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The role of the striatum in rule application: the model of Huntington's disease at early stage

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Summary

The role of the basal ganglia, and more specifically of the striatum, in language is still debated. Recent studies have proposed that linguistic abilities involve two distinct types of processes: the retrieving of stored information, implicating temporal lobe areas, and the application of combinatorial rules, implicating fronto-striatal circuits. Studies of patients with focal lesions and neurodegenerative diseases have suggested a role for the striatum in morphological rule application, but functional imaging studies found that the left caudate was involved in syntactic processing and not morphological processing. In the present study, we tested the view that the basal ganglia are involved in rule application and not in lexical retrieving in a model of striatal dysfunction, namely Huntington's disease at early stages. We assessed the rule–lexicon dichotomy in the linguistic domain with morphology (conjugation of non-verbs and verbs) and syntax (sentence comprehension) and in a non-linguistic domain with arithmetic operations (subtraction and multiplication). Thirty Huntington's disease patients (15 at stage I and 15 at stage II) and 20 controls matched for their age and cultural level were included in this study. Huntington's disease patients were also assessed using the Unified Huntington's Disease Rating Scale (UHDRS) and MRI. We found that early Huntington's disease patients were impaired in rule application in the linguistic and non-linguistic domains (morphology, syntax and subtraction), whereas they were broadly spared with lexical processing. The pattern of performance was similar in patients at stage I and stage II, except that stage II patients were more impaired in all tasks assessing rules and had in addition a very slight impairment in the lexical condition of conjugation. Finally, syntactic rule abilities correlated with all markers of the disease evolution including bicaudate ratio and performance in executive function, whereas there was no correlation with arithmetic and morphological abilities. Together, this suggests that the striatum is involved in rule processing more than in lexical processing and that it extends to linguistic and non-linguistic domains. These results are discussed in terms of domain-specific versus domain-general processes of rule application.

Keywords: striatum; Huntington disease; language; rule application; lexical retrieving

Abbreviations: HD = Huntington's disease; HD1 = Huntington's disease at stage 1; HD2 = Huntington's disease at stage 2; TFC = total functional capacity; UHDRS = Unified Huntington's Disease Rating Scale

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Introduction

Several studies have outlined the importance of the striatum (caudate plus putamen) in executive functions: attention, planning and working memory (for a review see Brandt, 1991). In addition, various observations of degenerative disorders (see Brandt, 1991) and of vascular lesions (see Kumral *et al*., 1999) point to its role in language. However, these results have been diverse and range from various aphasic profiles in vascular disorders (Cambier *et al*., 1979; Fromm *et al*., 1985; Puel *et al*., 1986; Pozzilli *et al*., 1987; Kumral *et al*., 1999; Kreisler *et al*., 2000) to isolated dysarthria (Caine *et al*., 1978; Ludlow *et al*., 1987), disorganization of semantic knowledge (Smith *et al*., 1988; Frank *et al*., 1996) and syntactic impairments

(Illes, 1989) in Huntington's disease. This picture was clarified recently when Ullman (2001) proposed that the striatum is implicated specifically in the application of rules in a dichotomic model of language processing. Linguists divide the language faculty into two components: a mental lexicon and a computational grammar. The mental lexicon is the repository of all idiosyncrasies in language, containing phonological, syntactic and semantic specification of morphemes, words or whole phrases such as in idioms. The computational grammar contains rules that can be applied in a combinatorial and recursive fashion. The combination of these two systems accounts for the language user's ability to process indefinitely novel sentences through finite means (Pinker, 1999). Ullman *et al*. (1997) proposed an anatomic correlate of the grammar–lexicon distinction: frontal-striatal circuitry (impaired in Huntington's disease and in Parkinson's disease) underlies the use of grammatical rules, whereas temporal lobe circuits (impaired in Alzheimer's disease) are implicated in retrieving of stored information. This hypothesis was tested in the morphological domain of conjugation. Ullman *et al*. showed that Parkinson's disease subjects are impaired in rule application because they suffixed regular verbs incorrectly (e.g. 'jump-id' instead of 'jump-ed'), and that Huntington's disease subjects tend to over-apply suffixation when confronted with irregular verbs (e.g. 'dig-ed' instead of 'dug'). Conversely, Alzheimer's disease subjects are impaired in lexical knowledge of irregular forms ('dag' instead of 'dug') but not in rule application.

The Ullman hypothesis is of considerable importance for theories both of language and of brain functions, but the evidence is still very fragmentary. First, the results of Ullman *et al*. (1997) showing rule impairment in Huntington's disease were not statistically significant (performance with regulars and irregulars were similar, while over-regularizations were more frequent in Huntington's disease than in controls), and these results were restricted to the domain of verbal morphology. In order to test the full generality of the Ullman proposal, it is important to demonstrate striatal involvement in other domains of grammar. In a PET imagery study, Moro *et al*. (2001) showed that the detection of syntactic errors in sentences activates the left caudate nucleus in healthy volunteers. However, in contrast to the prediction of Ullman (2001), morphological errors (gender agreement errors) did not yield metabolic activation of the left caudate. This discrepancy might follow from the use of different linguistic tasks across the Ullman and Moro studies, which may involve different working memory components. Alternatively, it may indicate that rules do not use the same circuitry across linguistic domains. Secondly, aphasia studies have indicated only a moderate role for the striatum in language, and this has been primarily in lexical disorders. For instance, Cambier *et al*. (1979) claimed that caudate aphasia mostly involves lexical processing problems (semantic and fantastic paraphasias) in accordance with Kreisler *et al*. (2000). In a broad review of subcortical aphasia, Alexander *et al*. (1987) claimed that damage to the putamen and head of the caudate nucleus only mildly impairs word finding. Thirdly, the dichotomy between the retrieving of stored information versus the application of a rule could potentially extend to domains outside of language: motor control, mathematical abilities, music, etc. This raises the issue as to whether the putative rule application function of the striatum is specific to language or whether it would extend beyond language to other domains.

Here, we propose to examine the rule versus lexicon hypothesis in Huntington's disease patients. Huntington's disease is an inherited neurodegenerative disorder with primary neuronal dysfunction and death in the neostriatum (caudate and putamen) (Vonsattel *et al*., 1985; for a review see Peschanski *et al*., 1995). Therefore, at least in the early stages, Huntington's disease is a reliable model of striatal dysfunction (see Kuhl *et al*., 1982; Mazziotta *et al*., 1987). To evaluate the implication of the striatum in linguistic and non-linguistic rules, we tested patients at stage I and at stage II, which are both targets of experimental therapeutic studies. We contrasted rule application and lexical processes in the linguistic domain using tests drawn from morphology and syntax, and, in a non-linguistic domain, we selected tasks involving numerical competence. In addition, we correlated these results with clinical parameters such as scores on the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996), and with anatomical parameters such as the bicaudate ratios provided by MRI.

Subjects and methods

Participants

Thirty Huntington's disease patients (15 early HD at stage I and 15 at stage II), using the classification based on the Total Functional Capacity (TFC) scale (Shoulson, 1981), and 20 healthy volunteers were tested in the conjugation and the sentence–picture matching tasks. HD patients were recruited from an out-patient clinic follow-up programme within the framework of interventional therapy approved by the ethics committee of the Henri Mondor Hospital. The patients had no previous neurological or psychiatric history except HD, and their diagnosis was confirmed genetically. The control subjects had no neurological or psychiatric disorders and were paired with the patients in stage I (HD1) as well as in stage II (HD2) according to their age [HD1, $F(1,33) = 1.58$, $P > 0.1$; HD2, $F(1,33) = 1.83$, $P > 0.1$], level of education [HD1, $F(1,33) = 1.1$, $P > 0.1$; HD2: $F(1,33) = 1.68$, $P > 0.1$] and laterality [HD1, $\chi^2(1) < 1$, $P > 0.1$; HD2, $\chi^2(1) < 1$, $P > 0.1$]. All subjects gave informed consent. Demographic data are summarized in Table 1.

General assessment

All patients were evaluated using the UHDRS (Huntington Study Group, 1996) and the Mattis Dementia Rating Scale (MDRS; Mattis, 1976). Furthermore, atrophy of the caudate was assessed in 23 patients with MRI by measuring the bicaudate ratio (namely the minimal distance between the caudate indentations of the frontal horns divided by the distance between the inner tables of the skull along the same line, multiplied by 100). Data are summarized in Table 2.

Table 1 *Demographic data of Huntington's disease patients and control subjects*

	Huntington's disease patients at stage I (HD1)	Huntington's disease patients at stage II (HD2)	Controls
No.	15	15	20
Sex	5 F/10 M	9 F/6 M	14 F/6 M
Age (years)	48.9 ± 6.6	43 ± 6.8	46.1 ± 6.6
Educational level (years)	13.7 ± 4.2	11.5 ± 3.3	13.2 ± 4.3
Evolution duration (years)	6.7 ± 2.8	8.9 ± 2.4	–
CAG repeats	43.5 ± 1.8	46.6 ± 3.2	–
Laterality	12 R/3 L	15 R/0 L	19 R/1 L

F = female; M = male; R = right; L = left.

Table 2 *Clinical performance and bicaudate ratios in Huntington's disease patients*

	Performance in Huntington's disease patients (means ± SD)		Normal published range
	[Stage I] (HD1)	[Stage II] (HD2)	
TFC	11.6 ± 0.8	8.8 ± 1.4	13
UHDRS motor score	36.8 ± 16.9	51.3 ± 15.6	0
MDRS	128.6 ± 11.6	120.5 ± 10.1	⩾136
Stroop colour/word	28.3 ± 10.3	19.3 ± 8.1	⩾35+
Fluency 'P' in 2 min	17.9 ± 11.6	8.7 ± 5.2	18§
Symbol Digit code	28.5 ± 13	21.5 ± 12.5	⩾37†
Bicaudate ratio	19.9 ± 4.6*	22 ± 2.1**	<10‡

TFC = total functional capacity; MDRS = Mattis Dementia Rating Scale; *$n = 13$; **$n = 10$; The norms are from +Golden (1978); §Cardebat *et al*. (1990); †Wechsler (1981); and ‡Starkstein *et al*. (1989).

Conjugation task

This task contrasts lexical and rule processing abilities in morphology using conjugation. Lexical abilities were tested using real verbs and more specifically irregular verbs that, in contrast to regular ones, cannot be conjugated following any rules (Ullman *et al*., 1997). In order to obtain a condition that would probe purely for rule application, we used invented verbs (or non-verbs) because they are not by definition part of the lexicon and their conjugation relies exclusively on the ability to apply rules (e.g. splush→splush-ed). They were built following two types of French conjugation rules, providing two levels of difficulties (Table 3): the default or main rule which applies to verbs ending in *-er* (as in 'arriver'; to arrive) and what we will refer to as subrules for verbs that end in *-ir* or in *-oire* (as in 'finir'; to end). The main rule specifies that the suffixes *-e* and *-era* should be appended to the verb stem in the third singular person, respectively, of the present tense (e.g. 'il arrive'; he arrives) and in the future tense ('il arrivera'; he will arrive). The subrule specifies that the suffixes *-it* or *-oit* (present, e.g. 'il finit'; he ends, or 'il boit'; he drinks) and *-ira* or *-oira* (future, e.g. il finira; he will end, or il boira; he will drink) should be appended to the verb stem.

The materials were selected in two steps. First, we selected 40 irregular and 40 regular and subregular verbs globally matched for frequency of occurrence and length. Then, we constructed their corresponding 80 non-verbs by adding an initial syllable and by changing one phoneme of the verb stem of the real verb, while avoiding any phonetic neighbours of existing verbs. To ensure that the selected irregular verbs were really irregular i.e. that their conjugation could not be provided by chance or by any strategy, all their derived non-verbs were submitted as a pre-test for conjugation (third person singular in present and future tenses) to 30 undergraduate students. The irregular verbs were selected only when <10% of the subjects proposed the expected conjugation in the non-verbs in accordance with their irregular source verbs. Conversely, to ensure that the non-verbs (used in the non-verbs condition) were conjugated through the application of rules (main and subrules), they were selected only when >90% of the subjects gave the same conjugation for a single item.

This selection process yielded 23 irregular and 24 regular verbs matched for their number of syllables [$F(1,45) = 2.22$, $P > 0.1$] and of phonemes [$F(1,45) < 1$, $P > 0.1$] and for frequency of occurrence according to the Brulex database (Content *et al*., 1996) [$F(1,45) = 2.04$, $P > 0.1$], as well as the selection of 24 regular and 18 subregular non-verbs matched for their number of syllables [$F(1,40) = 1.56$, $P > 0.1$] and phonemes [$F(1,40) < 1$, $P > 0.1$].

The subjects were first tested with verbs, then with non-verbs. They were instructed to conjugate orally the stimuli in the third person singular first in the present tense, then in the future tense. The infinitive forms were presented in a random order for each subject. In order to familiarize the subjects with the task, four practice items were given and feedback was provided (two regular verbs, two irregular verbs). Conjugation was facilitated by an initial carrier sentence: 'Aujourd'hui, il . . . ' ('Today, he . . . ') for the present tense and 'Demain, il . . . ' ('Tomorrow, he . . . ') for the future tense. Answers containing verb stem phonetic errors, infinitive repetition (perseveration) or tense errors (e.g. verb put in the past tense) led to repeated presentation of the item (up to three times). The examiner transcribed all the answers.

Responses were considered as errors when they differed from the official conjugation tables (Bescherelle, 1997) for verbs and from the dominant answers in the pre-test for non-verbs. Errors were classified in three different types considering their mechanisms: over-regularizations, double suffixations and 'other errors'. Over-regularizations correspond to conjugation of the subregular non-verbs or of irregular verbs using the main rule (e.g. in English *comed* instead of *came* for an irregular verb and, in French, *saurentera* instead of *saurentira* for a subregular non-verb, or *venira* instead of *viendra* for an irregular verb). Double suffixations correspond to appending the regular *-era* suffix excessively in subregular and regular non-verbs (e.g. in French, 'saurent-*ir-era*' or 'garoust-*er-era*'). Other errors were aberrant suffixations (e.g. 'saurent-*ure*' instead of 'saurent-*ira*'; knowing that the suffix '-*ure*' cannot be a French suffixation for conjugation in the third person singular) and unchanged forms. Because over-regularizations and double suffixations refer to excessive use of rules, they were analysed first separately and then as 'errors of rules'.

Sentence–picture matching task

This task assesses sentence comprehension taking into account syntax and word processing. We used passive–active and subject–object relatives, paired with one picture at a time, and asked the

Table 3 *Rule application and lexical knowledge in conjugation as a function of the verb type (regular/irregular, real/invented)*

Stimulus	Infinitives	Present	*n* (P)	Future	*n* (F)	Rule application	Lexical storage
Verbs (V)							
Regular (*n* = 24)	Arriver (to arrive)	il arrive (he arrives)	13	il arrivera (he will arrive)	11	+	+
Irregular (*n* = 23)	Venir (to come)	il vient (he comes)	13	il viendra (he will come)	10	–	+
Non-verbs (non-verbs)							
Regular (*n* = 24)	Garouster	il garouste	13	il garoustera	11	+	–
Subregular (*n* = 18)	Siralloire; Saurentir	il siralloit; il saurentit	9	il siralloira; il saurentira	9	+	–

+ = useful; – = useless; (P) used for conjugation in the present; (F) used for conjugation in the future.

Table 4 *The five sentence types and the available different strategies that allow matching them with the corresponding picture*

Sentences	Condition	[Comprehension strategies]			
		Lexical (word choice)	Canonicity (word order parsing)	Plausibility (pragmatic reasoning)	Syntax (syntactic parsing)
La fille traîne le sac qui est blanc (The girl pulls the bag that is white)	Control condition	+	+	+	+
La fille arrose la fleur qui est blanche (The girl waters the flower that is white)	Can + pl +	–	+	+	+
La fleur arrose la fille qui est blanche (The flower waters the girl that is white)	Can + pl–	–	+	–	+
La fleur est arrosée par la fille qui est blanche (The flower is watered by the girl that is white)	Can– pl +	–	–	+	+
La fille est arrosée par la fleur qui est blanche (The girl is watered by the flower that is white)	Can– pl–	–	–	–	+

Can + pl + = Canonical plausible; Can + pl– = Canonical non-plausible; Can– pl + = non-canonical plausible; Can– pl– = non-canonical non-plausible.

participants to decide whether the picture matched the sentence. The sentences were presented in four conditions, corresponding to the crossing of two variables: canonical (actives or subject relatives) or non-canonical order (passives or object relatives), and describing a plausible (a girl watering a flower) or a non-plausible action (a flower watering a girl). Comprehension was assessed by presenting a given sentence either with an image that matched the content of the sentence (e.g. in the case of the plausible sentence, a girl watering a flower), or an image representing the same action, but with the agent and theme swapped around (e.g. a flower watering a girl). The error rate averaged across the two pictures allows for a measure of the exact comprehension of the sentence. The four sentential conditions allowed testing for the various strategies that subjects might put to use for comprehending linguistic materials. As shown in Table 4, in a plausible canonical sentence, subjects may use three different strategies to get the correct response: they may use the semantic information of the words retrieved from their lexicon and guess the meaning of the sentence based on pragmatic constraints (girl, flower, watering→the girl waters the flower). They may use the lexical categories to reconstruct the thematic roles, based on the canonical word order of the sentences in their language [girl$_{\text{(noun)}}$ waters$_{\text{(verb)}}$ flower$_{\text{(noun)}}$→girl$_{\text{(agent)}}$ waters$_{\text{(action)}}$ flower$_{\text{(theme)}}$]. Finally, they may use a full-blown syntactic analysis of the sentence, which delivers the thematic roles, based on word categories and the syntactic rules of the language. In contrast, non-plausible canonical sentences differ in whether the non-syntactic strategies can be used. The non-plausible sentences make the pragmatic strategy impossible to use. The non-canonical sentences make the canonical strategy impossible to use. In sentences that are both non-canonical and non-plausible, only syntactic computations can allow meaning to be recovered. We predicted that the HD patients would be especially impaired in this last condition; the availability of lexical information should allow them to apply the other two strategies, and hence we predicted good performances in the three other sentence types. To check further for their access to lexical materials, we also included a control condition with sentences containing lexical items not present in the pictures (see Table 4).

The experiment used a total of 37 sentences (32 experimental, 5 control) and eight pictures. The pictures were drawn (size A4) to represent the plausible and non-plausible configuration of four different 'scenes' (e.g. in scene 1, the plausible configuration depicted a 'girl watering a flower'; and the non-plausible configuration 'a flower watering a girl'). The 32 experimental sentences were obtained by crossing three factors: canonicity (canonical versus non-canonical), plausibility (plausible versus non-plausible) and structure (active–passive versus subject–object relatives) for each of the corresponding 'scenes' (see Fig. 1). A relative clause that was not critical for sentence comprehension was added to the active and passive sentences so that all sentences of the group contained the same words, thereby avoiding biases resulting from differences of sentence length or lexical frequency [e.g. the active sentence 'the girl waters the flower (that is white)' was matched with the

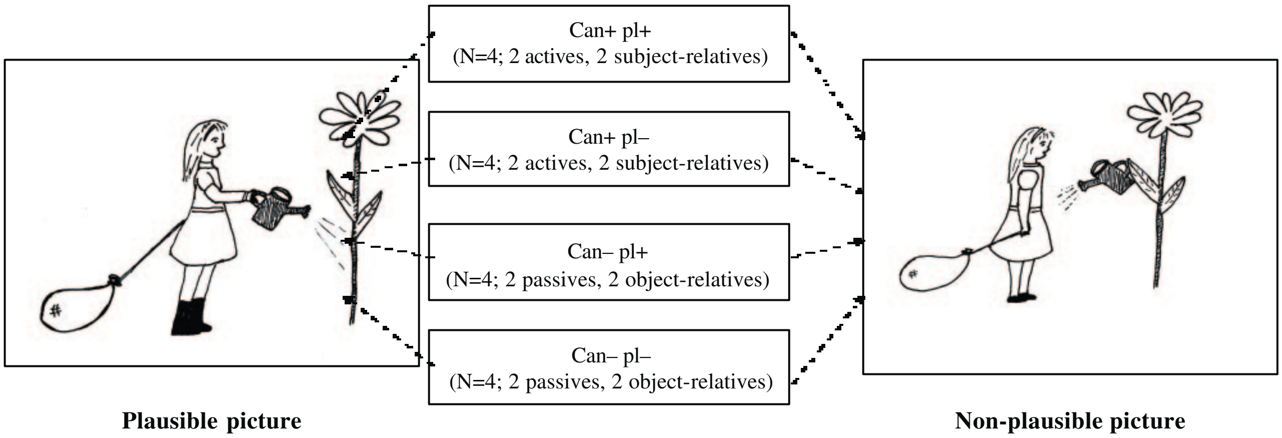

Fig. 1 Design of the picture–sentence pairs in the 'rule condition'. Sentences (4 × 4) were each paired with a plausible (pl +) and non-plausible (pl–) picture, giving a total of 32 sentence–picture pairs. Can + pl + = Canonical plausible; Can + pl− = Canonical non-plausible; Can− pl + = non-canonical plausible; Can− pl− = non-canonical non-plausible.

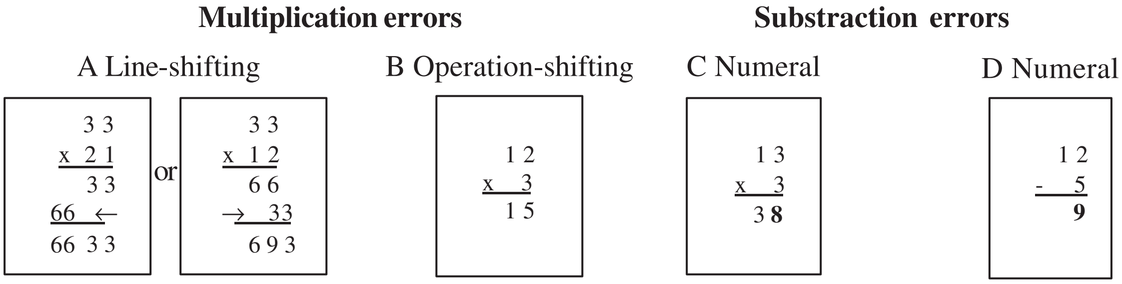

Fig. 2 Errors types in Experiment 3a and 3b.

subject-relative 'the girl that waters the flower is white']. The five additional sentences were paired with five of the eight pictures and assessed lexical abilities. They contained words that did not correspond to the objects on the paired picture (e.g. 'the girl waters the car that is white' was paired with the picture that represents a girl that waters a flower). They were of the same syntactic complexity as the experimental sentences. Regardless of syntactic capacities, subjects should judge as incorrect these sentence–picture pairs if lexical knowledge is spared.

The 37 picture–sentence pairs were presented in a random order for each subject. The examiner read a sentence and showed a picture at the same time. In contrast to usual syntactic tasks which present a sentence and several pictures in a forced choice, we reduced task demands by asking subject to say whether the auditory sentence describes correctly (or not) the picture, presenting in each trial just one sentence with one picture. Only yes/no responses were expected. In order to familiarize subjects with the task, two examples with feedback were provided (using a correct and an incorrect picture–sentence pair).

Arithmetic tasks

Like language, mathematical abilities are acquired during childhood and become automatic in adults. They can also be viewed through the 'rule–lexicon' dichotomy (see Warrington, 1982). Common arithmetic facts or results are stored in what might be referred to as an arithmetic lexicon (such as multiplication tables); conversely, new arithmetic operations (multiplication, addition, etc.) can only be executed though the use of specific combinatorial rules.

Task A used 30 multiplication problems presented visually with their solution. Ten problems were presented with an erroneous solution, which was due to incorrect application of the multiplication rule [six contained line shifting errors and four contained erroneous suboperations, i.e. additions instead of multiplications (examples are provided in Fig. 2A and B, respectively)]. Ten more problems were incorrect because of wrong arithmetic facts (Fig. 2C). Finally, 10 problems were correct (control condition). To minimize memory and attentional demands, all intermediate results were inferior to '10' with no carry over. The three conditions were paired according to arithmetic complexity (i.e. the number of digits that comprised the two operands). Task A was run on a subgroup of 20 HD patients: 9 HD1 and 11 HD2. Patients were paired with 20 control subjects according to their age [$F(1,38) < 1, P > 0.1$], level of education [$F(1,38) < 1, P > 0.1$) and laterality [$\chi^2(1) < 1, P > 0.1$].

Task B contrasted 20 simple multiplications and 20 subtractions with carry over. It was reasoned that simple multiplication problems only involve a table look-up procedure, whereas even simple subtraction problems are usually not stored, but rely on the application of a rule (especially if there is a carry over (Fig. 2D) see also Dehaene, 1997). The multiplication and subtraction problems were matched according to the number of digits they contained. Half of them had an incorrect solution, and the other half were correct (examples are provided in Fig. 2C and D, respectively).

In both tasks, the problems and their solutions were printed on cards (10 cm × 5 cm) and presented one after another in a random order. Subjects were instructed to check whether the solution to the problems was correct or not. Only yes/no responses were expected. Time was limited to 10 min. Task B was run on 10 HD1 and 6 HD2 patients, and 16 control matched subjects according to their age [$F(1,30) < 1$, $P > 0.1$], level of education [($F(1,30) < 1$, $P > 0.1$] and laterality [$\chi^2(1) < 1$, $P > 0.1$].

Data analysis

Statistical analysis of the data was performed for each task using analyses of variance (ANOVAs) with group (HD1, HD2 and controls) and conditions as independent factors. The analyses were run by items and by subjects, but, for the sake of simplicity, only analyses by subjects are provided here. Results of the analyses by items are provided only when they differed from the analyses by subjects.

Correlation analyses were performed using multiple linear regression. They included scores in the tasks that were specific to rule application (for morphological rules subregular non-verbs, for syntactic rules non-canonical non-plausible sentences, and for arithmetical rules subtractions), and executive function scores as well as disease progression scores (UHDRS motor score, TFC and the bicaudate ratios, see Table 2).

Results

Conjugation task

Overall performance in HD was 85.25% correct with no significant difference between HD1 and HD2 [HD1, 86.22%; HD2, 84.27%, $F(1,28) < 1$ and $P > 0.1$ by subjects, and $F(1,85) = 3.66$, $P = 0.06$ by items]. This trend of better performance in the analysis by items in HD1 compared with HD2 was due to three HD2 subjects who differed from the others, having rather low performance of 52.2; 78.2 and 78.2%. The results are displayed in Fig. 3. The ANOVA revealed a significant effect of category [$F(3,84) = 129.76$, $P < 0.0001$] but no interaction between group and category [$F(3,84) < 1$, $P > 0.1$ by subjects, and $F(3,85) = 2.59$, $P = 0.058$ by items]. In *post hoc* analyses, the only difference between the two HD groups was with irregular verbs, with better performance in HD1 than in HD2; this was only significant in the analysis by items [$F(1,22) = 14.06$, $P = 0.001$] but not in the analysis by subjects [$F(1,28) = 3.43$, $P = 0.074$]. Control subjects had a very high performance, and the effect of category did not reach significance [either by subjects $F(3,57) = 2.59$, $P = 0.062$ or by items $F(3,85) = 1.96$, $P > 0.1$].

Because HD1 and HD2 did not differ in performance, their results were combined in a two-way ANOVA comparing HD patients and controls. Controls had better performance than HD patients [$F(1.48) = 113.9$, $P < 0.0001$]. There was an effect of category [$F(3,144) = 133.42$, $P < 0.0001$] and an interaction between group and category [$F(3,144) = 79.43$, $P < 0.0001$]. In a restricted analysis, HD patients performed better with irregular verbs than with non-verbs, but in both cases less well than controls [with a group effect, $F(1,48) = 128.38$, $P < 0.0001$; a category effect, $F(1,48) = 128.39$, $P < 0.0001$; and an interaction between category and group, $F(1,48) = 78.25$, $P < 0.0001$]. Finally, HD patients had a lower performance in non-verbs than controls, worse in subregular non-verbs than in regular non-verbs [with a group effect, $F(1,48) = 122.41$, $P < 0.0001$; a category effect, $F(1,48) = 143.83$, $P < 0.0001$; and an interaction between group and category, $F(1,48) = 86.28$, $P < 0.0001$].

We ran two-way ANOVAs by subjects, with group (HD1, HD2 and controls) and error type (over-regularizations, double suffixations and other errors) as independent factors. The results are displayed in Table 5. HD1 and HD2 followed the same pattern of errors [$F(1,28) < 1$, $P > 0.1$] with an effect of error type [$F(2,56) = 34.74$, $P < 0.0001$], but there was no interaction between error type and group [$F(2,56) = 0.6$, $P > 0.1$]. This effect of error type was also found in controls [$F(2,38) = 5.59$, $P < 0.01$]. Because HD1 and HD2 did not differ in performance, a two-way ANOVA compared HD (combining the results of HD1 and HD2) and controls. HD patients made more errors than controls [$F(1,48) = 114.46$, $P < 0.0001$] and differed in their repartition [$F(2,96) = 39.04$, $P < 0.0001$] with an interaction between group and error type

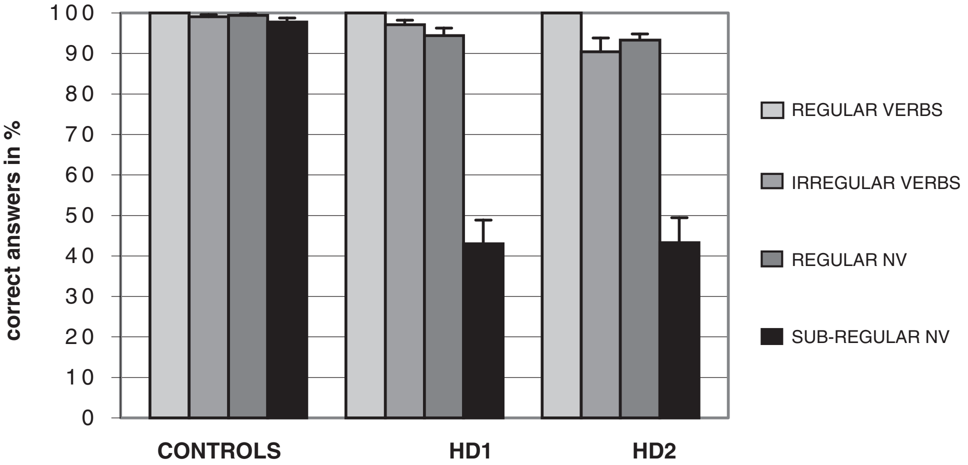

Fig. 3 Conjugation performance in controls and HD patients with regular verbs, irregular verbs, regular non-verbs and subregular non-verbs.

Table 5 *Percentage of errors by types and by conditions for HD1, HD2 and controls*

	Subregular non-verbs			Regular non-verbs			Irregular verbs		
	HD1	HD2	Controls	HD1	HD2	Controls	HD1	HD2	Controls
Over-regularizations	32.3	36.3	3	–	–	–	1.1	2	0.9
Double suffixations	8.2	5.7	0.6	0.3	0	0	–	–	–
Other errors	16.7	14.2	2.7	5.3	6.1	0.6	2.5	6.7	0
Total	57.2	56.2	6.3	5.6	6.1	0.6	3.6	8.7	0.9

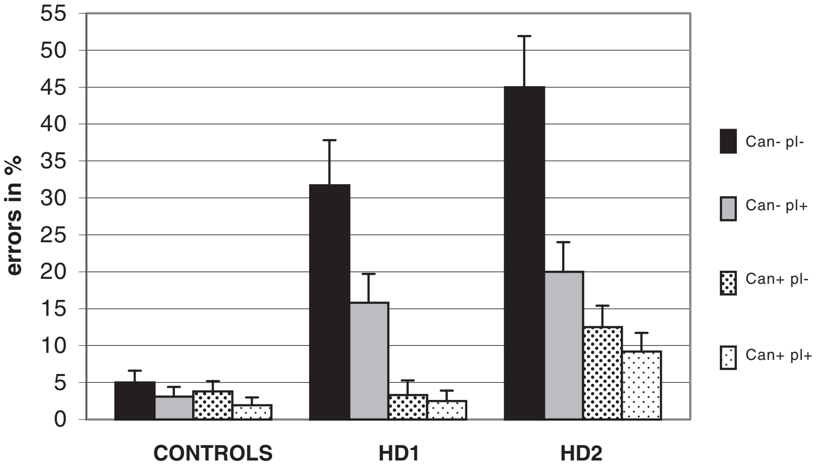

Fig. 4 Performance with sentences contrasting canonicity and plausibility. Can + = canonical; Can– = non-canonical; pl + = plausible; pl– = non-plausible sentences. The non-canonical and non-plausible sentences that cannot be understood without the use of syntax are the more prone to errors in HD1 and HD2.

[*F*(2,96) = 17.76, *P* < 0.0001]. Restricted analyses showed that there were more 'errors of rule' than 'other errors' [*F*(1,48) = 10.75, *P* < 0.01] and that HD patients made more errors than controls [*F*(1,48) = 103.61, *P* < 0.0001]. The interaction between group and the comparison between 'errors of rule' or 'other errors' were significant [*F*(1,48) = 5.82, *P* = 0.02] because, in contrast to controls [*F*(1,19) = 1.11, *P* > 0.1], HD patients made mostly errors of rule [*F*(1,29) = 10.14, *P* < 0.001]. Finally, a two-way ANOVA with the factor rule/other errors and the category (irregular verbs, regular non-verbs and subregular non-verbs) showed in HD that there was an effect of category [*F*(2,58) = 129.26, *P* < 0.0001], with an interaction between category and error type [*F*(2,58) = 31.89, *P* < 0.0001], because 'rule errors' were more frequent than 'other errors' in subregular non-verbs [*F*(1,29) = 27.39, *P* < 0.0001], although this was observed neither with irregular verbs [*F*(1,29) = 2.93, *P* = 0.097] nor with regular non-verbs, for which 'other errors' were more frequent than 'rule errors' [*F*(1,29) = 27.36, *P* < 0.0001] in HD.

Sentence–picture matching task

We ran three ANOVAs, one comparing HD1 and HD2, one testing the controls and another one comparing HD and control subjects. In these ANOVAs, canonicity (canonical/non-canonical sentences), plausibility (plausible/non-plausible sentences) and sentence structure (object and subject relatives/active and passive relatives) were entered as independent factors. The results are displayed in Fig. 4.

The first analysis concerned only the HD patients. Their overall performance was 82.5%. HD2 performed worse than HD1 [78.33 and 86.67%, respectively; *F*(1,28) = 9.34, *P* < 0.01]. Canonical sentences yielded better performance than non-canonical ones [*F*(1,28) = 64.28, *P* < 0.0001] and plausible sentences yielded better performance than non-plausible ones [*F*(1,28) = 23.01, *P* < 0.0001]. Sentence structure also influenced performance, with active–passive generating less errors than object–subject relatives [*F*(1,28) = 56.76, *P* < 0.0001]. The interactions between canonicity, plausibility and sentence structure were all significant [canonicity × plausibility, *F*(1,28) = 30.45, *P* < 0.05; canonicity × structure, *F*(1,28) = 30.99, *P* < 0.05; structure × plausibility, *F*(1,28) = 13.39, *P* < 0.05; and canonicity × plausibility × structure, *F*(1,28) = 17.81, *P* < 0.05 by subject, with *F*(1,24) = 3.88, *P* = 0.06 by items]. These sentence factors did not interact with the group factor [group × canonicity, *F*(1,28) < 1, *P* > 0.1; group × plausibility, *F*(1,28) = 1.55, *P* > 0.1; and group × structure, *F*(1,28) = 1.88, *P* > 0.1].

The second analysis only included controls, whose overall performance was 96.56% correct with no effect of canonicity [$F(1,19) < 1, P > 0.1$] or plausibility [$F(1,19) = 3.35, P > 0.08$] but an effect of the sentence structure by subjects [$F(1,19) = 4.75, P = 0.04$] although not by items [$F(1,24) = 0.09, P = 0.09$]. There were no interactions between these factors [canonicity × plausibility, $F(1,19) < 1, P > 0.1$; plausibility × structure, $F(1,19) < 1, P > 0.1$; structure × canonicity, $F(1,19) < 1, P > 0.1$; and canonicity × plausibility × structure, $F(1,19) = 1.13, P > 0.1$].

Finally, we combined the two groups of HD patients and compared them with the controls. HD patients performed globally worse than controls [$F(1,48) = 50.06, P < 0.0001$], with significant interactions between group and the different sentence factors: group × canonicity, $F(1,48) = 34.61, P < 0.05$; group × plausibility, $F(1,48) = 9.6, P < 0.05$; and group × structure, $F(1,48) = 24.87, P < 0.05$.

Arithmetic tasks

We ran separate analyses for tasks A and B. In task A, responses in HD were globally 89.67% correct. There was no significant difference between HD1 and HD2 [$F(1,18) < 1, P > 0.1$), no difference between the three conditions [rule violation condition 89%, lexical violation condition 89%, correct condition 91%; $F(2,36) < 1, P > 0.1$] and no interaction between conditions and group [$F(2,36) < 1, P > 0.1$]. Overall performance in controls was high in the three experimental conditions [95.17% correct, rule condition 94.5%, lexical condition 94%, control condition 97%; $F(2,38) < 1, P > 0.1$]. Because HD1 and HD2 did not differ in performance, their results were combined in a two-way ANOVA with group (HD and controls) and condition (rule condition and lexical condition) as independent factors. There was no difference in performance between HD patients and controls [$F(1,38) = 3.62, P = 0.07$], no difference between 'rule' and 'lexical' condition [$F(1,38) < 1, P > 0.1$] and no interaction between group and condition [$F(1,38) < 1, P > 0.1$].

In task B, HD patients were 84.69% correct, with no significant difference between HD1 and HD2 [HD1, 83.75%; HD2, 86.25%, $F(1,14) < 1$ and $P > 0.1$]. Because HD1 and HD2 did not differ in performance, their results were combined in a two-way ANOVA comparing HD patients and controls. Controls had better performance (96.72%) than HD [$F(1.30) = 25.59, P < 0.0001$]. There was an effect of category (multiplication/subtraction) [$F(1,30) = 8.71, P < 0.001$] and an interaction between group and category [$F(1,30) = 7.88, P < 0.01$]. Planed comparisons showed that performance with subtractions (78.44%) was worse than performance with multiplications (90.94%) in HD patients [$F(1,15) = 8.43, P < 0.05$] but not in controls [96.56 versus 96.87%, respectively; $F(1,15) < 1, P > 0.1$]. The results are displayed in Fig. 5.

Correlation analyses

The correlations were performed for the two groups of HD pooled together. The results are summarized in Table 6. Globally, all the disease progression scores (MDRS, TFC, UHDRS motor score and bicaudate ratio) correlated significantly with one another ($R > 0.40, P < 0.02$), except for the bicaudate ratio and UHDRS motor scores which only tended to correlate ($R = 0.39, P = 0.06$). Executive function scores (fluency, Symbol Digit Test and Stroop) correlated with these measures, and with one another ($R > 0.38, P < 0.05$), except symbol digit and TFC where only a trend was observed ($R = 0.35, P = 0.057$). Rule application in the morphological domain was assessed with the score, which yielded the strongest difference between the HD patients and controls: performance in subregular non-verbs. This score did not correlate with any disease progression or executive function

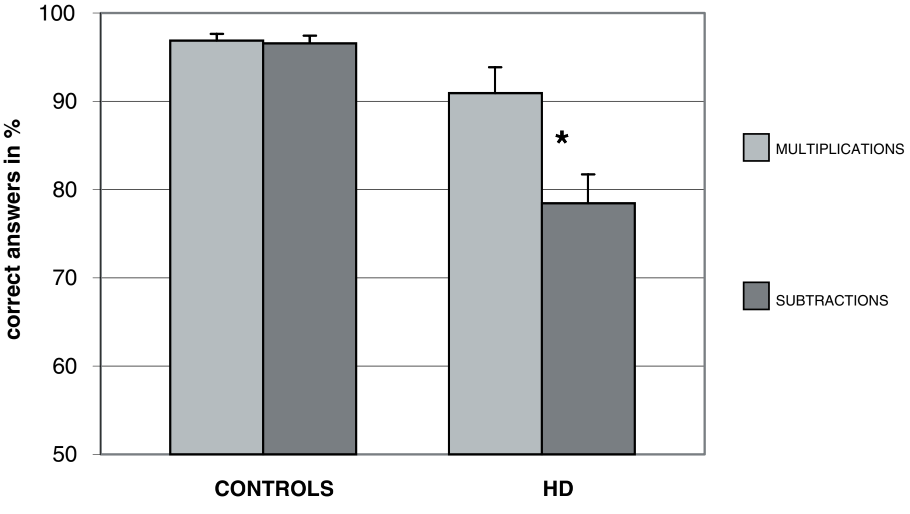

Fig. 5 Performance of HD patients and controls with subtractions and multiplications (Experiment 3b).

Table 6 *Correlation analyses in Huntington's disease*

		Disease progression scores			Executive function scores			Rules scores		
		TFC	UHDRS motor	BC	Literal fluency	Symbol Digit Test	Stroop WC	Morpho non-verbs	Syntax Can-Pl	Arithmetic (subtraction)
MDRS	*R*	0.461*	−0.530**	−0.546**	0.620**	0.754**	0.750**	0.266	−0.447*	0.166
	P	0.010	0.003	0.007	0.000	0.000	0.000	0.155	0.013	0.540
	n	30	30	23	30	30	30	30	30	16
TFC	*R*		−0.557**	−0.491*	0.473**	0.351∼	0.483*	0.157	−0.406*	0.081
	P		0.001	0.017	0.008	0.057	0.007	0.407	0.026	0.766
	n		30	23	30	30	30	30	30	16
UHDRS motor	*R*			0.398∼	−0.378*	−0.572**	−0.640**	−0.166	0.513**	−0.025
	P			0.060	0.040	0.001	0.000	0.381	0.004	0.926
	n			23	30	30	30	30	30	16
BC	*R*				−0.598**	−0.519*	−0.446*	−0.272	0.497*	−0.588∼
	P				0.003	0.011	0.033	0.210	0.016	0.057
	n				23	23	23	23	23	11
Literal Fluency	*R*					0.397*	0.576**	0.131	−0.430*	0.171
	P					0.030	0.001	0.490	0.018	0.528
	n					30	30	30	30	16
Symbol Digit Test	*R*						0.781**	0.192	−0.304	0.447∼
	P						0.000	0.309	0.102	0.083
	n						30	30	30	16
Stroop WC	*R*							0.157	−0.384*	0.310
	P							0.406	0.036	0.243
	n							30	30	16
Morpho (non-verbs)	*R*								−0.245	0.191
	P								0.192	0.478
	n								30	16
Syntax (Can-Pl-)	*R*									−0.407
	P									0.117
	n									16

R = correlation coefficient; **P* is significant at the 0.05 level (two-tailed) and ***P* is significant at the 0.01 level (two-tailed) and p∼ is a trend, $0.05 < p < 0.1$. *n* = number of subjects where the data were available; TFC = total functional capacity; BC = bicaudate ratio; Stroop WC = word-colour subpart of the Stroop task; Morpho non-verbs = performance in subregular non-verbs in the conjugation task; Syntax Can-Pl- = performance in the non-canonical non-plausible sentence in sentence comprehension.

score ($P > 0.1$). Performance in syntactic rules was assessed with the error rate in non-canonical and non-plausible sentences. This score correlated with all the disease progression scores ($R > 0.44$, $P < 0.03$), as well as with Stroop and fluency ($R > 0.38$, $P < 0.04$). Finally, performance in arithmetic rules was assessed with the error rate in subtractions. This score did not correlate with any of the HD impairment scores nor with any task ($P > 0.1$), except a trend for correlation between the bicaudate ratio and the Symbol Digit Test ($0.05 < P < 0.1$). The three rule scores (morphological, syntactic and arithmetic) did not correlate with one another ($P > 0.1$). An additional set of analyses revealed correlation between these three scores when the group of control subjects was added to the group of HD patients ($R > 0.49$, $P < 0.001$).

Discussion

The main result of this series of experiments is the identification of a specific role for the striatum in the application of rules in the language and mathematical domain. This was obtained through the analysis of defects in morphological, syntactic and arithmetic tasks in patients with known dysfunction of the striatum and relative cortical sparing, namely HD patients at an early stage (Vonsattel *et al.*, 1985; see Peschanski *et al.*, 1995).

Morphological processing

Morphological processing was assessed by using a conjugation task; patients were provided with regular or irregular verbs, as well as novel verbs that triggered either the default French conjugation rule (regular non-verbs) or more restricted conjugation patterns (subregular non-verbs). The overall pattern is relatively preserved conjugation ability compared with controls in all categories, with the exception of subregular non-verbs, where patients performed dramatically worse than controls. The good performance in regular and irregular verbs confirms the fact that HD patients have intact access to stored lexical information. Note, however, the small decrement with irregular verbs, which was more marked in more advanced HD patients. This could reflect either lexical impairment in HD, or a conflict between lexical retrieval and default rule application. The small number of errors with irregulars, however, does not give sufficient data to distinguish between these two hypotheses. The good performance in regular non-verbs shows that HD patients are not affected by the presentation of novel linguistic materials, and that they readily apply the default conjugation rule in this case. Prima facie, this contradicts the claim of Ullman *et al.* (1997), that the rule system is impaired in HD. Obviously, this claim does not hold for the default conjugation rule in French, at least in early HD. Yet, the strong impairment in subregular non-verbs is consistent with the rule versus lexicon hypothesis. HD patients were unable to apply the more infrequent conjugation rules of French. Instead they mostly performed over-regularizations, which reflect the use of the default rule, and double suffixations that could be an overactivation of this rule (overaffixation) even if it could also reveal a perseverative mechanism (see Ullman *et al.*, 1997).

To sum up, our results substantiate language impairment in morphological processing in HD; however, this impairment results mostly from the breakdown of sub-rule application.

Sentence comprehension

Sentence comprehension was assessed through a sentence–picture matching task manipulating two variables: whether the sentences were in canonical form, and whether the sentences depicted a pragmatically plausible situation. In addition, sentence–picture pairs involve either a contrast between subject–object relative clauses or active–passive contributions. We found an effect of the two main variables, canonicity and plausibility, and an additive interaction between the two. In brief, non-plausible sentences in non-canonical forms were by far the most difficult case for the HD patients. Sentences of this nature can only be dealt with by relying on syntax. Any other non-syntactic response strategy (guessing using the lexical items plus pragmatic plausibility or canonical order) would fail to yield a correct answer to these sentences. The data show that the patients approached chance performance in this condition (38% errors, chance = 50%), compared with <18% errors in all the other conditions. This deficit for non-plausible non-canonical sentences was even more pronounced in object–subject relatives, where patients made 63% errors; a performance worse than chance. The HD2 patients were significantly worse than the HD1 patients, but they had the same overall profile of results. One might think that 'weirdness' of the non-plausible sentences might explain the pattern of impairment in our patients. However, this is not the case because, first, patients made less errors in the canonical non-plausible sentences than in the non-canonical plausible sentences [7.9% error versus 17.9% error, $F(1,29) = 8.59$, $P < 0.01$]. Secondly, the high impairment in non-plausible non-canonical sentences was greater than expected by the additive effects of the two factors (shown by the interaction between canonicity and plausibility). Finally, both HD groups showed excellent performance in the control lexical condition, where the sentences contained inappropriate lexical items.

These results are consistent with the broad claim that syntactic rule operations are critically impaired in HD, but that lexical access is spared (Ullman *et al.*, 1997). Of course, the situation is somewhat different from what has been done for the case of morphology. In our experiment, lexical information was defined at the level of individual words, whereas the rules were defined at the entire sentence level. It remains to be shown whether or not HD patients are also spared when it comes to lexical information relevant to phrases or whole sentences, such as in the case of fixed expression, idioms, or proverbs (Ullman, 2001). In the meantime, both the control lexical condition and good performance with plausible sentences suggest that patients are able to retrieve and exploit stored grammatical and semantic information for the words of the sentence.

Yet, there are several aspects of our data that do not fit squarely within the rule versus lexicon hypothesis (Ullman 2001). First, HD patients could use pragmatic and word order strategies to compensate for their syntactic deficits, as evidenced by their relatively good performance with plausible and canonical sentences. In particular, the use of word order information suggests that some form of syntactic analysis is preserved. Syntactic processing comprises two steps: (i) parsing of the sentence into phrasal constituents and words (requiring access to lexical categories and word order analysis); and (ii) subsequent analysis of phrasal structure and long-distance dependencies by means of syntactic rules (Townsend and Bevers, 2001). Our results suggest that some form of procedural exploitation of category and word order information is preserved in HD patients. Moreover, the pragmatic strategy that was used by the HD patients is perhaps more sophisticated than the retrieval of a stored experienced situation, and may involve computations over abstract categories (it is non-plausible that a flower can water a girl, not because it is an infrequent event, but because flowers are inanimate objects, and hence can hardly be agents of any voluntary actions). Finally, we found that object–subject relatives were more impaired than active–passive constructions, suggesting that all syntactic operations are not evenly impaired in HD patients.

In brief, we found that HD patients were impaired in the use of purely syntactic operations, in the presence of preserved compensation strategies.

Rules versus facts in arithmetics

Two experiments contrasted 'lexical knowledge' and 'rule processing' in a non-linguistic domain, namely, arithmetic. Experiment 3A contrasted numeral (lexical) errors and line shifting or operation shifting errors in multiplication and did not show any difference between the two conditions in HD1 and HD2 patients; moreover, the performance of the patients was quite high. This suggests that HD patients were able to handle rule-governed procedures such as line shifting and to detect operations that are distinct from multiplication (addition). However, in Experiment 3B, we found that HD patients were impaired in subtractions compared with multiplications. The multiplication problems we used involved only two-digit results and could all be done by retrieving stored information that is typically well memorized at school (multiplication tables). In contrast, the subtraction problems also used two-digit results but were unlikely to be stored. This is because these operations, involving the process of carry over, are never studied as such and can easily be computed using simple rules.

These results suggest that in a non-linguistic domain, HD patients can be impaired in rule application compared with retrieval of stored information. Note, however, that they are not similarly impaired in all rule application situations. Experiment 3A suggests that HD patients were able to handle rule-governed procedures such as line shifting and to detect the application of an inappropriate operation (addition instead of multiplication). It is of course possible that this performance could be attributed to relatively simple checking strategies instead of genuine rules. For instance, the line shifting errors could be spotted by applying a visual template typical of multiplication problems; inappropriate operation selection could be spotted by checking for correct single-digit multiplications.

To sum up, the rule–lexicon dissociation that was evidenced in the linguistic domain seems to hold also in the arithmetical domain. However, it also seems that simple rules or strategies are relatively unimpaired in HD, and only complex ones, such as subtraction with carry over, yield a pattern of deficit.

Language and the striatum

To sum up, apart from the small decrement observed in HD2 with the processing of irregular verbs, our results favour the hypothesis that the striatum is mainly concerned with the application of rules, and not with lexical processing. It is important to note that the linguistic performance of the patients was globally good, as attested by their ability to conjugate frequent verbs with only few errors, and their flawless comprehension of simple and plausible sentences. This coincides with the usual observation that early HD patients exhibit no apparent impairment in their everyday use of language (Brandt, 1991). It is only when very specific linguistic tests, using novel words, or syntactically complex sentences are used that the patients display abnormal performance. This suggests that HD patients are impaired in sufficiently discrete processes such that they can compensate for this deficit by the use of alternative mechanisms that operate well in usual language situations. This result is at odds with the notion of subcortical dementia (for a review see Whitehouse, 1986) which excludes language disorders at an early stage at the subcortical level. However, it supports the view that language is subdivided into a procedural or rule component and a declarative or lexical subcomponent (Pinker, 1991), and that the basal ganglia are involved in the former (Ullman, 2001).

How is it then that several authors have suggested lexical impairment in HD (Butters *et al*., 1986; Smith *et al*., 1988; Frank *et al*., 1996). We can offer three types of answers. First, lexical disorders in HD were mostly reported in more advanced stages of the disease and could therefore be due to impairments at the cortical level (Vonsattel *et al*., 1985). Secondly, most of the studies used tasks which make it difficult to separate linguistic processes from other cognitive functions. For example, the verbal fluency task (Butters *et al*., 1986) or the naming tasks (Frank *et al*., 1996), which have shown impairments in HD patients, rely heavily on executive and/or visual components in addition to lexical access. More implicit tests of lexical access, such as lexical priming, have shown more normal lexical performance in HD (Salmon *et al*., 1988; although see Smith *et al*., 1988). Thirdly, it is possible that degenerative disease shows a profile different from vascular lesions: indeed, semantic paraphasias were reported after caudate strokes (Cambier *et al*., 1979; Mega and Alexander, 1994). Yet, even there, some caution is warranted. For example, the patient with a left caudate lesion described in Cambier *et al*. (1979) displayed some semantic paraphasias that can in fact be reanalysed as morphological over-regularization errors. In an antonym finding task, the patient produced ‘antiheureux’ (antihappy) for ‘heureux’ (happy), instead of ‘malheureux’ (unhappy). This type of error was classified as semantic but could reflect inappropriate application of productive affixation rules. Other errors such as ‘pommade révulsive’ (repulsive cream) instead of ‘pâte dentifrice’ (toothpaste) are more difficult to interpret in this view and could reflect a visual misinterpretation as well as a genuine disorder of the lexical knowledge. This calls for more extensive studies contrasting various types of striatal dysfunctions.

Conclusions: domain-specific rules or rule complexity?

Globally speaking, we found that the HD patients were impaired in rule application in three domains: morphology, syntax and arithmetics. This is consistent with the broad hypothesis that the striatum is involved in the computational application of linguistic rules (Ullman, 2001). We substantiated this claim in the original domain where it was initially observed (morphological rules), extended it to a novel case of linguistic rule application (syntax) and further extended the observation to a case of non-linguistic rule application in the domain of arithmetic. However, the details of our findings qualify the rule versus lexicon hypothesis in two respects.

The first one is that in the three domains that we explored, we found cases of unimpaired application of rules: in the domain of morphology, we found very well preserved processing of regular verbs and non-verbs, suggesting unimpaired application of the default conjugation rule. In the domain of syntax, we found very well preserved comprehension strategies based on canonical sentence order and pragmatic knowledge. Although these comprehension strategies may not exist within a system of rules in the same sense as syntactic rules, they nevertheless reflect the application of procedural knowledge, which applies productively to novel situations. Finally, we found in the domain of arithmetic unimpaired abilities to detect procedural errors in complex multiplications.

The dichotomy between procedural application in striatal–frontal circuits versus associative or declarative knowledge in associative areas falls short of explaining this pattern of results. Perhaps the relevant dichotomy could rather be formulated in terms of rule complexity as in Christoff *et al*. (2001). In this study, there is a contrast between primary rules and secondary rules. Primary rules operate on perceptual primitives, whereas secondary rules operate on the output of primary rules. In that way, secondary rules require the storage and retrieval of intermediate computations. Within this framework, syntactic operations in non-canonical sentences involve the reactivation in short-term memory of distant antecedent elements at a certain position in the sentence. Similarly, the subtraction operations we used all involved a carry over, which requires the subject to hold in memory the output of a first subtraction. To find an agreement between these results and those in morphology, one would have to say that there is a distinction in French between the main rule which applies by default in an encapsulated way, and subrules, which perhaps necessitate the decomposition of verbs into root and terminations in order to determine what type of non-default rule to apply. This latter assumption might fall into the more classical view that both the default rules and subrules require the decomposition of verbs into roots and terminations, suggesting a more fine-grained hypothesis. Recently, Koechlin *et al*. (2003) proposed that secondary rules should be defined in terms of a cascade of additional temporal processing to be held within the frontal lobe, rather than in terms of processing complexity *per se*. Further research is needed to evaluate this more refined distinction, i.e. the distinction between primary and secondary rules.

A second aspect in which the rule versus lexicon hypothesis needs to be refined further is the issue regarding whether all rule types involve the same computational circuits within the striatum, or whether different rules use distinct subcircuits, which would be topographically organized in this brain structure. The correlation analysis we ran bears on this issue. We found that although syntactic rule operation correlates well with disease progression, the other two types, morphological and arithmetic, do not. Furthermore, these two latter subtypes do not correlate with one another. In brief, even though the three types of rules are globally impaired in HD, they are not homogeneously impaired across this population. This is consistent with the claim that these three types of rules involve different circuits, and that different patients have different patterns of impairments of the area encompassing these circuits. The way to conceive these circuits is still speculative. They might mimic the description by Alexander *et al*. (1990) and Lawrence *et al*. (1998) of subcortico-frontal loops with respect to rule application in different domains such as language and arithmetic. The lack of a correlation between morphology and arithmetics and bicaudate ratio might reflect differential impairments of these different circuits. It has to be noted that the progressive degeneration of the striatum in HD follows a postero-anterior gradient from the posterior putamen to its anterior part, with partial involvement of the accubems nucleus and an oblique gradient starting from the dorsal and medial parts from the caudate and the nucleus extending toward ventral and lateral regions (Vonsattel *et al*., 1985). If it were possible to make more fine-grained distinctions in the degree of HD impairment, or to test pre-symptomatic gene carriers of HD, one might find a gradient or several gradients of rule application deterioration across domains or rule types. Of course, postulating distinct rule application loops can only be very tentative, given the limited subject size, and the lack of precise localization of striatal impairment across individual subjects. Finally, our study indicates that in addition to a role in executive functions, the striatum encompasses one or several circuits which are involved in linguistic and non-linguistic rule application. Further work is needed to investigate in more detail potential distinctions in rule application within the striatum.

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References

Alexander MP, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990; 13: 266–71.

Alexander MP, Naeser MA, Palumbo CL. Correlations of subcortical CT lesion sites and aphasia profiles. Brain 1987; 110: 961–91.

Bescherelle. La conjugaison pour tous. Paris: Hatier, 1997.

Brandt J. Cognitive impairments in Huntington's disease: insights into the neuropsychology of striatum. In: Boller F, editor. Handbook of neuropsychology. Vol. 5. New York: Elsevier; 1990. p. 241–64.

Butters N, Wolfe J, Granholm E, Martone M. An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. Cortex 1986; 22: 11–32.

Caine ED, Hunt RD, Weingartner H, Ebert MH. Huntington's dementia. Clinical and neuropsychological features. Arch Gen Psychiatry 1978; 35: 377–84.

Cambier J, Elghozi D, Strube E. [Haemorrhage of the head of the left caudate nucleus: disorganization of speech and graphic expression, and disturbances in gestures (author's translation)]. Rev Neurol (Paris) 1979; 135: 763–74.

Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. Acta Neurol Belg 1990; 90: 207–17.

Christoff K, Prabhakaran V, Dorfman J, Zhao Z, Kroger JK, Holyoak KJ, et al. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage 2001; 14: 1136–49.

Content A, Mousty P, Radeau M. Brulex: Une base de données lexicales informatisées pour le français écrit et parlé. L 'Année Psychologique 1996; 90: 551–66.

Dehaene S. The number sense: how the mind creates mathematics. New York: Oxford University Press; 1997.

Frank EM, McDade HL, Scott WK. Naming in dementia secondary to Parkinson's, Huntington's, and Alzheimer's diseases. J Commun Disord 1996; 29: 183–97.

Fromm D, Holland AL, Swindell CS, Reinmuth OM. Various consequences of subcortical stroke. Prospective study of 16 consecutive cases. Arch Neurol 1985; 42: 943–50.

Golden CJ. Stroop color and word test. Chicago: Stoelting; 1978.

Illes J. Neurolinguistic features of spontaneous language production dissociate three forms of neurodegenerative disease: Alzheimer's, Huntington's, and Parkinson's. Brain Lang 1989; 37: 628–42.

Koechlin E, Ody C, Kouneiher F. The architecture of cognitive control in the human prefrontal cortex. Science 2003; 302: 1181–5.

Kreisler A, Godefroy O, Delmaire C, Debachy B, Leclercq M, Pruvo JP, et al. The anatomy of aphasia revisited. Neurology 2000; 54: 1117–23.

Kuhl DE, Phelps ME, Markham CH, Metter EJ, Riege WH, Winter J. Cerebral metabolism and atrophy in Huntington's disease determined by 18FDG and computed tomographic scan. Ann Neurol 1982; 12: 425–34.

Kumral E, Evyapan D, Balkir K. Acute caudate vascular lesions. Stroke 1999; 30: 100–8.

Lawrence AD, Sahakian BJ, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends Cogn Sci 1998; 2: 379–88.

Ludlow CL, Connor NP, Bassich CJ. Speech timing in Parkinson's and Huntington's disease. Brain Lang 1987; 32: 195–214.

Mattis S. Mental status examination for organic mental syndrome in elderly patients. In: Bellak L, Karasu TB, editors. Geriatric psychiatry. New York: Grune & Straton; 1976: 77–121.

Mazziotta JC, Phelps ME, Pahl JJ, Huang SC, Baxter LR, Riege WH, et al. Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. N Engl J Med 1987; 316: 357–62.

Mega MS, Alexander MP. Subcortical aphasia: the core profile of capsulostriatal infarction. Neurology 1994; 44: 1824–9.

Moro A, Tettamanti M, Perani D, Donati C, Cappa SF, Fazio F. Syntax and the brain: disentangling grammar by selective anomalies. Neuroimage 2001; 13: 110–8.

Peschanski M, Cesaro P, Hantraye P. Rationale for intrastriatal grafting of striatal neuroblasts in patients with Huntington's disease. Neuroscience 1995; 68: 273–85.

Pinker S. Rules of language. Science 1991; 253: 530–5.

Pinker S. Words and rules: the ingredients of language. New York: Basic Books; 1999.

Pozzilli C, Passafiume D, Bastianello S, D'Antona R, Lenzi GL. Remote effects of caudate hemorrhage: a clinical and functional study. Cortex 1987; 23: 341–9.

Puel M, Cardebat D, Demonet JF, Elghozi D, Cambier J, Guiraud-Chaumeil B, et al. [Role of the thalamus in subcortical aphasias]. Rev Neurol (Paris) 1986; 142: 431–40.

Salmon DP, Shimamura AP, Butters N, Smith S. Lexical and semantic priming deficits in patients with Alzheimer's disease. J Clin Exp Neuropsychol 1988; 10: 477–94.

Shoulson I. Huntington disease: functional capacities in patients treated with neuroleptic and antidepressant drugs. Neurology 1981; 31: 1333–5.

Smith S, Butters N, White R, Lyon L, Granholm E. Priming semantic relations in patients with Huntington's disease. Brain Lang 1988; 33: 27–40.

Starkstein SE, Folstein SE, Brandt J, Pearlson GD, McDonnell A, Folstein M. Brain atrophy in Huntington's disease. A CT-scan study. Neuroradiology 1989; 31: 156–9.

Townsend DJ, Bever TG. Sentence comprehension: the integration of habits and rules. Cambridge (MA): MIT Press; 2001.

Ullman MT. The declarative/procedural model of lexicon and grammar. J Psycholinguist Res 2001; 30: 37–69.

Ullman MT, Corkin S, Coppola M, Hickok G, Growdon JH, Koroshetz WJ, et al. A neural dissociation within language: evidence that the mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. J Cogn Neurosci 1997; 9: 266–76.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–42.

Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 1985; 44: 559–77.

Warrington EK. The fractionation of arithmetical skills: a single case study. Q J Exp Psychol A 1982; 34: 31–51.

Wechsler D. Wechsler adult intelligence scale-revised manual. New York: Psychological Corporation; 1981.

Whitehouse PJ. The concept of subcortical and cortical dementia: another look. Ann Neurol 1986; 19: 1–6.