified model of basal ganglia function has been provided by Houk and Wise, and colleagues[a,b]. They postulate that each of the corticostriatal-thalamo-cortical loops (described in Fig. 1, main article) in turn comprises a large array of modules, each being organized according to the same 'parallel and segregated' principles as the loops themselves (see Fig). These modules act as 'context detectors' and their function arises from the theoretical capacity for the striatal spiny neurons for pattern recognition. Each spiny neuron receives from around 10,000 afferent fibres originating from diverse areas of the cortex, from where there is striking convergence. This type of architecture is analogous to the network architecture of 'perceptrons', a pattern-recognizing network described by Rosenblatt and Minsky[c], consistent with the hypothesis that striatal spiny neurons are specialized for detecting different patterns of input from potentially diverse sources. Most electrophysiological studies of the basal ganglia have emphasized the context dependence of striatal single unit activity[d]. A further postulate of Houk *et al.*[a,b] is that this neuronal architecture learns to recognize and register complex contextual patterns relevant for behavioural output that might include the internal state, the perceptual environment, the effects of previous actions and so on. A burst generated by a spinal neuron will thus signify the detection of a behaviourally significant context within a corticostriatal loop, and produce a pause in pallidal firing that initiates activity in the appropriate sector of (generally prefrontal) cortex and leads to the initiation of a novel action or plan. The learning and recognition of these contextual patterns of activity by the striatal spiny cells is further postulated to depend on reinforcing signals provided by the midbrain dopamine neurons[e].

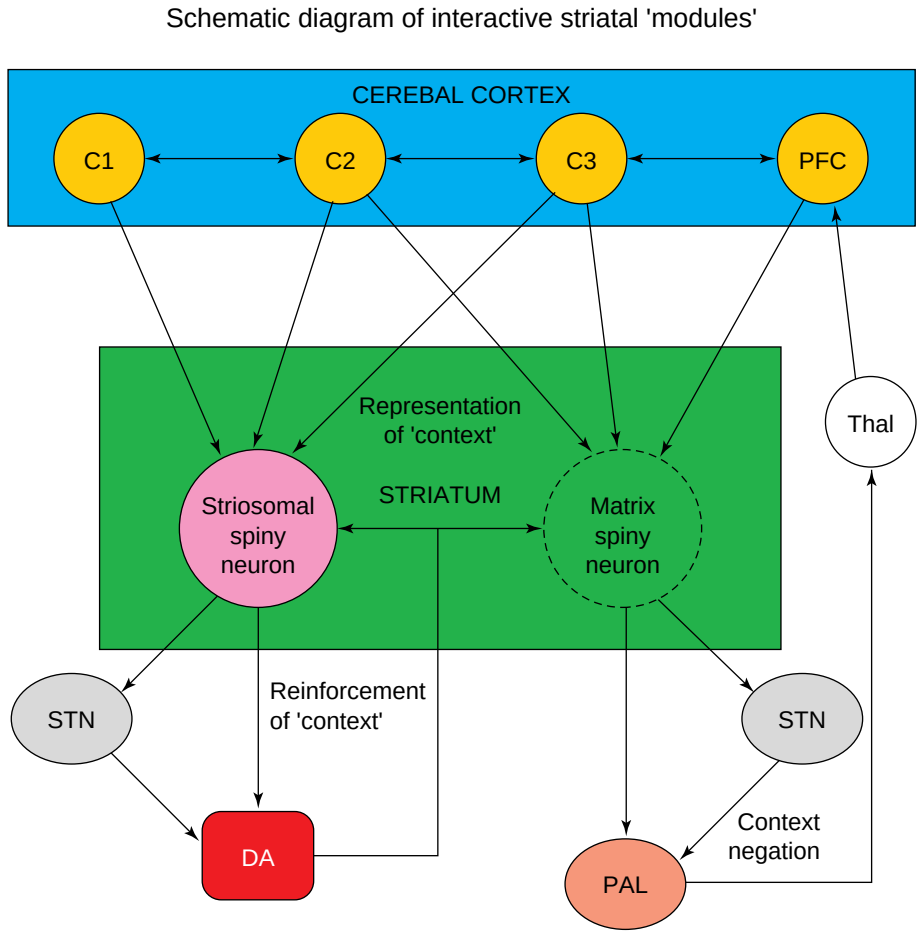

Fig. Illustration of convergence of cortical (C) inputs from different regions of neocortex to the medium spiny neurons of the striatum, striosome and matrix compartments. This provides a hypothetical context for striatal output to influence mechanisms of response selection. Note how the matrix compartment targets the prefrontal cortex (PFC) via the striato–pallidal (PAL)–thalamic (Thal) 'loop'. Hypothetical roles for the midbrain dopamine (DA) systems and the 'indirect pathway' via the subthalamic nucleus (STN) are shown as reinforcement and context negation, respectively. Note that there is little evidence to support the existence of a projection from the striosomal compartments to the STN. (Modified from Houk *et al.*[b])

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probably mediated by the visual loop circuitry. While this range of deficits might be related to the diversity of information processing achieved by the striatum, it is unclear to what extent the four principal forms of deficit outlined above for HD can be explained by a *unitary* cognitive processing deficit. The impairments in spatial working memory and planning can be linked on the grounds of evidence of common processing and neural requirements[63]. This is less clear in the case of the attentional set-shifting paradigm, although the inhibitory control processes also constitute aspects of executive function and might contribute to the cognitive flexibility sometimes required in formulating solutions to the Tower of London problems. The impairments in visual stimulus orienting are less clearly related to frontal-executive deficits, and might represent a separate class of cognitive deficits in HD.

Although a number of different models of information processing in corticostriatal circuits have been proposed, there is a common computational theme running throughout these models, based on the unique neuronal architecture of these regions[1,2]. The recurrent corticostriatal circuit or loop architecture, in which virtually the entire cortex projects onto the striatum, which then projects onto the smaller pallidum, before returning via the thalamus to select cortical regions

(see Fig. 1), suggests that some form of selection/modification process is occurring within this circuitry[1,2]. Indeed, most researchers emphasized that the striatum plays some role in *context-dependent* response selection[1,2,34,53] (see Box 2). Context-relevant information processing would allow the striatum to instruct cortical areas as to which sensory inputs or patterns of motor output are behaviourally significant in a given context. That is, the striatum might be performing some form of pattern classification computation, modifying coarsely coded cortical representations of memories, sensory features, or motor intentions into representations which are context-appropriate[1].

A breakdown in such mechanisms would presumably lead to the kinds of deficits we have described in HD patients: impaired response selection on tasks such as self-ordered spatial memory, Tower of London planning, discrimination and shift learning, as well as impaired orienting to the behaviourally-significant aspects of visual stimuli in recognition memory tasks. But how much further as an explanation can this account be taken? On the face of it, almost any form of cognitive function would be susceptible to deficit according to this model. However, it might be possible to develop the model further, based on the staging of deficits and also on their specificity as brought out by particular aspects of the test paradigms. For example, if as has been suggested[64], the direct and indirect pathways (Fig. 1 and Box 2) mediate respectively the registration and negation of contexts for processing by the prefrontal cortex, then many of the deficits in HD can be understood in terms of a preferential loss of the negation of contexts via loss of the influence of the indirect pathway. This would lead, for example, to perseveration of responses appropriate to contexts that have not yet been negated and explains why the extra-dimensional shift is so sensitive to early, even asymptomatic, HD (Ref. 44) and why the deficit is indeed one of perseveration (A. Lawrence, unpublished observations, using the paradigm of Ref. 43). The formation of linkages or mappings between particular stimulus dimensions (e.g. 'shapes'; Fig. 3) and responding can be postulated to be related to the further subdivision of the segregated corticostriatal loops of Fig. 1 into modules that represent these specialized contexts, perhaps as a result of learning. The negation of the context is then directly related to an extra-dimensional shift, possibly in the visual loop. Taking this line of reasoning further, we might also postulate the role of the direct pathway to detect and register contexts as being crucial in PD, as this condition appears to involve a mixture of deficits of set formation and maintenance, as well as shifting[23]. Further formal specification of what is meant precisely by 'context' and electrophysiological evidence for the nesting of functional modules that encode contexts (subsuming stimulus dimensions) within the segregated loops would lend added support to this model.

In this review, we hope to have illustrated how the neuropsychological study of cognitive deficits of patients with basal ganglia disorders, in particular Huntington's disease, can interact profitably with other approaches, including primate neuropsychology, electrophysiology and computational modelling. It seems likely that such an integrated approach will be necessary for improving our understanding of the functions of the striatum, with attendant clinical, as well as theoretical, benefits.

Outstanding questions

- Do the basal ganglia send 're-entrant' outputs to regions of the cortex other than the frontal and temporal lobes, for example the parietal lobes and early visual cortices?
- What is the degree of segregation in corticostriatal circuitry? What level of convergence occurs? What is the nature of organization *within* the segregated loops?
- Do different sectors within the striatum perform the same computation on different types of input, or do different computations occur in different striatal regions? Can the triadic cognitive, motor, and affective disorders in HD be caused by disruption of a common mechanism operating on different inputs?
- What exactly are the relative contributions of cortical and striatal dysfunction to impaired corticostriatal information processing in HD? Can these contributions be meaningfully separated?
- How precisely do the 'direct' and indirect' striatal output pathways interact?
- What precise roles do neuromodulators such as dopamine play in corticostriatal information processing?

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