Striatal degeneration impairs language learning: evidence from Huntington's disease.

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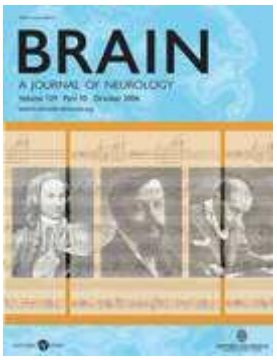

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Striatal Degeneration Impairs Language Learning: Evidence from Huntington's Disease

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Abbreviations: HD = Huntington's disease; TFC = total functional capacity; UHDRS = Unified Huntington's Disease Rating Scale

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Abstract

Although the role of the striatum in language processing is still largely unclear, a number of recent proposals have outlined its specific contribution. Different studies report evidence converging to a picture where the striatum may be involved in those aspects of rule-application requiring non-automatized behavior. This is the main characteristic of the earliest phases of language acquisition that require the online detection of distant dependencies and the creation of syntactic categories by means of rule learning. Learning of sequences and categorization processes in non-language domains has been known to require striatal recruitment. Thus, we hypothesized that the striatum should play a prominent role in the extraction of rules in learning a language. We studied 13 pre-symptomatic gene-carriers and 22 early stage patients of Huntington's disease (HD), both characterized by a progressive degeneration of the striatum and 21 late stage patients HD (18 stages II, 2 stage III and 1 stage IV) where cortical degeneration accompanies striatal degeneration. When presented with a simplified artificial language where words and rules could be extracted, early stage HD patients (stage I) were impaired in the learning test, demonstrating a greater impairment in rule than word learning compared to the twenty age- and education- matched controls. HD patients at later stages were impaired both on word and rule learning. While spared in their overall performance, gene-carriers having learned a set of abstract artificial language rules were then impaired in the transfer of those rules to similar artificial language structures. The correlation analyses among several neuropsychological tests assessing executive function showed that rule learning correlated with tests requiring working memory and attentional control, while word learning correlated with a test involving episodic memory. These learning impairments significantly correlated with the bicaudate ratio. The overall results support striatal involvement in rule extraction from speech and suggest that language acquisition requires several aspects of memory and executive functions for word and rule learning.

In the last 20 years, the role of subcortical structures in higher brain functioning has become a major field of research. In particular, the role of the striatum in executive functions, such as attention, planning, and working memory is becoming better understood [see Brandt 1991 for a review]. However, its role in language remains a controversial and unresolved issue. Most of the classical evidence of the striatum's involvement in language learning comes from the study of patients with subcortical lesions. Still, the deficits observed in these patients are variable [Kumral *et al.,* 1999; Kreisler *et al.,* 2000; Frank *et al.,* 1996; Illes, 1989] and some deficits can be explained by their concomitant cortical abnormalities [Hillis *et al.,* 2004; Rowan *et al.,* 2007]. Thus, the specific role of subcortical structures within the cortico-subcortical network is still a challenging issue.

Indeed, several studies have outlined the importance of the fronto-striatal circuit in processing the rule-based knowledge of language. Recently, Ullman [, 2001] proposed that the striatum is implicated in the application of rules in a dichotomic model of language processing. According to this view, the knowledge of the words composing language relies on declarative memory handled by the temporo-parietal lobe. This information is dissociable from the knowledge of the rules that determine the way words are combined and how they change their form depending on the constituents of the sentence they relate to. In this approach, this rule-based knowledge relies on procedural memory handled by the fronto-striatal circuit. Although this view does not differentiate the contribution of the striatum from that of the frontal lobe, more recent proposals have addressed this question. Related to this rule-based component, Friederici and colleagues [Friederici and Kotz 2003] have proposed a specific role of the striatum in late stages of syntactic processing involved in controlled reanalysis in ambiguous or incorrect sentences. In the same vein, Teichmann and colleagues [Teichmann *et al.,* 2005] have shown that striatal degeneration leads to impairments in rule application (morphology and syntax) only for non-automatized rules,

while sparing both the application of the default rules and the lexical knowledge. In contrast, similar work by Longworth and colleagues [Longworth *et al.,* 2005] has proposed that the relation between the striatum and language processing would not involve linguistics but, would involve executive functioning, such as lexical selection, requiring the inhibition between different related candidates [Copland 2003;Longworth, Keenan, Barker, Marslen-Wilson, and Tyler 2005]. Thus, the evidence so far sustains little relation of the striatum with lexical processing, aside from those aspects related to executive control; whereas it does sustain a prominent role for those features of language requiring the processing of rules when those rules are not automatized. Although it is clear that this is especially the case in the initial stages of language acquisition, when rules have to be learned, our knowledge of the implication of the striatum in language learning is limited. Language processing should be closely related to language acquisition; however, current approaches to the topic do not take into account that language processing and language acquisition may involve different cognitive demands. This is nevertheless an important issue not only because this may have implications for language development in infancy, but also because adults continue to learn new words throughout their lifespan, and are able to learn new rules when confronted with foreign languages.

The possibility that the striatum plays a major role in language acquisition is reinforced by the inherent characteristics of the language system. Language processing is sequential in nature and requires categorization processes to create syntactic classes (i.e., verb, noun, etc.). Research outside the language domain has shown that both abilities heavily rely on striatal functioning [Ashby *et al.,* 2007; Koechlin *et al.,* 2002; Smith and McDowall 2006]. Striatal degeneration in HD induces difficulties in procedural and sequence learning [Gabrieli *et al.,* 1997; Willingham *et al.,* 1996]. In the categorization domain the striatum seems to be required for information-integration tasks [Filoteo *et al.,* 2007; Filoteo *et al.,* 2005] where two stimulus dimensions have to be integrated to perform a task. These tasks rely on procedural learning [Ashby and O'Brien 2005], but they are often difficult to assimilate into language

learning because i.) they are most often tested in the visual domain, ii.) they often require a motor response, and iii.) they usually give feedback to the participants. These aspects do not necessarily characterize natural language acquisition. However, it is clear that learning sequential relations is necessary for the acquisition of various aspects of language. Sequential contingencies between phonemes are extracted for the acquisition of phonotactics [Chambers *et al.,* 2003; Onishi *et al.,* 2002], between adjacent syllables for word segmentation [Saffran *et al.,* 1996a], and between non-adjacent elements for morphosyntactic rules [Peña *et al.,* 2002]. In addition, the extraction of structural dependencies in a language guides the process of creating syntactic categories such as noun, verb, etc. [Endress and Bonatti 2007; Mintz 2003]. As previously mentioned, these aspects of language are related to procedural learning and to rule-based acquisition. In parallel, word learning also requires tracking sequential information during the early segmentation process [Aslin *et al.,* 1998; Saffran, Aslin, and Newport1996a]. However, once words have been segmented from speech, word consolidation might be less dependent on sequential information, but more dependent on progressive enhancement of memory traces by encountering repeated instances of those words [De Diego-Balaguer *et al.,* 2007].

In addition, cognitive functions such as executive control of attention and working memory are essential for both sequence and category learning [Ashby and O'Brien2005; Ashby, Ennis, and Spiering2007]. Little is known about the involvement of these functions in language acquisition, but the characteristics mentioned previously speak for their contribution. Classical theories have proposed a relevant role of working memory [Baddeley *et al.,* 1998] in language learning and there is evidence that this involvement may relate to both word learning [Baddeley *et al.,* 1988; Hansson *et al.,* 2004] and syntactic acquisition [Williams and Lovatt 2005]. In addition, recent evidence has pointed out that attentional control may have a specific role for the extraction of regularities from the speech stream [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007; Pacton and Perruchet 2007; Toro *et al.,* 2005; Williams 2001]. Finally, in this context it is also relevant to note that,

several studies have outlined the importance of the striatum (caudate and putamen) in different aspects of cognitive control [Abutalebi *et al.,* 2007; Brandt1991; Hikosaka *et al.,* 1989]. Therefore, the position of the striatum as a convergent structure for different cognitive functions may be very relevant for this possible interaction between language learning and executive control.

Thus, altogether many arguments plea for the fundamental role of the striatum in language acquisition; (i) its role in sequence acquisition and categorization, (ii) its role in language processing, executive functions and memory, and (iii) its key position in the brain, receiving and projecting connections to practically all cortical areas, making it a liable candidate for modulation and coordination of different cognitive functions required in the learning process. Surprisingly, the role of the striatum in language acquisition has been overlooked, and its implication in human language processing is just starting to be understood. Our goal in the current study is to broaden our knowledge about the specific implications of the striatum in rule-based aspects of language acquisition. At the same time, we are interested in studying the possible contribution of executive control in language learning.

For this matter, in the present work we report data about the effects of striatal lesions in the acquisition of a new artificial language. We conducted a cross-sectional study with pre-symptomatic HD gene-carriers, early stage, and moderate to severe stages of HD to differentiate striatal from cortical dysfunction. HD is an inherited neurodegenerative disorder with primary neuronal dysfunction and death in the striatum (caudate and putamen) at early stages of the disease, making it a valuable model of striatal dysfunction [Myers *et al.,* 1988;Peschanski *et al.,* 1995;Vonsattel *et al.,* 1985], while later stages also include neuronal degeneration in cortical areas [Douaud *et al.,* 2006]. Although cortical abnormalities have also been reported in HD patients, including at a preclinical stage, these are, in early stages, rather inconsistent in the different studies compared to the reliable striatal atrophy reported systematically. At a preclinical stage, abnormal thin sulci and enlargement of gyral growns,

broader and flatter than healthy controls have been reported in a study [Nopoulos *et al.*, 2007] with no difference in overall cortical volume [Nopoulos *et al.*, 2007; Beglinger *et al.,* 2005] suggesting a neurodevelopmental rather than neurodegenerative aetiology, while another study has reported reductions in bilateral intra-parietal sulcus and insula compared to gene-negative controls [Thieben *et al.,* 2002]. In early stage patients, although some studies report unremarkable differences in nonstriatal structures [Vonsattel and DiFiglia, 1998], one recent study has found atrophy in the opercular and right paracentral cortex [Kassubek *et al.*, 2004], two [Kassubek *et al.*, 2004; Rosas *et al.,* 2003] in the hypothalamus and one widespread degeneration in the cortex [Rosas *et al.,* 2003]. Studies showing early cortical atrophy have analysed stage I and II patients together while Sotrel *et al* [1991] found a loss in large pyramidal cells in layers II, IV, and V of prefrontal cortices in stage II and Vonsattel and DiFiglia [1998] report no cortical abnormalities at stage I. In contrast, all studies [Harris *et al.* 1999;Kassubek *et al.* 2004;Nopoulos *et al.* 2007;Rosas *et al.* 2003;Rosas *et al.* 2005;Thieben *et al.* 2002], using different techniques have systematically found atrophy in striatal structures more prominent in dorsal caudate and putamen, starting in the head of caudate in preclinical individuals, and cortical atrophy in moderate to late stages of the disease [Douaud *et al.,* 2006; Vonsattel and DiFiglia, 1998]. Thus, in order to avoid effects of cortical atrophy as much as possible: our early stage patients were only stage I patients, later stages were studied aside and the bicaudate ratio, calculated as an index of striatal degeneration, took into account cortical atrophy.

In order to study language learning abilities, we presented participants with a simplified artificial language [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007;Peña, Bonatti, Nespor, and Mehler2002] containing new words that followed specific rules. The same material allowed us to assess both the ability of the same patients to learn the words, repeatedly presented in the language stream, and the rules characterizing those words in the artificial language. We wanted to contrast the ability to extract patterns of regularities to that of progressive rote memorization. As we previously mentioned,

segmentation of words from the speech stream requires the extraction of sequential information between syllables when no other information is available [Aslin, Saffran, and Newport1998; Saffran, Aslin, and Newport1996a; Saffran *et al.,* 1996b]. Thus, in order to avoid word learning's performance dependence on this initial segmentation learning, language streams were already segmented by the introduction of subtle pauses between words. This ensured that word segmentation could be overcome by simple detection of syllable sequences between pauses, not requiring any rule-extraction. Thus, word acquisition would be more likely to be successful through enhancement of memory traces owing to repetition of already segmented words, than through sequence learning. This manipulation aimed to test whether rule learning alone or both rule and word learning are compromised in progressive striatal degeneration. In addition, the correlation of the performance in these tasks with results from various neuropsychological tests of executive function (memory and attention) allowed us to assess the possible relation between language learning and other cognitive processes.

Material and Methods

Participants

Fifty-nine genetically tested HD gene-carriers (mean CAG repeat values are summarized in Table 1) at different stages of the disease were tested. According to the Shoulson [1981] classification, following the Total Functional Capacity score [The Huntington Study Group 1996], 24 were at an early stage of the disease (stage I: HD_1), and 22 were at a later stage (18 stage II, 3 stage III, 1 stage IV: HD_2). Thirteen additional HD participants were pre-symptomatic HD gene-carriers (pre-HD). Pre-HD participants were carriers of the genetic mutation following a pre-symptomatic diagnostic demand, with absence of functional or psychiatric signs and UHDRS score equal to 0 or for whom their follow-up neurologist has scored a motor sign ≤ 5, non specific from HD, with a lower than 50% certainty. HD

participants were recruited from an out-patient clinic follow-up program approved by the ethical committee of the Henri Mondor hospital. Twenty healthy control participants were also tested. They were matched in age and educational background with the stage I and later stages patient groups (all *P*s > .1) but were older than the pre-HD group ($t(31) = -2.95$, $p < .01$). Three HD patients were excluded from the study (two HD_1 patients due to comprehension problems; one HD_2 patient due to severe articulatory, motor problems causing ambiguity in response interpretation). Table 1 summarizes the demographic data from participants included in the analyses. None reported hearing problems, nor previous history of neurological or severe psychiatric disorders, aside from HD for the patient groups.

Clinical Evaluation

All patients were evaluated using the Mattis Dementia Rating Scale (MDRS; [Mattis 1976] and the United Huntington Disease Rating Scale (UHDRS; The Huntington Study Group 1996); the Stroop test [Golden 1978], the verbal letter fluency test [Butters *et al.,* 1986], and the Symbol Digit Test [Wechler *et al.,* 1981]. In addition, patients completed the Hopkins Verbal Learning Test [Rieu *et al.,* 2006] and the Trail Making Test parts A and B (TMT; Tombaugh 2004). The data are summarized in Table 2. Furthermore, atrophy of the caudate nucleus was assessed in 18 of the patients who had an MRI scan performed within three months of the clinical evaluation (Table 1). Caudate atrophy was calculated from the MRI scans with an adjusted bicaudate ratio, which took into account cortical atrophy. It was calculated from the MRI scans by measuring the minimal distance between the caudate indentations of the frontal horns divided by the width of the brain along the same line multiplied by 100 [Aylward *et al.,* 1991]. All the measurements were performed on 5mm thick T2 weighted images obtained in orbito-meatal plane. The retained value was the one on the slice were the bicaudate distance was minimal.

Stimuli and Procedure

Four artificial language streams were used. The simplified artificial language used [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007;Peña, Bonatti, Nespor, and Mehler2002] consisted in the concatenation of trisyllabic items following a rule that established that their initial syllable determined their ending irrespective of the middle element (e.g., **le**ka**di**, **le**fi**di**, **le**ro**di**), thus forming a structure similar to some morphosyntactic rules (**is**play**ing**, **is**work**ing** **is**walk**ing; un**treat**able, un**bear**able, un**believe**able**, etc.). The materials were already validated in our previous study in healthy participants [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007]. Thus, we knew that words and rules could be learned from all the language streams. Within the same materials, words could be identified through the repetition of the same systematic trisyllabic sequences (see Figure 1) independently from the rules. There were three different structures and the intervening middle syllable could take up to three values, for a total of nine different words per language (see Appendix 1). None of the syllables were repeated across languages. Streams and test items were synthesized using the MBROLA speech synthesizer software [Dutoit *et al.,* 1996] concatenating diphones at 16 kHz from http://tcts.fpms.ac.be/synthesis/mbrola.html. Words were separated by 25 ms pauses. Their duration in the language streams was 696 ms each. They were concatenated in pseudorandom order such that the same word was never repeated immediately in the stream.

The experiment involved a *learning* and *recognition* phase. Each participant heard the four languages. The order of presentation of the languages and the order of the learning test (word or rule learning) was counterbalanced across subjects. During the *learning phase* of the experiment, each language was presented for 4 minutes leading to 333 word expositions (37 presentations of each specific word, thus 111 presentations of each structure). Participants were told that they would hear a nonsense language, and that their task was simply to pay attention to it because after listening they would be asked to recognize the

nonsense words forming this language. Participants were not informed of the presence of rules in the languages, and no feedback was offered at any time in the experiment.

After listening to each stream, participants were behaviorally tested using a two-alternative forced choice *recognition* test. Isolated test items were created for this matter and presented in pairs. The two test items of each trial were separated by 704 ms. Test items were 9 words, 9 rule-words, 18 non-words. Two of the language streams were tested for *word acquisition* and the other two for *rule acquisition.* In the test for word acquisition, in each trial, participants had to choose between a word from the exposed language and a non-word. Non-words were new items formed with the same three syllables of a previously exposed word in the wrong order: The first and last syllables were placed in the inverse order (e.g., **di**ka**le** from the word **le**ka**di**, see Appendix 1). For the other two language streams, *rule learning* was evaluated and participants had to choose between a non-word and a rule-word. Rule-words were new words maintaining the same initial and final syllable of a word from the exposed language while inserting a syllable corresponding to another word in the middle position (e.g., **le**bo**di** for the le__di structure, see Appendix 1). Thus, even though they followed the structure of words in the artificial language, the participants never heard these rule-words before. In order to distinguish between non-words and rule-words participants must encode both the co-occurrence of the first and last syllable at the boundary position in their precise order and the relation of dependency between initial and final syllables irrespective of the syllable in the middle. If subjects learned the rule they should be able to generalize the rule to new words ands thus, discriminate rule-words from non-words. Each test item appeared twice. Participants were instructed to listen to the two alternative stimuli before responding. In order to avoid response errors due to the motor impairments of the patients, all participants were instructed to respond orally whether the first or the second word of the presented pair of stimuli was a possible word in the exposed language. Each subsequent test trial was manually triggered by the experimenter once the participant gave a

response. The overall performance in the two learning tests measured the ability to extract the underlying words and rules in the specific languages exposed.

In addition, having two different languages for each type of learning (words and rules) allowed us to assess also the extent of the rule learning ability. During the second learning test, participants should benefit from the previous exposition to a language: They should improve their performance when listening to a new language that follows the same structural dependency (first syllable determining the last syllable). Thus, the improvement in performance in the second compared to the first language reflects the ability to apply the rule at a more abstract level transferring the previously extracted structure to completely new material. This *transfer* effect is more abstract than the generalization, within the same specific language, necessary to learn during the first language presented. The abstract nature of this transfer effect has been shown with similar materials not only within the language modality, but also to non-linguistic stimuli following presentation of a language with the same structural dependencies as the non-linguistic stimuli [Marcus *et al.,* 2007].

The experiment was run individually on a portable computer using the Presentation Software (http://nbs.neuro-bs.com/). Stimuli were played through headphones connected to the computer, via a SigmaTel Audio SoundCard.

Results

Learning Effects

Success rates were log-transformed for statistical analyses [Winer *et al.,* 1991]. For the *learning effects*, an ANOVA was performed for each group of subjects (pre-HD, HD_1 and HD_2). Each ANOVA included one within factor (word learning vs. rule learning test), and one between factor (presentation order of learning tests). In addition, each group of patients was

compared to the healthy control group in a separate ANOVA adding in the factor group (HD vs. controls). Pair-wise *t-test* comparisons between the HD and healthy control groups for both learning tests (word and rule learning) were then performed.

Figure 2A shows the performance in the word and rule learning test for each group of HD gene-carriers and the healthy control group. In the healthy control group the performance for word learning was better than for rule learning in agreement with previous research using the same material [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007] (effect of test: $F(1,18) = 7.32$, $p < 0.014$) and both types of information were extracted from the languages better than chance (rules: $t(19) = 6.74$, $p < 0.0001$; words: $t(19) = 7.53$, $p< 0.0001$).

As can be observed in Figure 2A, the pre-HD group showed the exact same pattern as the healthy control group (Group effect and Group x Test: *P*s < .2). Both groups were able to extract the words and rules of the languages in both tests (rules: $t(12) = 4.78$, $p < .0001$; words: $t(12) = 12.6$, $p < .0001$) with better performance for word than rule learning (effect of test: $F(1,11) = 15.28$, $p< .002$).

In contrast, performance in the HD_1 group was worse than in the healthy control group (Group effect: $F(1,38) = 4.99$, $p < .03$) showing a general drop in the learning abilities of these patients. The overall profile of performance in the two groups was comparable (Group x Test: F < 1), nevertheless, it is crucial to highlight that whereas the groups did not differ in the word learning test ($t(40) = 1.71$, p <.1), critically, they differed for rule learning ($t(40) = 2.18$, $p < .035$). Patients were still able to learn both the words ($t(21) = 3.96$, $p < .001$) and the rules of the language ($t(21) = 2.57$, $p <.02$) better than chance, however, as the scores in the HD_1 group were closer to a floor effect (50% chance level), the difference between conditions was slightly reduced. Thus, the advantage for word compared to rule learning previously described did not reach significance ($F(1,20) = 3.1$, $p < .095$).

The absence of differences between word and rule learning ($F < 1$; Figure 2A) was much clearer in the case of HD_2. And in this case, HD_2 patients demonstrated performance at chance for both word and rule learning tests (both *Ps* < .5). Although their profile was not different from the healthy control group (Group x Test: $F(1,37) = 2.36$, $p < .2$), controls clearly had a better learning performance overall (Group effect: $F(1,37) = 25.8$, $p < 0.0001$). Indeed, pair-wise comparisons for the two learning tests revealed that patients at later stages of the disease had a reduced performance in both word ($t(39) = 3.9$, $p < .0001$) and rule learning ($t(39) = 3.23$, $p < .003$) compared to the healthy control group (Figure 2A).

According to this first analysis, while pre-HD patients showed a comparable performance to the healthy control group, as the disease progresses an overall decrease in language learning ability is observed. Although there was an overall decrease in learning performance, the pair-wise comparisons suggested that the disease may have a greater impact on rule than word learning, hinted at by the worse performance in HD_1 compared to the healthy control group in this specific condition.

Thus, to confirm this result, we performed a post-hoc analysis in a subgroup of patients, matched for their word learning abilities to the control group, in order to see if their rule learning ability would demonstrate a comparable or impaired profile. Twelve participants were matched from these groups. Thus, we discarded one participant with the greatest word learning performance from the pre-HD group and kept the 12 HD_1 patients with the greatest word learning performance to match the control group (respectively $p > .8$ and $p < .7$). The resulting subgroups were all matched in age and educational background ($p > .2$). As is noticeable in Figure 2B, the results of this second analysis support a specific impairment of rule acquisition when groups were matched for their word learning ability. Pre-HD and healthy control groups still displayed a comparable profile (Group x Test: $F < 1$). In contrast, the HD_1 group showed reduced rule learning compared to the healthy control group despite

their spared word learning ability (Group x Test : $F(1,22) = 4.96$, $p < .036$). While HD_1 patients learned the words of the language ($t(11) = 8.87$, $p < .0001$), performance for rule learning was at chance level ($t(11) = 1.51$, $p < .2$), differing from the healthy control group ($t(22) = 2.24$, $p < .035$). HD_2 participants were excluded from this analysis because even a subgroup of HD_2 patients with the greatest scores showed a reduced performance compared to the healthy control participants ($t(22) = 5.03$, $p < .0001$).

Thus, the results of the learning tests as a whole showed a progressive decrease in language learning starting as soon as the disease manifests (HD_1). The rule learning capacity showed a specific impairment in patients compared to healthy control participants when matched on their spared word learning ability. This deficit was not present in the pre-HD group.

Transfer Effects

In addition, the *transfer* capacity was calculated by the difference between the scores in the second block of word and rule learning tests compared to the first block of tests [transfer = ($2^{nd} - 1^{st}$ word learning test) + ($2^{nd} - 1^{st}$ rule learning test)]. The analyses from this abstract rule generalization measure revealed that transfer capacity was compromised even earlier than learning ability (Figure 3). Analyzing the entire sample of participants, the capacity to transfer the structural rule learned in the first exposition to a new instance, sharing the same structural dependency, was impaired in all patient groups, including the pre-HD group. While the healthy control group showed a significant transfer effect ($F(1,18) = 6.02$, $p < .02$), the transfer effect was not significant in any of the HD groups ($p > .4$), including the pre-HD group (Figure 3). This point is especially relevant considering that pre-HD patients did not differ from healthy control participants in their rule learning ability ($p > .7$). Like the overall learning ability ($F(1,75) = 33,0$ $p < .0001$), the slope of the transfer capacity showed a lineal decline as a function of disease progression ($F(1,75) = 4.65$, $p < .034$).

Note however that, surprisingly, pre-HD patients had a greater, although non-significant, learning ability in the first language test compared to healthy control participants (Figure 3). Presumably, pre-HD patients' greater performance in the first block of tests gave less room for transfer than those with lower scores and could have masked their transfer capacity. Thus, we performed a second analysis to control for this possibility. The residual value of the regression between the scores in the first block and the transfer capacity provided us with a transfer measure in which the influence of the starting point was partialled out. These values displayed the linear decrease with the progression of the disease previously observed ($F(1,75) = 14.84$, $p < .0001$) and healthy control participants were again the only group showing a significant transfer effect($t(19) = 2.1$, $p < .05$). Transfer capacity for pre-HD and HD_1 patients was not significant ($p > .2$) and HD_2 patients showed worse performance in the second compared to the first block ($t(20) = -3.2$, $p < .001$).

Correlations with Clinical Assessment Scores

The neuropsychological results across the different HD groups, depicted in Table 2, showed that the performance of the HD_1 and HD_2 groups was pathological in all the tests (all $p < .05$). One-sample t-tests were performed for this matter comparing the performances of each group with the mean of the corresponding normative data (from The Huntington Study Group [1996] for the UHDRS motor score, Mattis [1976] for the MDRS, Rieu *et al.* [2006] for the Hopkins Verbal Learning Test, Cardebat *et al.,* [1990] for Letter Fluency, Golden [1978] for the Stroop test, Wechsler [1981] for the Symbol Digit Code test and Tombaugh [2004] for the TMT). The performances of the pre-HD group were significantly better than the normative means on all tests according to the published norms for each test, except for the Hopkins C and the TMT A and B where pre-HDs performed within the normative range. This improved performance might be due to the strong motivation of this specific group to demonstrate good

cognitive abilities and due to the presence of some subjects in this group that were younger than the normative age range available.

In order to evaluate the relationship between executive function and word and rule acquisition we performed a partial correlation analysis between the results of the language learning tests and the tests for clinical assessment. The partial correlation analyses controlled for the effect of rule learning ability in the word learning correlations, and for word learning ability in the rule learning correlations. A subset from the neuropsychological tests, specific for cognitive assessment, was selected for these analyses (memory: MDRS-memory scale, Hopkins Verbal Learning Test; executive function and sequencing: TMT A-B, Symbol Digit Test; cognitive conflict: Stroop interference score; attention: MDRS-attention scale; and Verbal letter fluency -score for 2 minutes-). The UHDRS-motor score and UHDRS-Total Functional Capacity Score, as indexes of HD progression; and the bicaudate ratio values, as an index of striatal degeneration, were also included in the correlation analyses (Table 3).

The partial correlations between the cognitive tests and the language learning tests showed similarities, but also differences, between the tests related to word and rule learning (see Table 3). Although both language learning tasks correlated with neuropsychological tests involving sequencing (TMT A-B, Symbol digit code) and cognitive conflict (Stroop interference score), some tests correlated only with one of the language tasks. The rule learning test specifically correlated with the MDRS-Attention subscale, with tests involving working memory (immediate free recall from the Hopkins Verbal Learning Test), and with the Letter Fluency test. The word learning test did not correlate with these tests, but did correlate with the MDRS-memory scale, tapping episodic memory, perhaps demanding less working memory capacity than the Hopkins Verbal Learning Test immediate recall (Table 3). The word learning, but not the rule learning performance, correlated with the UHDRS-motor score. In addition, as suggested by the previous results, both the rule and word learning performance correlated with the progression of the disease (TFC). Finally, the index of

striatal degeneration (bicaudate ratio) tended to correlate with the rule learning performance ($r(15) = -.44$, $p < .07$), but it did not correlate with word learning performance ($r(15) = -.38$, $p < .2$). Actually, striatal atrophy correlated with the overall learning capacity ($r(18) = -.48$, $p < .044$) while it did not correlate with the transfer scores ($p > .8$).

General Discussion

In this research, we sought to study the role of the striatum in the earliest stages of language acquisition when no semantic information is available. In a novel approach, we used exactly the same material to test the two main components of language learning; rule and word extraction from speech. By testing HD patients at different phases of the disease, we have shown that even at early stages of the disease (HD_1), striatal degeneration in Huntington's disease impairs language learning. This language impairment progresses along with the disease showing a correlation with striatal degeneration. Moreover, due to the sequential nature of rule-based information in language and its importance for the creation of syntactic categories, we hypothesized that the striatum would be more relevant to learn the rules characterizing the language than the words composing it. In agreement with this hypothesis, HD progression and striatal degeneration seemed to affect more strongly the rule-based acquisition of language than purely word learning abilities. This result was made even clearer when we matched a subset of HD patients and healthy control participants on their word learning ability. Patients at the earliest stages of HD (HD_1), when neural degeneration is mostly confined to the striatum, showed only a poor rule learning ability, whereas both word and rule learning abilities were compromised at later stages of HD (HD_2) when cortical degeneration may also have been present [Douaud, Gaura, Ribeiro, Lethimonnier, Maroy, Verny, Krystkowiak, Damier, Bachoud-Levi, Hantraye, and Remy2006; Rosas *et al.,* 2003].

Interestingly, although the pre-symptomatic gene-carriers (pre-HD) showed a spared performance in the learning tests, a qualitative difference was observed compared to healthy control participants. The rule acquired by the latter was more abstract than that of the pre-HD group. The degree of abstractness of the rule acquired was assessed by the data from the *transfer* capacity, representing the ability to transfer acquired structural knowledge from one language to a completely new one when rules are organized in the same manner. This transfer capacity also showed a linear decline throughout the progression of the disease. More importantly, its impairment seemed to appear even earlier in the course of the disease than the ability to generalize the rule within the specific language learned. Both pre-HD and HD_1 patients showed limited transfer abilities, while the HD_2 group showed an interference effect. Previous studies have reported grey-matter loss in the left striatum [Thieben *et al.,* 2002] in addition to reduced dopamine D_1 and D_2 receptor binding in this structure [Lawrence *et al.,* 1998]. It is possible that in pre-HD patients the striatum could already be compromised before clinical onset of HD. Unfortunately, the bicaudate ratios for the healthy control participants and for all but one pre-HD patient were not available and these groups contained more subjects showing transfer effects. Lacking these bicaudate ratios reduced our chances of observing a correlation between striatal degeneration and transfer capacities; however the limited transfer result in pre-HD and HD_1 patients suggests that transfer impairments can be present at a preclinical stage of HD.

In addition, the results of the correlation analyses supported the involvement of executive functions in language learning. Word and rule learning performances in the current study showed a large correlation with various aspects of executive functions. The partial correlation analyses pointed, also, to a functional dissociation between the two types of learning. The scores from the rule learning test, when controlling for the influence from performance in the word learning test, correlated with working memory and with tests requiring sequencing ability. In contrast, the largest correlation for word learning arose with a test engaging episodic memory. These relations cannot be fully accounted for by a simple overall cognitive

decline in HD because there were differences in the way the neuropsychological tests correlated with one type of learning test and not the other. It is also unlikely that the effects reflect only drug therapy. Antipsychotic medication, such as sulpiride or haloperidol, is sometimes prescribed at low doses for relieve of choreic movements [Bonelli and Wenning 2006]. These drugs tend to affect attention and working memory. However, because these drugs have side effects that may exacerbate parkinsonian symptoms or may produce sedative effects [Handley *et al.,* 2006], this treatment was present in only seven of our HD_1 patients and eleven of the HD_2. In post-hoc analyses for each group, the medicated and unmedicated groups did not differ in their word and rule learning abilities (all *P*s > .1). In addition, impairments in the ability to transfer the acquired rule were detected even in pre-HD patients whereas none of them were under medication.

Studies on syntactic processing had already pointed out a close relation between working memory and grammatical processing for the processing of syntactic dependencies [Fiebach *et al.,* 2001; Santi and Grodzinsky 2007b;Santi and Grodzinsky 2007a]. Our results may suggest that this relation is necessary in the early stages of language acquisition and may apply at different levels of language processing (i.e., phonotactics, morphology, and syntax) as a function of the need to track sequential information for the learning of distant dependencies within the material. This functional relation is in agreement with Baddeley's proposal of a prominent role of working memory in language learning [Baddeley, Gathercole, and Papagno1998]. Moreover, correlations between tests requiring attentional control were also found for our rule learning test. These relationships add support for the involvement of attentional control in language learning already suggested by our previous electrophysiological results in healthy individuals [De Diego-Balaguer, Toro, Rodriguez-Fornells, and Bachoud-Levi2007]. This explanation is also consistent with recent work showing that early HD patients display impairment in the reorienting of attention due to a deficit in attentional disengagement from previously cued locations [Couette *et al.,* in press]. Thus, in the language learning tests, HD patients might be unable to disengage their focus of

attention from the whole word, disrupting the acquisition of intraword initial-final syllable dependencies characterizing the rules of those words.

The results are also consistent with the neurofunctional distinction between different memory systems. Working memory and executive control processes, necessary for sequence learning [Curtis and D'Esposito 2003; Hikosaka, Sakamoto, and Usui1989], are sustained by the fronto-striatal loop connecting the lateral prefrontal cortex and the caudate. Episodic memory, necessary for the creation of memory traces, [Fernandez *et al.,* 1998; Vargha-Khadem *et al.,* 1997] relies mostly on the hippocampal and parahippocampal structures. Consistently, these latter structures have been related to word learning ability in previous brain imaging studies [Breitenstein *et al.,* 2005]. Such a neurofunctional dichotomy fits with the profile of HD patients having an early degeneration of the caudate while preserving temporal areas [Douaud, Gaura, Ribeiro, Lethimonnier, Maroy, Verny, Krystkowiak, Damier, Bachoud-Levi, Hantraye, and Remy2006; Vonsattel, Myers, Stevens, Ferrante, Bird, and Richardson, Jr.1985; although see also Rosas *et al*., 2003 for reports of hippocampal degeneration in early and mid-stages of HD]. The functional role of the striatum, as a structure managing the interaction between executive functions and rule learning in language, resonates with the anatomical overlap between the areas of the caudate connecting to the lateral prefrontal cortex related to executive functions, and those connecting to BA 45, closely related to syntactic processing [Lehericy *et al.,* 2004b]. These convergent projections on the striatum could uphold the coordination between these two functions. The obtained correlations within this study may extend the declarative/procedural model [Ullman2001] to the word/rule model of language learning with an additional contribution from executive control during this early process of language acquisition.

It is worth noting that, in addition to the learning deficits reported here, previous results have shown that rule application is impaired in a comparable sample of early HD patients [Teichmann *et al.,* 2006;Teichmann, Dupoux, Kouider, Brugieres, Boisse, Baudic, Cesaro,

Peschanski, and Bachoud-Levi2005]. It is thus necessary to better understand how learning interacts with various cognitive functions and to better distinguish the different brain structures that are responsible for early stages of learning and that are responsible for the application of automatized rules. Our results suggest that both the acquisition and application of acquired rules implicate the striatum, within the fronto-striatal loop. From this view, either the exact same structures are involved throughout the learning process or there might be a shift from anterior to more dorsal parts of the striatum during the learning process [Mair *et al.,* 2002; Yin and Knowlton 2006]. Studies on habit formation have shown that the anterior part of the striatum is needed in the early stages of acquisition of goal-directed associations. When responses become automatized habits, the putamen seems to take over control [Williams and Eskandar 2006; Yin *et al.,* 2004; Yin *et al.,* 2006]. This anatomical dissociation is consistent with the differences in connectivity, plasticity and distribution of receptors in the caudate and the putamen [Joel and Weiner 2000;Lehericy, Ducros, Van de Moortele, Francois, Thivard, Poupon, Swindale, Ugurbil, and Kim2004b;Lehericy *et al.,* 2004a;Partridge *et al.,* 2002]. Although this anatomical data comes mostly from animal studies and bridging the gap to the language domain may be difficult, such a hypothesis would accommodate the results from acquisition and application of consolidated rules. However, outside the language domain an alternative account has been proposed for a putative shift between brain structures (within the same fronto-striatal circuit) involved in acquisition versus application of a rule. Reports on single-cell recordings in monkeys have shown that the acquisition of simple associations induce an early rapid response from the striatum followed by gradual implication of the dorsolateral prefrontal cortex [Pasupathy and Miller 2005] leading to frontal engagement for the application of automatized rules [Wallis *et al.,* 2001]. The same dichotomic dynamic has been proposed in studies on category learning [Ashby, Ennis, and Spiering2007]. This alternative hypothesis would be consistent with proposals of language processing indicating that rule-application impairments by striatal lesions are associated with concomitant deficits in those aspects requiring executive control [Longworth, Keenan, Barker, Marslen-Wilson, and Tyler2005;Kotz *et al.,* 2002;Friederici and

Kotz2003]. If this were to be the case, once rules have been automatized, the striatum may only be needed when executive control is necessary, in terms of working memory demands or changes in attentional focus. Follow-up studies with high resolution structural and functional imaging in patients and healthy control participants could disentangle the possible neural and functional differences within the fronto-striatal loops in the course of learning.

Conclusions

In conclusion, the present study highlights the role of the striatum in language learning showing that learning declines with striatal degeneration in the course of Huntington's disease, beginning in its earliest stages. Indeed, the prominent role of the striatum in sequence and category learning, processes related to rule-based knowledge in language acquisition, suggests that deficits within this structure impact rule learning more than word learning. Our results enhance the hypothesis of cooperation between language and other cognitive functions, namely the control of attention and working memory within the early stages of language acquisition.

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Table 1. Demographic, genetic CAG information and bicaudate ratios for the Huntington's Disease patients analyzed in the study. Pre-HD: Pre-symptomatic gene-carriers of Huntington's Disease; HD_1: Huntington's Disease patients at stage I; HD_2: Huntington's Disease patients at stages II, III and IV.

	Pre-HD	HD_1	HD_2	Controls
N	13	22	21	20
TFC	13	11.7 ± 0.8	8 ± 2	-
Sex	4 M/ 9 F	13 M/ 9 F	11 M/ 10 F	5 M/ 15 F
Age in years	35.4 ± 7.7	46.6 ± 8.8	51.7 ± 9.5	48.1 ± 14.2
Education in years	12.2 ±2.5	12.2 ± 2.9	13.2 ± 4	13.7 ± 2.2
Years from onset	-	5.7 ± 3	8.5 ± 3	-
CAG repeats[a]	42.2 ±1.3	44.2 ± 2.9	45.3 ± 4	-
Bicaudate ratio[b]	11.6	18 ± 4	21.5 ± 4.4	-

[a] Pathological threshold > 35, [b] Normal value <10 (Starkstein et al., 1989) bicaudate ratio sample size: pre-HD N=1, HD_1 N=7, HD_2 N=8; HD: Huntington's Disease; F: Female/ M: Male; TFC: Total Functional Capacity score

Table 2. Results from the neurological and neuropsychological assessments. Pre-HD: Pre-symptomatic gene-carriers of Huntington's Disease; HD_1: Huntington's Disease patients at stage I; HD_2: Huntington's Disease patients at stages II, III and IV. UHDRS: Unified Huntington Disease Rating Scale; MDRS: Mattis Dementia Rating Scale; TMT: Trail Making Test.

	Pre-HD	HD_1	HD_2
UHDRS motor score	2.6 ± 5	27* ±17.9	46*** ± 16.5
MDRS	141.5 ± 2.2	129.5** ± 9.1	123.3*** ± 10
Hopkins A	29.6 ± 2.7	17.4*** ± 6.4	16.9*** ± 4.5
Hopkins B	11.1 ± 1	4.6*** ± 2.7	4.6*** ± 3.6
Hopkins C	11.9 ± 0.4	9.7*** ± 2	9.6*** ± 2
Letter Fluency [a]	70.6 ± 20.5	43.9* ± 21.9	28.6*** ± 16.9
Stroop interference	47.5 ± 8.4	26*** ± 10.4	18.8*** ± 9
Symbol Digit Code	49.5 ± 9.9	26.7*** ± 8.7	17.3*** ± 6.9
TMT A	34.9 ± 11.7	71.3*** ± 42.2	92.7*** ± 40.4
TMT B	59.9 ± 20.4	159*** ± 72.9	206.2*** ± 47.4

[a] Value for 2 minutes for the three letters P, R, and V; Pathological scores compared with the mean normative data are marked with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Results of the partial correlation analyses between the language learning and clinical assessment measures. The partial correlation analyses controlled for the effect of the rule learning ability in the word learning correlations and of the word learning ability in the rule learning correlations. Values of correlations of tests of executive function specific to one type of learning (in the word or rule test) are highlighted in bold.

	Rule learning test	**Word learning test**	**d.f**
Cognitive Assessment			
Hopkins A-immediate recall	**0.34***	n.s.	42
Hopkins delayed recall	**0.37***	n.s.	42
Hopkins C -recognition	n.s	n.s.	43
MDRS-Memory	n.s.	**0.37****	43
MDRS-Attention	**0.46*****	n.s.	43
Letter Fluency[a]	**0.59*****	n.s.	46
Stroop interference	0.61***	0.49***	46
Symbol Digit Code	0.52***	0.53***	43
TMT A	-0.53***	-0.40**	43
TMT B	-0.40**	-0.54***	43
General Assessment			
UHDRS Motor score	n.s.	**-0.32***	44
UHDRS TFC score	0.34*	0.47***	49

[a] Value for 2 minutes for the three letters: PRV for French norms; UHDRS: Unified Huntington Disease Rating Scale; TFC: Total Functional Capacity; TMT: Trail Making Test; d.f: degrees of freedom; "n.s.": non-significant ($p > .05$); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Appendix 1. Syllables used in the different artificial languages. Middle syllables could be combined with the three structures of the language.

	Embedded structures	Middle syllables	Examples of test items	
			Word	**Rule-word**
Language 1	le__di bo__ma to__ne	ka, fi, ro	lerodi	lemadi
Language 2	ba__gu do__ke mo__ti	fe, pi, lo	bapigu	badogu
Language 3	pa__mi nu__de ri__bu	te, la, ko	patemi	pabumi
Language 4	da__lu me__po re__bi	na, tu, go	dagolu	dabilu

Figure captions

Figure 1. Illustration of the material used in the learning phase. Words (i.e., patemi) and rules (i.e., the structure pa__mi) could be acquired from the same material.

Figure 2. Mean performance (± standard error of the mean) of the healthy control group and the Huntington's Disease gene carriers (HD) for the word and the rule learning tests. A. Rule and word learning performance of the healthy control group and all the HD patients of the study at different stages of the disease. B. Rule learning performance of the healthy control group, Pre-HD and stage I HD patients when matched for their word learning performance. Pre-HD: Pre-symptomatic gene-carriers of HD; HD_1: HD patients at stage I; HD_2: HD patients at stages II, III and IV.

Figure 3. Proportions of correct responses in the first and second block of the learning tests. Transfer scores are superimposed, calculated as the difference in performance from the first to the second block of languages tested (scores for words and rules together). * $p < .021$. Bars indicate ± standard error of the mean.

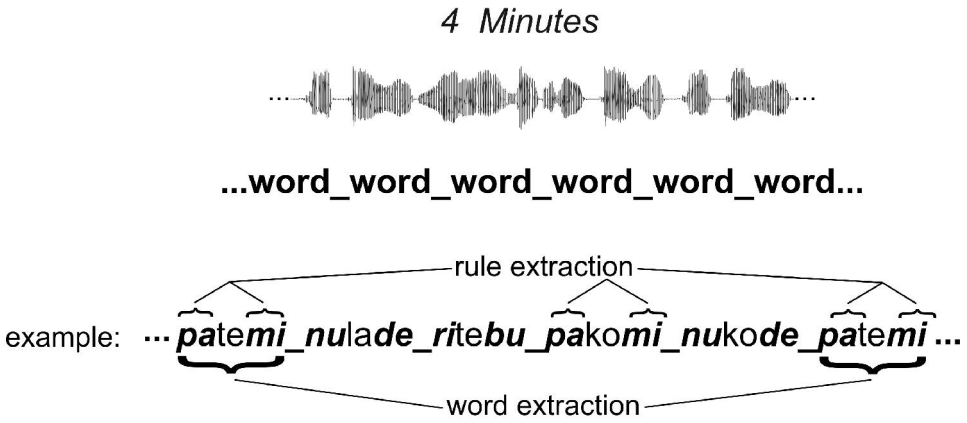
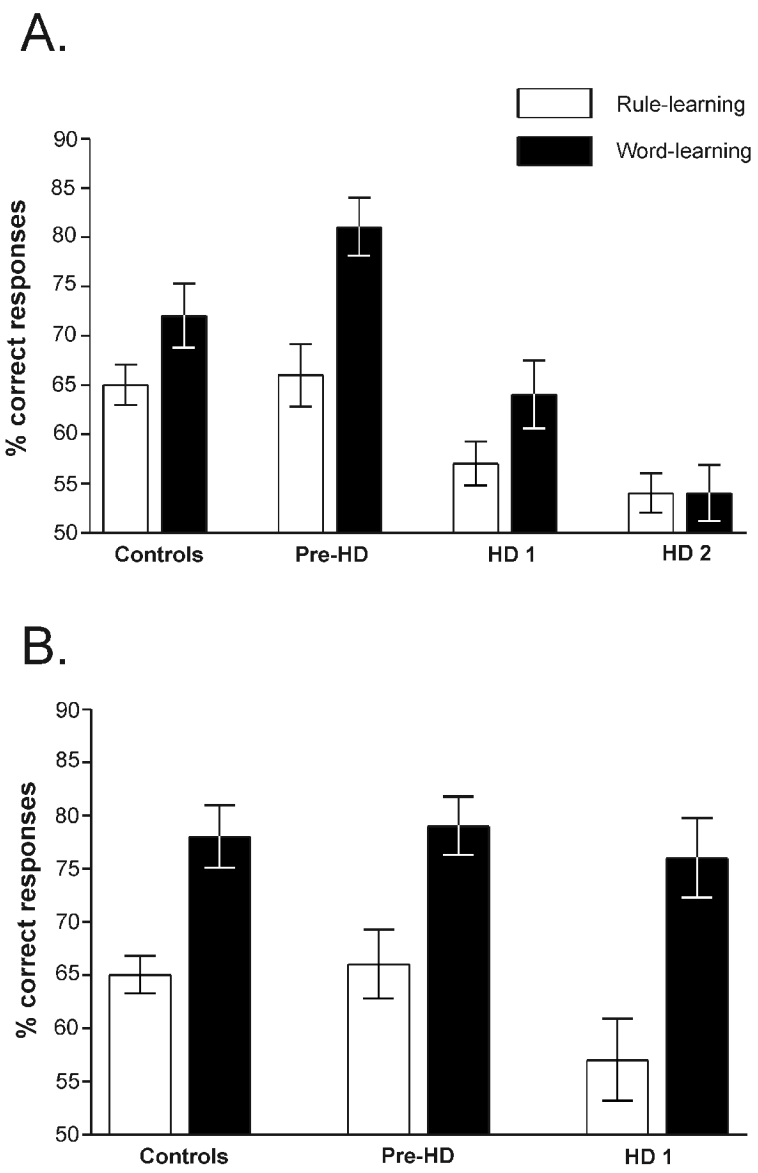
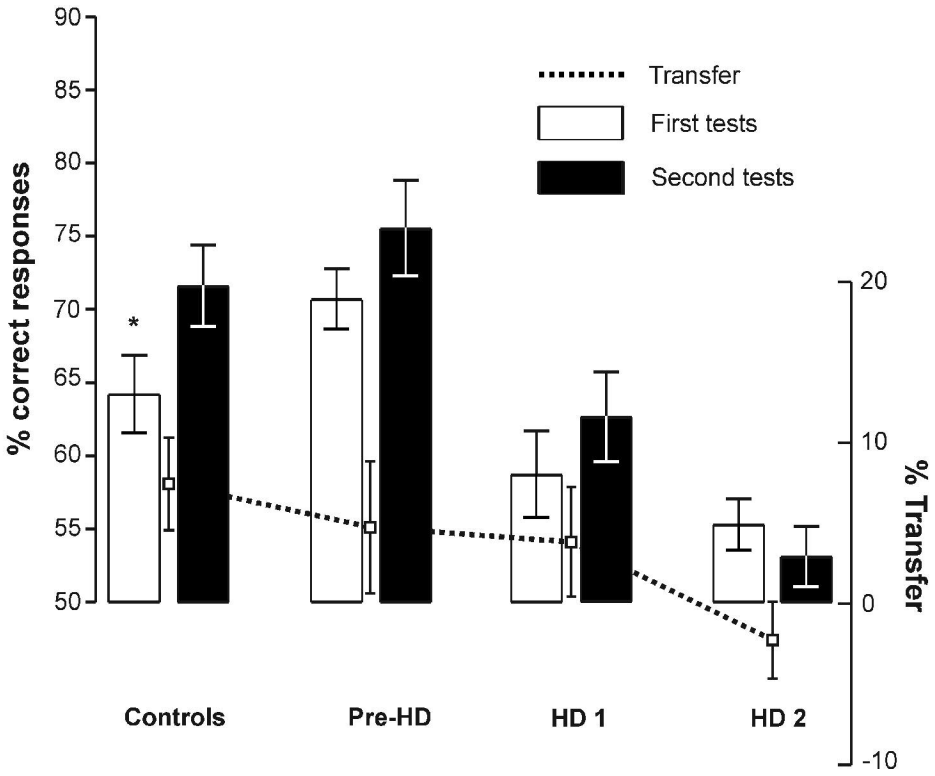


Illustration of the material used in the learning phase. Words (i.e., patemi) and rules (i.e., the structure pa__mi) could be acquired from the same material.



Mean performance (± standard error of the mean) of the healthy control group and the Huntington's Disease gene carriers (HD) for the word and the rule learning tests. A. Rule and word learning performance of the healthy control group and all the HD patients of the study at different stages of the disease. B. Rule learning performance of the healthy control group, Pre-HD and stage I HD patients when matched for their word learning performance. Pre-HD: Pre-symptomatic gene-carriers of HD; HD1: HD patients at stage I; HD2: HD patients at stages II, III and IV.



Proportions of correct responses in the first and second block of the learning tests. Transfer scores are superimposed, calculated as the difference in performance from the first to the second block of languages tested (scores for words and rules together). * $p < .021$. Bars indicate ± standard error of the mean.