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Action-semantic and syntactic deficits in subjects at risk for Huntington's disease

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Frontostriatal networks play critical roles in grounding action semantics and syntactic skills. Indeed, their atrophy distinctively disrupts both domains, as observed in patients with Huntington's disease (HD) and Parkinson's disease, even during early disease stages. However, frontostriatal degeneration in these conditions may begin up to 15 years before the onset of clinical symptoms, opening avenues for pre-clinical detection via sensitive tasks. Such a mission is particularly critical in HD, given that patients' children have 50% chances of inheriting the disease. Against this background, we assessed whether deficits in the above-mentioned domains emerge in subjects at risk to develop HD. We administered tasks tapping action semantics, object semantics, and two forms of syntactic processing to 18 patients with HD, 19 asymptomatic first-degree relatives, and sociodemographically matched controls for each group. The patients evinced significant deficits in all tasks, but only those in the two target domains were independent of overall

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cognitive state. More crucially, relative to controls, the asymptomatic relatives were selectively impaired in action semantics and in the more complex syntactic task, with both patterns emerging irrespective of the subjects' overall cognitive state. Our findings highlight the relevance of these dysfunctions as potential prodromal biomarkers of HD. Moreover, they offer theoretical insights into the differential contributions of frontostriatal hubs to both domains while paving the way for innovations in diagnostic procedures.

Huntington's disease (HD) is caused by a mutation that expands CAG repeats in the huntingtin gene (Tabrizi *et al.*, 2009). As it is an autosomal dominant disorder, patients' children have a 50% chance of inheriting the condition. In pre-clinical stages, which may last up to 15 years, the ensuing neuropathological process mainly involves atrophy of the dorsal striatum (Tabrizi *et al.*, 2009), although subjects remain mostly asymptomatic. Progressive cell degeneration eventually leads to a clinical stage, in which weakening of frontostriatal connections (Harrington *et al.*, 2015) compromises the exchange of signals between the basal ganglia and cortical hubs (Watkins *et al.*, 2000). Concomitantly, worsening abnormalities become manifest in the motor domain (e.g., chorea, incoordination, bradykinesia) as well as in high-level functions (e.g., linguistic deficits, executive dysfunction) (Montoya, Price, Menear, & Lepage, 2006).

While HD remains incurable, early (and, ideally, pre-clinical) detection is acknowledged as a cornerstone to reduce its impact through timely treatment (DeKosky & Marek, 2003). Among other options, this can be achieved via clinical or cognitive biomarkers, which, despite their limitations, have the advantage of being inexpensive and non-invasive. In this sense, two high-order domains have recently emerged as sensitive indexes of subtle frontostriatal disruptions: action semantics (as tapped via pictorial or verbal stimuli) and syntax. Relevant findings come not only from HD, but also from Parkinson's disease (PD), another model of frontostriatal damage – for reviews, see Bak (2013), Cardona *et al.* (2013), and García and Ibáñez (2014).

For example, HD involves difficulties to integrate action verbs with ongoing manual movements (Kargieman *et al.*, 2014) and to compute complex syntactic relations (Sambin *et al.*, 2012). Notably, these two patterns emerge independently of the patients' executive (e.g., working memory) skills. Compatibly, action semantics and syntax in PD are disturbed in samples with and without mild cognitive impairment (Bocanegra *et al.*, 2015), further highlighting the primary nature of the deficits. Even more interestingly, similar dysfunctions have been observed in potential or confirmed mutation carriers who manifest no clinical symptoms. For instance, the natural integration of manual action verbs and congruent hand movements (García & Ibáñez, 2016b) is compromised in asymptomatic first-degree relatives of patients with HD (Kargieman *et al.*, 2014). Also, the ability to transfer newly learnt grammatical rules can be reduced in pre-symptomatic HD gene carriers despite spared performance on general language tests (De Diego-Balaguer *et al.*, 2008). Finally, *sui generis* syntactic impairments have been found in pre-clinical mutation-carrying relatives of genetic patients with PD (García *et al.*, 2017). Thus, available evidence points to a transnosological role of frontostriatal disruptions in these primary high-level impairments.

The above findings are highly promising as they suggest that inexpensive, non-invasive, and easily implementable tasks could reveal frontostriatal dysfunctions in individuals *at risk* for HD. A good model to assess this possibility is found in asymptomatic

subjects with a familial history of HD. Indeed, such individuals constitute a vulnerability group who possess a high probability of developing the disease or some of its associated deficits (Panegyres & Goh, 2011) and who can exhibit specific high-order impairments without manifest signs of disease (Baez *et al.*, 2015, 2016; Kargieman *et al.*, 2014). Thus, these subjects offer valuable opportunities to assess cognitive disturbances in the absence of full-blown symptoms.

Yet, as action semantics and syntax are not routinely included in HD assessments, further research is needed to ascertain their usefulness as indexes of such abnormalities. A first step towards the identification of sensitive subject-level biomarkers is to examine whether those domains are distinctively impaired in relevant *samples*: if a task fails to reveal robust differences at the group level, then it is likely to be superfluous; but if it does, then it emerges as a candidate to be further assessed for robustness in studies designed to explore single-subject results. Indeed, this very strategy has yielded important insights in previous studies assessing language (e.g., De Diego-Balaguer *et al.*, 2008; Kargieman *et al.*, 2014) and other cognitive domains (e.g., Baez *et al.*, 2015, 2016) in pre-clinical HD samples. In this context, we conducted the first joint investigation of both functions in Huntington's disease patients (HDPs) and asymptomatic first-degree relatives (HDRels). Furthermore, we assessed the extent to which these potential deficits depend on the participants' overall cognitive profile. This way, we aimed to contribute to the ongoing search of sensitive clinical biomarkers favouring timely detection of HD and other neurodegenerative disorders (DeKosky & Marek, 2003).

Methods

Participants

The study involved 74 participants. The first group (HDPs) was composed of 18 symptomatic patients (six female) genetically and clinically diagnosed with HD (mean age = 43.83, *SD* = 10.39). The second group (HDRels) was comprised of 19 HDPs' first-degree relatives (six female) featuring no signs of the disease (mean age = 29.26, *SD* = 9.65). Although this sample did not receive genetic testing, it belongs within a well-characterized vulnerability group (for details, see Data S1). In fact, HDRels can give signs of familial vulnerability even if not confirmed as mutation carriers, as variously shown in biological (Markianos, Panas, Kalfakis, & Vassilopoulos, 2008), clinical (Dorsey, 2012), and cognitive (Baez *et al.*, 2015, 2016; Giordani *et al.*, 1995; Kargieman *et al.*, 2014) studies.

Both HDPs and HDRels underwent a neurological evaluation and were assessed with the motor section of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996). Additionally, the patients' functional skills were rated with the Huntington's Disease Functional Capacity Scale (Shoulson & Fahn, 1979). Patients and relatives did not report any history of drug abuse, previous neurological, or major psychiatric disorder.

The study also included 37 healthy individuals divided into two control groups, one for HDPs (n = 18) and one for HDRels (n = 19). Each of these samples was matched for gender, age, and education level with their corresponding target group. None of the controls presented neurological illnesses or psychiatric conditions. See Table 1 for full demographic and clinical data of all groups, including statistical comparisons between HDPs, HDRels, and their respective controls.

Table 1. Demographic and clinical data

	HDPs $n = 18$	Controls $n = 18$	HDPs versus controls p-value	HDRels $n = 19$	Controls $n = 19$	HDRels versus controls p-value
Demographic data						
Gender (F:M)	6:12	7:11	.73*	6:13	7:12	.73*
Age (years)	43.83 (10.39)	49.50 (12.11)	.11**	29.26 (9.65)	34.63 (11.3)	.11**
Education (years)	9.56 (5.07)	11.89 (3.1)	.06**	11.53 (2.7)	12.89 (4.21)	.25**
Clinical variables						
UHDRS motor score	20.56 (8.64)	.21 (.42)				
Years since diagnosis	3.55 (3.01)					
Years since disease onset	39.72 (8.22)					
HDFCS	11.89 (1.53)					

Notes. Data presented as mean (*SD*) with the exception of gender.
HDPs = Huntington's disease patients; HDRels = asymptomatic first-degree relatives; UHDRS = Unified Huntington's Disease Rating Scale (total motor score); HDFCS = Huntington's Disease Functional Capacity Scale (total score).
*p-values were calculated using chi-square test (χ^2).
**p-values were calculated using Mann–Whitney U-test.

The study was approved by the institutional ethics committee and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Materials

All participants completed a cognitive evaluation aimed to assess their general cognitive state as well as their semantic and syntactic skills.

Assessment of general cognitive state

The patients' overall cognitive functioning was examined through the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005), a sensitive tool for detecting cognitive dysfunction in motor disorders, such as HD (Bezdicek *et al.*, 2013; Gluhm *et al.*, 2013; Mickes *et al.*, 2010; Videnovic *et al.*, 2010) and PD (Dalrymple-Alford *et al.*, 2010; Gill, Freshman, Blender, & Ravina, 2008; Hoops *et al.*, 2009; Kandiah *et al.*, 2014; Nazem *et al.*, 2009). Assessed domains include orientation, attention, memory, and language, alongside viso-spatial and executive abilities. The MoCA has a maximum of 30 points, and its total score is corrected for the participant's years of education.

Assessment of semantic and syntactic skills

Semantic and syntactic domains were evaluated through tasks that have revealed subtle deficits in neurodegenerative motor diseases, including HD (Azambuja *et al.*, 2012;

Kargieman *et al.*, 2014), PD (Bocanegra *et al.*, 2015; Cardona *et al.*, 2014; Ibáñez *et al.*, 2013), and motor neuron disease (Bak & Hodges, 2004).

Object semantics. Processing of object semantics was assessed through the Pyramids and Palm Trees (PPT) test (Howard *et al.*, 1992), a task that has proven useful to reveal semantic deficits in motor disorders involving frontostriatal damage (Bocanegra *et al.*, 2015; Cardona *et al.*, 2014; García *et al.*, 2017; Ibáñez *et al.*, 2013). Participants were presented with 52 triads of pictures representing different objects, and they had to choose which of the two bottom pictures was most closely associated with the picture at the top. The maximum score in the PPT test is 52.

Action semantics. Semantic representation of actions was evaluated through the Kissing and Dancing Test (KDT; Bak & Hodges, 2003), which has also proven successful to detect specific semantic impairments in motor conditions caused by frontostriatal disruptions (Bocanegra *et al.*, 2015; Cardona *et al.*, 2014; García *et al.*, 2017; Ibáñez *et al.*, 2013). The KDT mirrors the logic of the PPT test, but all of its pictures depict human actions as opposed to objects. Although the images in this task are not matched with those of the PPT test in terms of fine-grained variables (e.g., visual complexity, familiarity, age of acquisition), both instruments are analogous in structure, difficulty, instructions, and scoring procedure (Bak & Hodges, 2003). As in the PPT test, the maximum score in the KDT is 52.

Syntax. Syntactic processing was evaluated through two subtests from an extended version of the Boston Diagnostic Aphasia Examination (Goodglass, Kaplan, & Barresi, 2001): 'Touching A with B' and 'Embedded Sentences'. These tasks have evinced subtle deficits in samples with frontostriatal alterations, including patients with HD (Azambuja *et al.*, 2012), patients with PD (Bocanegra *et al.*, 2015), and even asymptomatic PD gene carriers (García *et al.*, 2017). We calculated a global syntactic score by adding the participants' scores in each subtest, and we also assessed their performance on each subtest separately.

In each trial of both subtests, participants were shown four pictures and they had to choose the one that more accurately depicted a statement read by the examiner (Azambuja *et al.*, 2012). In 'Touching A with B', each of its 12 trials featured four pictures which depicted a hand touching or holding objects. Accurate performance depends on identifying the functional role of nouns within verb phrases (e.g., *tocando las tijeras y el peine* [*touching the scissors and the comb*] vs. *tocando las tijeras con el peine* [*touching the scissors with the comb*]). Crucially, this task depends more on sequential than hierarchical processing, as its verbal stimuli involve no long-distance relationships and the functional role of the second noun can be determined by reference to its immediately previous word – when preceded by *and*, it manifests the same function as its preceding noun phrase (direct object); when preceded by *with*, it is necessarily an instrumental adjunct (Bocanegra *et al.*, 2015; García *et al.*, 2017). The maximum score in this task is 12.

On the other hand, accurate performance on 'Embedded Sentences' requires complex syntactic processing. Each of its 10 trials includes four pictures of two interacting characters and the examiner's sentence features subordinate clauses as a

part of their subject (e.g., *La mujer que es gorda está besando a su esposo* [*The woman who is fat is kissing her husband*]) or their object (e.g., *El niño está golpeando a la niña que está sentada* [*The boy is hitting the girl who is sitting down*]). Hence, relative to 'Touching A with B', this subtest involves parsing long-distance dependencies (to establish subject-verb agreement) and it requires more complex hierarchical processing (Bocanegra *et al.*, 2015; García *et al.*, 2017). The maximum score in this task is 10.

Statistical analysis

Normal distribution of the data was evaluated through the Shapiro–Wilk test. Clinical and demographic variables were analysed with descriptive statistics. Between-group comparisons of demographic and clinical variables were conducted using Mann–Whitney tests, or chi-square tests, as needed. General cognitive function, semantic processing, and syntactic performance were compared between groups through Mann–Whitney tests, and effect sizes were calculated via Cohen's d – as in previous studies (Bak & Hodges, 2003, 2004; Bocanegra *et al.*, 2015; García *et al.*, 2017; Ibáñez *et al.*, 2013), results from the PPT test and the KDT were subjected to separate between-subject analyses. Also, to evaluate the effect of general cognitive state on semantic and syntactic performance, we conducted ANCOVA tests adjusting for MoCA scores. Results from both domains are reported before and after co-variation. All statistical tests were two-tailed, and alpha values were set at $p < .05$. Analyses were carried out on SPSS 24.0 statistical software (IBM, New York, NY, USA).

Results

Results of HDPs and HDRels on all measures and statistical comparisons with their respective controls are presented in Tables 2 and 3, respectively, and graphically summarized in Figure 1. All the results reported in this section and in the tables emerged

Table 2. Performance of HDPs on general cognition, semantic, and syntactic tasks

	HDPs $n = 18$	Controls $n = 18$	HDPs versus controls p-value	ANCOVA with MoCA test p-value	Cohen's d
MoCA test	24.94 (2.62)	27.94 (1.51)	<.005[a]*		1.44
PPT	47.17 (5.37)	51.33 (.97)	<.001[a]*	.1	1.11
KDT	45.5 (5.03)	51.17 (.79)	<.001[a]*	<.005[a]	1.62
Global syntactic performance	17 (3.4)	21.11 (1.02)	<.001[a]*	<.001[a]	1.68
Touching A with B	9.5 (2.6)	12 (.0)	<.001[a]*	<.005[a]	1.4
Embedded Sentences	7.5 (1.42)	9.11 (1.02)	<.001[a]*	.01[a]	1.34

Notes. Data presented as mean (*SD*).
HDPs = Huntington's disease patients; MoCA = Montreal Cognitive Assessment; PPT = Pyramids and Palm Trees test; KDT = Kissing and Dancing Test; d = Cohen's effect size.
[a]Alpha level set at .05.
*p-values were calculated using Mann–Whitney U-test.

Table 3. Performance of HDRels on general cognition, semantic, and syntactic tasks

	HDRels		Controls		HDRels versus controls	ANCOVA with MoCA test	
	n = 19		*n* = 19		*p*-value	*p*-value	Cohen's *d*
MoCA test	27.74	1.45	29	1.45	.01[a]*		.89
PPT	50.42	1.35	50.68	1.2	.54[a]*	.92	.21
KDT	50.16	1.01	51.11	.88	.01[a]*	.02[a]	1.03
Global syntactic performance	19.26	1.63	20.68	.95	<.001[a]*	.01[a]	1.09
Touching A with B	11.53	1.17	11.95	.23	.08*	.2	.41
Embedded Sentences	7.74	.56	8.74	.99	<.005[a]*	<.005[a]	1.28

Notes. Data presented as mean (*SD*).
HDRels = asymptomatic first-degree relatives; MoCA = Montreal Cognitive Assessment; PPT = Pyramids and Palm Trees test; KDT = Kissing and Dancing Test; *d* = Cohen's effect size.
[a]Alpha level set at .05.
**p*-values were calculated using Mann–Whitney *U*-test.

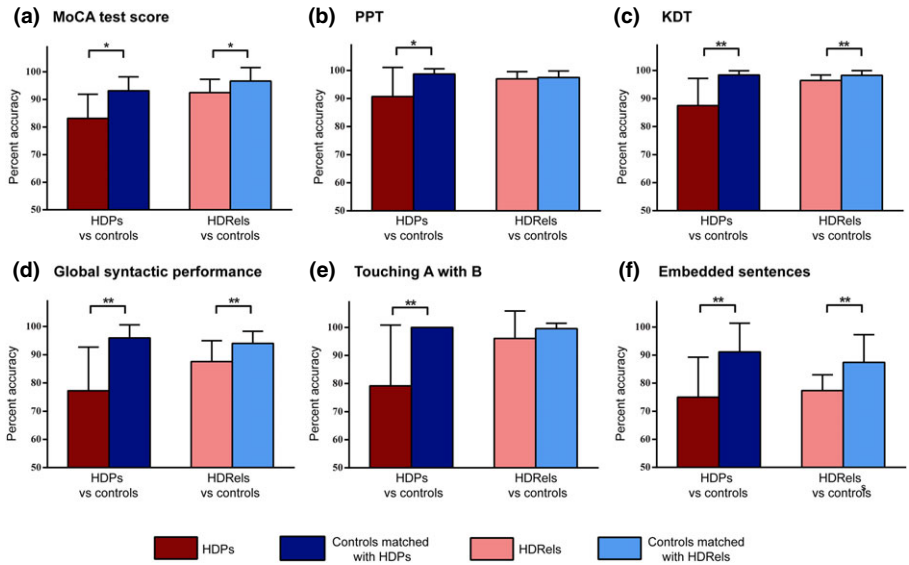

Figure 1. Between-group comparisons of performance on general cognition, semantic, and syntactic tasks (HDPs vs. matched controls and HDRels vs. matched controls). Statistically significant differences between groups are indicated by asterisks (*). Statistically significant differences after covariation by MoCA are shown by (**). Black vertical bars indicate standard deviations. While all statistical analyses were performed on the participants' raw scores, results are presented in percentage values to ease visual comparability between tasks featuring different numbers of items. (a) MoCA test score. (b) Pyramids and Palm Trees (PPT) test. (c) Kissing and Dancing Test (KDT). (d) Global syntactic performance. (e) Touching A with B. (f) Embedded Sentences. All results are shown in percentage values.

from analyses performed on the participants' raw scores. However, as not all tasks had the same number of items, outcomes are presented in percentage values in Figure 1 to ease visual comparability across measures.

HDPs

Huntington's disease patients were outperformed by their controls in all tasks. They obtained significantly lower scores on the MoCA ($U = 56.5$, $p < .005$), the PPT test ($U = 49, p < .001$), and the KDT ($U = 22.5, p < .001$). Also, syntactic impairments were revealed by their global syntactic scores ($U = 28, p < .001$) as well by separate analysis of their performance on 'Touching A with B' ($U = 45, p < .001$) and 'Embedded Sentences' ($U = 61$, $p < .001$). The difference between HDPs and controls in the PPT test, F (1, 33) = 2.95, $p = .10$, disappeared after adjusting for MoCA scores. On the contrary, the pattern observed in KDT, F (1, 33) = 11.66, $p < .005$, was preserved after covariate analysis. The same was true for global syntactic performance, $F(1, 33) = 16.03, p < .001$, 'Touching A with B', F (1, 33) = 13.55, $p < .005$, and 'Embedded Sentences', F (1, 33) = 7.32, $p = .01$. In sum, the patients exhibited impairments in object semantics, action semantics, and syntactic processing, and deficits in the latter two domains were uninfluenced by their overall cognitive status.

HDRels

Compared to their controls, HDRels obtained significantly a lower score in the MoCA test ($U = 95.5$, $p = .01$). Also, while no significant differences emerged on the PPT test ($U = 160.5$, $p = .54$), HDRels showed significantly poorer performance on the KDT ($U = 89$, $p = .01$). Significant differences were also observed in the groups' global syntactic scores ($U = 72, p < .001$). This result was driven by an impairment of HDRels on 'Embedded Sentences' ($U = 90, p < .005$), as their performance on 'Touching A with B' was preserved ($U = 142, p = .08$). Further analyses with MoCA scores as covariate showed the same between-group differences on the KDT, $F(1, 35) = 6.08, p = .02$, global syntactic performance, F (1, 35) = 8.91, $p = .01$, and 'Embedded Sentences', F (1, 35) = 12.83, $p < .005$. Also, after covariation, both groups remained without significant differences on the PPT test, $F(1, 35) = .01, p = .92$ and 'Touching A with B', $F(1, 35) = 1.68, p = .2$. In brief, HDRels evinced significant dysfunctions in action semantics and complex syntactic processing, which occurred independently of their general cognitive functioning.

Discussion

This is the first study jointly assessing action semantics and syntax in HDPs and HDRels. Our findings highlight the sensitivity of both domains to tap probable frontostriatal alterations even before the onset of clinical symptoms. First, while patients showed difficulties to process both action- and non-action-related concepts, asymptomatic subjects were selectively impaired in the former skill. Second, whereas the patients were impaired in two separate syntactic tests, their relatives showed deficits only in the most demanding one. Notably, these disturbances held even when controlling for the patients' overall cognitive state. Such results highlight the relevance of these high-order functions as candidate biomarkers to be further assessed for robustness at the single-subject level. Below we discuss each set of findings in turn.

Action semantics

Huntington's disease patients were significantly impaired in associating both action and object concepts. *Prima facie*, this result may seem surprising, given that whereas action

semantics is critically grounded in frontostriatal networks, object-related information mainly relies on temporal and otherwise posterior brain regions (Bak & Hodges, 2003; García & Ibáñez, 2016b; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). However, in HD and other neurodegenerative diseases characterized by frontostriatal disruptions, various clinical stages involve widespread atrophy in temporal, parietal, and even occipital regions (Tabrizi *et al.*, 2009). This can be expected in our patient sample, given that it had a mean of over 3 years since diagnosis. In this sense, research on patients with PD a few years after diagnosis has revealed significant deficits in both semantic domains, as tapped through verbal (Cotelli *et al.*, 2007; Crescentini, Mondolo, Biasutti, & Shallice, 2008) and non-verbal (Bocanegra *et al.*, 2015) tasks. Thus, trans-categorical semantic deficits in HDPs may reflect the impact of neurodegeneration beyond the striatum and the frontal lobes.

Notwithstanding, the above studies converge in pointing to a differential link between frontostriatal networks and action-related concepts. Working with PD patients (Cotelli *et al.*, 2007; Crescentini *et al.*, 2008) found greater deficits for action verbs than nouns. By the same token, using the KDT and the PPT test, Bocanegra *et al.* (2015) found that only action-semantic deficits occurred independently of extralinguistic, domain-general dysfunctions. Our covariation results corroborate the latter pattern, as only KDT deficits held irrespective of the patients' overall cognitive status. Therefore, data from HDPs reinforce the view that action-semantic impairments constitute a *sui generis* disturbance following frontostriatal degeneration.

Results from HDRels align with the previous claim, as these subjects exhibited selective action-semantic difficulties with fully spared performance on the object association task. This extends findings by Kargieman *et al.* (2014), who found that motor-language coupling deficits in HDPs were also present in asymptomatic first-degree relatives. Such results are noteworthy in that they emerged although striatal disturbances cannot be assumed to be present in each of the sample's subjects.

The evidence, we propose, further highlights the distinctively critical role of frontostriatal circuits in grounding action semantics, despite their potentially more general role in lexical processing at large (García & Ibáñez, 2016b; García, Carrillo, *et al.*, 2016). Indeed, a recent study showed that whereas the striatum is implicated in processing both action (verbs) and non-action (nouns) stimuli, basal ganglia damage correlates with the recruitment of non-canonical (i.e., non-frontal) networks for processing the former category (Abrevaya *et al.*, 2017). Moreover, as was the case with the clinical group, the deficits in HDRels occurred independently of cognitive status, indicating that the proposed link between frontostriatal pathways and action semantics may not mediated by additional neurocognitive mechanisms.

Still, the point could be raised that action-semantic tasks involve higher processing demands than object-semantic tasks, so that the selective deficit observed in HDRels could be reflecting a difficulty-related effect. However, this possibility is undermined by studies comparing processing of action and abstract verbs. As the latter are less concrete and imaginable than the former (e.g., Dalla Volta, Fabbri-Destro, Gentilucci, & Avanzini, 2014; García & Ibáñez, 2016a), they are harder to process even when matched for other relevant variables. Despite such differences, patients with motor disorders evince selective action-verb deficits even when processing of the even more demanding abstract-verb category is spared, as observed in PD (Fernandino *et al.*, 2013) and genetic ataxia with preserved MoCA performance (García, Abrevaya, *et al.*, 2017). In line with this evidence, the selective action-semantic impairment in HDRels is probably reflects the specific relation between motor networks and action

semantics, rather than non-specific, demand-related effects. Thus, deficits in this domain may constitute selective high-order markers of subtle frontostriatal deterioration in prodromal stages of HD.

Syntax

Huntington's disease patients exhibited generalized syntactic deficits. In fact, difficulties in this group were significant for both sentence-processing tasks, despite their differential demands – whereas 'Touching A with B' has minimal working memory requisites and could in principle be performed by means of sequential processing, 'Embedded Sentences' relies heavily on working memory and involves more complex hierarchical computations (Bocanegra *et al.*, 2015). This suggests that full-blown frontostriatal disruptions can compromise syntactic abilities at large. Indeed, multiple tasks with sentences of varying complexity have revealed grammatical deficits in both patients with HD (De Diego-Balaguer *et al.*, 2008; Jensen, Chenery, & Copland, 2006; Saldert, Fors, Stroberg, & Hartelius, 2010; Sambin *et al.*, 2012; Teichmann, Dupoux, Cesaro, & Bachoud-Levi, 2008; Teichmann, Dupoux, Kouider, & Bachoud-Levi, 2006; Teichmann, Gaura, *et al.*, 2008) and PD (Grossman *et al.*, 2003; Hochstadt, Nakano, Lieberman, & Friedman, 2006; Lee, Grossman, Morris, Stern, & Hurtig, 2003; Lieberman *et al.*, 1992; Zanini *et al.*, 2004). Thus, our findings add to a growing empirical corpus pointing to the basal ganglia and their frontal connections as putative substrates of grammatical abilities (Ardila, Bernal, & Rosselli, 2015; Ullman, 2001, 2004).

Interestingly, the patients' deficits in both tests survived covariation with MoCA scores, which mirrors previous results showing that syntactic processing impairments in HD are independent of working memory skills (Sambin *et al.*, 2012). However, this does not imply that *all* grammatical deficits following frontostriatal damage are *sui generis* in nature. Indeed, research on clinical PD samples has shown that executive dysfunction was associated with performance on 'Embedded Sentences' but not with 'Touching A with B' scores (Bocanegra *et al.*, 2015; García *et al.*, 2017). Therefore, although the syntactic impairment in HDPs seems independent of their overall cognitive profile, this does not rule out a differential relation between specific grammatical subskills and executive functions in particular. Further research would be needed to explore such particularities.

Notwithstanding, our most important finding concerned HDRels. Crucially, these subjects also evinced significant syntactic deficits despite being fully asymptomatic. Together with evidence that pre-manifest HD mutation carriers have distinctive difficulties in transferring newly learnt grammatical regularities (De Diego-Balaguer *et al.*, 2008), our finding corroborates that language tasks may offer sensitive biomarkers of motor network degeneration, even before the onset of disease (García & Ibáñez, 2014, 2016b).

More particularly, in contrast to the generalized syntactic impairment observed in HDPs, global syntactic deficits in HDRels were driven by their performance on 'Embedded Sentences', given that they were as accurate as controls on 'Touching A with B'. Specific syntactic subskills would thus appear to be differentially compromised following striatal damage. Previous research on clinical HD samples supports this view, as patients exhibited deficits in some grammatical skills (processing of the so-called Principle C) but not in others (e.g., processing of centre-embedded and right-branching relatives) (Sambin *et al.*, 2012). In our case, the dissociative pattern may reflect the tasks' differential demands: whereas 'Touching A with B' involves identifying functional roles of nouns determined by an adjacent word, 'Embedded Sentences' requires more complex

hierarchical computations for a relative clause to be fully parsed before subject-verb agreement can be established (Bocanegra *et al.*, 2015).

Remarkably, asymptomatic mutation carriers at risk for PD also showed a dissociation between these very tasks (García *et al.*, 2017). However, they exhibited an opposite pattern, as they were impaired in 'Touching A with B' and unimpaired in 'Embedded Sentences'. These differences could be related to the differential physiopathology of HD and PD in pre-clinical stages. Whereas pre-manifest HD mainly involves atrophy of the caudate and the putamen (Tabrizi *et al.*, 2009), PD is first characterized by degeneration in the substantia nigra (Rodriguez-Oroz *et al.*, 2009). Very tentatively, given the tasks' processing requirements and the double dissociation just identified, it could be surmised that hierarchical aspects of syntactic parsing and functional role assignment are differentially subserved by telencephalic (caudate and putamen) and mesencephalic (substantia nigra) portions of the basal ganglia, respectively. Though speculative, this pattern aligns with computational evidence that different subportions of the striatum play distinct roles during syntactic processing (Szalisznyó, Silverstein, Teichmann, Duffau, & Smits, 2017).

Note, finally, that deficits in our study proved independent of the patients' overall cognitive profile, just like those reported by García *et al.* (2017) were independent of the patients' executive dysfunction. This suggests that the hypothesized differential roles ascribed to the above subregions may be specifically grammatical (i.e., not epiphenomenal or secondary to extralinguistic dysfunction). Such a conjecture, derived from two separate and complementary pre-clinical models, opens exciting opportunities to understand the fine-grained syntactic specializations of distinct substructures within the basal ganglia. Yet, the evidence already warrants non-trivial theoretical and clinical reflections, as detailed below.

Frontostriatal bases of action semantics and syntax: Why, how, and where to

Why should action semantics and syntax, two seemingly disparate high-order domains, become jointly compromised after damage to frontostriatal networks? The reason, we argue, is that both are functionally germane to the putative motor functions of these circuits. Specifically, our contention is that just like frontostriatal networks are critical for mapping and sequencing hierarchically organized movement patterns (Doyon *et al.*, 2009; Grillner, Hellgren, Menard, Saitoh, & Wikstrom, 2005; Matsumoto, Hanakawa, Maki, Graybiel, & Kimura, 1999; Turner & Desmurget, 2010), so are they specialized for the conceptual mapping of movement (action semantics) and the sequencing of hierarchically organized lexical patterns (syntax) (Bak, 2013; Cardona *et al.*, 2013; García & Ibáñez, 2016b; Pulvermüller, 2005; Ullman, 2001). Such a view aligns with the embodied cognition framework, which posits that high-order domains are grounded in sensorimotor mechanisms mediating relevant bodily and situated experiences (Barsalou, 1999; Gallese & Lakoff, 2005). Indeed, from an embodied perspective, joint action-semantic and syntactic deficits following frontostriatal disruptions are not only readily interpretable, but also predictable.

Importantly, these embodied links can be justifiably hypothesized to involve fine-grained contributions of specific hubs within the frontostriatal circuitry. First, consider action semantics. When atrophy is sufficiently widespread for subjects' to reach clinical stages, both action and object concepts may become compromised (Bocanegra *et al.*, 2015, 2017; Cotelli *et al.*, 2007; Crescentini *et al.*, 2008), although this is not necessarily the case (Bak, 2013; García & Ibáñez, 2014). However, evidence from HDRels suggests

that incipient and more focal damage of the neostriatum, in particular, could more selectively compromise the embodied domain of action semantics. Accordingly, the caudate and the putamen may be speculated to constitute the most critical hubs grounding action information within the basal ganglia (although this conjecture would require testing via neuroimaging techniques). Second, as argued above, functional specializations within the basal ganglia may also be postulated for syntactic subdomains. The caudate and the putamen, in combination with cortical regions, such as Brodmann area 44 (Zaccarella & Friederici, 2017), may prove more critical for processing complex hierarchical structures than for functional role assignment. This conjecture contradicts models assuming that the striatum plays an all-encompassing role for syntax at large (Ullman, 2001), and it mirrors conclusions from studies on HD (Sambin *et al.*, 2012) and PD (García *et al.*, 2017).

Whereas such fine-grained distinctions may be clouded in clinical samples (especially when neurodegeneration has surpassed a given threshold), research with prodromal samples offers unique opportunities to identify them. In this sense, while the relevance of clinical brain-lesioned samples has been underscored to better understand cognitive systems in the imaging era (Rorden & Karnath, 2004), our findings highlight the major importance of *pre-clinical* evidence to formulate even more detailed models of specific neurocognitive mechanisms. We believe that future research may greatly benefit from exploiting this sampling approach.

Clinical implications

Compared to other motor disorders, such as PD, HD stands out for its pervasive combination of motor, cognitive, and psychiatric deficits. With a prevalence of 2.71 per 100,000 individuals worldwide (and over 5.7 in Europe, North America, and Australia) (Pringsheim *et al.*, 2012), this condition undermines the daily life of myriad patients and their families. Moreover, its autosomal dominant nature means that the offspring of an affected person has a 50% chance of developing it and joining the clinical population. The associated social and financial burdens call for innovations to promote early detection, in the hope of delaying or reducing the disease's functional impact.

Several methods may afford relevant biomarkers, as recently illustrated in the TRACK-HD study (Tabrizi *et al.*, 2009). Available options range from genetic (e.g., exome sequencing), biochemical (e.g., cerebrospinal fluid), and neuroimaging (e.g., grey matter density, connectivity) measurements to behavioural assessment (DeKosky & Marek, 2003). Our study highlights the potential benefits of the latter. First, we observed reduced MoCA scores in HDRels, as previously reported in other studies (e.g., Baez *et al.*, 2015). This suggests that a brief, domain-general screening test may be sensitive enough to detect possible subclinical deterioration of frontostriatal circuits. However, syntactic and action-semantic tasks may be even more sensitive to such an end. Evidence from other motor disorders, such as PD (Bocanegra *et al.*, 2015) and genetic ataxia (García, Abrevaya, *et al.*, 2017) shows that both domains can become compromised even when MoCA scores are normal. Moreover, HDRels may feature high-order difficulties even in the absence of MoCA deficits (e.g., Baez *et al.*, 2016), whereas mutation carriers at risk for other frontostriatal motor conditions have been observed to feature syntactic deficits even when performance in domain-general batteries is spared (García *et al.*, 2017). In addition, performance on the MoCA is significantly reduced across the most varied neuropsychiatric disorders (e.g., Copersino *et al.*, 2009; Davis *et al.*, 2015; Oudman *et al.*, 2014), whereas action semantics and syntax are typically spared in conditions which do not

affect motor networks (García & Ibáñez, 2014; Ullman, 2001). Thus, action-semantic and syntactic tasks seem even more sensitive and specific than domain-general instruments to reveal possible subclinical frontostriatal disruptions – although more direct assessments of this issue are needed in future research.

Despite their limitations, these tools are non-invasive, inexpensive, and easy to apply. Thus, they can be administered repeatedly through the course of pre-clinical stages to indirectly monitor the integrity of specific neurofunctional systems. Moreover, they allow researchers to quickly fine-tune stimuli and experimental conditions to hone their specificity as new findings emerge in relevant fields. Although more replication is needed, task tapping action semantics and syntax, together with action-language coupling paradigms (Kargieman *et al.*, 2014), may offer robust indications of subtle frontostriatal disruptions (García & Ibáñez, 2016b; García *et al.*, 2017).

Of course, these claims should be entertained with caution. As HDRels lacked genetic testing, we were unable to ascertain how many of them carried huntingtin mutations. Therefore, as in previous works with similar samples (Baez *et al.*, 2015, 2016; Kargieman *et al.*, 2014), the main clinical contribution of our work is showing that these domains are compromised at the group level, which constitutes a crucial step to conduct further research on single subjects with a well-established genetic profile. Therein lies the ultimate test to assess the validity of these embodied domains as pre-clinical biomarkers of HD.

Such an endeavour would involve several steps. First, the instruments reported herein should be complemented with other semantic and syntactic tasks featuring a larger number of trials and more scrupulous control of fine-grained variables – for example, see the reviews by Cardona *et al.* (2013) and García and Ibáñez (2016b). If necessary, abridged versions of those tasks could be constructed to be incorporated in time-constrained screening protocols.

Second, individual subjects confirmed to be gene carriers and non-carriers should perform those tasks and their performance should be compared to that of healthy control samples, on the assumption that only the former should evince the deficits documented herein. The necessary analysis could be performed, for example, through Crawford's modified two-tailed *t*-test (Crawford & Garthwaite, 2002, 2012; Crawford, Garthwaite, & Howell, 2009; Crawford, Garthwaite, & Ryan, 2011; Crawford & Howell, 1998), which proves robust for non-normal distributions, presents low rates of type-I error, and has been successfully used in previous single-case studies (Couto *et al.*, 2013, 2014; García, Sedeño, Herrera Murcia, Couto, & Ibáñez, 2017; García, Abrevaya, *et al.*, 2017; Straube *et al.*, 2010). The evidence thus obtained would be critical to test the usefulness of the proposed domains to detect pre-clinical deficits at the single-subject level.

Third, the most sensitive instruments should be subjected to norming studies, so as to establish reliable parameters of performance in neurotypicals across multiple age ranges. Ideally, normative data should be gleaned in various socio-geographical settings, to account for the possible impact of cultural variability. Finally, individual HDRels could be tested with the selected tasks and their performance could be compared with that of demographically relevant norms. Evidence for selective deficits, such as the ones documented in our study, could then be considered valid and reliable indexes of incipient frontostriatal dysfunction.

This would be particularly useful in families for whom genetic, biochemical, or imaging studies are too costly or scantily available, which is often the case in communities characterized by a high prevalence of neurodegenerative disorders. For example, the

region targeted in our study (Juan de Acosta, Colombia) is a genetic isolate including high rates of poverty alongside high rates of familial HD (Castilhos *et al.*, 2016; De Castro & Restrepo, 2015). In contexts such as this, the proposed extensions of the present study could promote useful breakthroughs in the quest for sensitive, affordable, and widely available biomarkers of prodromal frontostriatal atrophy.

Limitations and avenues for further research

Our work features a number of limitations which pave the way for further research. Unfortunately, HDRels lacked genetic testing, which prevented us from assessing correlations between behavioural results and the expression of possible mutations. Although asymptomatic relatives constitute a well-established vulnerability group at risk for HD, even in the absence of confirmed genetic alterations (Baez *et al.*, 2015, 2016; Dorsey, 2012; Giordani *et al.*, 1995; Kargieman *et al.*, 2014; Markianos *et al.*, 2008; Panegyres & Goh, 2011), it would be most informative to replicate our study in combination with exome sequencing or other forms of genetic assessment – for an example, see García, Abrevaya, *et al.* (2017). Also, we were unable to collect neuroimaging data to corroborate the hypothesized roles of specific frontostriatal hubs to different subdomains. Future studies should aim to replicate and extend our findings with genetic testing and imaging (e.g., fMRI) correlates. It would also be useful to more directly test our functional hypotheses via deep brain stimulation of specific basal ganglia substructures during task performance – see Tomasino *et al.* (2014), Zanini *et al.* (2009). Third, while our results seem robust at the group level, they should be further tested in studies designed to assess their relevance as potential subject-level biomarkers. Finally, our assessment of extra-linguistic functions was restricted to only one test. Although our findings are consistent with the view that action-semantic and syntactic deficits in HDPs and HDRels are *sui generis* in nature, this claim should be more thoroughly tested through the incorporation of additional domain-general tests and further relevant analyses. In sum, future elaborations of our study along these lines may afford both theoretical developments and translational innovations to detect and track alterations leading to HD.

Conclusion

This is the first study to jointly assess action semantics and syntactic skills as possible prodromal markers of frontostriatal disruption in individuals at risk for HD. Our key finding was that these subjects were impaired in both domains, and that their deficits were unrelated to their overall cognitive state. This highlights the relevance of tasks tapping embodied mechanisms as potential markers of incipient neurofunctional alterations, while showcasing the possibilities of research on pre-clinical samples for neurocognitive modelling. Replications and extensions of our study could inspire breakthroughs in both areas.

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Supporting Information

The following supporting information may be found in the online edition of the article:

Data S1. Characterization of HDRels.