

Language Deficits as a Preclinical Window into Parkinson's Disease: Evidence from Asymptomatic Parkin and Dardarin Mutation Carriers



INS is approved by the American Psychological Association to sponsor Continuing Education for psychologists. INS maintains responsibility for this program and its content.

Adolfo M. García,^{1,2,3} Lucas Sedeño,^{1,2} Natalia Trujillo,^{4,5,6} Yamile Bocanegra,^{5,6} Diana Gomez,^{4,6} David Pineda,^{5,6} Andrés Villegas,⁶ Edinson Muñoz,⁷ William Arias,⁸ AND Agustín Ibáñez^{1,2,9,10,11}

¹Laboratory of Experimental Psychology and Neuroscience (LPEN), Institute of Cognitive and Translational Neuroscience (INCYT), INECO Foundation, Favaloro University, Buenos Aires, Argentina

²National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

³Faculty of Elementary and Special Education (FEEyE), National University of Cuyo (UNCuyo), Mendoza, Argentina

⁴Mental Health Group, School of Public Health, University of Antioquia (UDEA), Medellín, Colombia

⁵Group of Neuropsychology and Conduct (GRUNECO), Faculty of Medicine, University of Antioquia (UDEA), Medellín, Colombia

⁶Neuroscience Group, Faculty of Medicine, University of Antioquia (UDEA), Medellín, Colombia

⁷Departamento de Lingüística y Literatura, Facultad de Humanidades, Universidad de Santiago de Chile, Santiago, Chile

⁸Molecular Genetics Laboratory, University of Antioquia (UDEA), Medellín, Colombia

⁹Universidad Autónoma del Caribe, Barranquilla, Colombia

¹⁰Center for Social and Cognitive Neuroscience (CSCN), School of Psychology, Universidad Adolfo Ibáñez, Santiago de Chile, Chile

¹¹Centre of Excellence in Cognition and its Disorders, Australian Research Council (ACR), Macquarie University, Sydney, Australia

(RECEIVED March 5, 2016; FINAL REVISION June 6, 2016; ACCEPTED July 25, 2016)

Abstract

Objectives: The worldwide spread of Parkinson's disease (PD) calls for sensitive and specific measures enabling its early (or, ideally, preclinical) detection. Here, we use language measures revealing deficits in PD to explore whether similar disturbances are present in asymptomatic individuals *at risk* for the disease. **Methods:** We administered executive, semantic, verb-production, and syntactic tasks to sporadic PD patients, genetic PD patients with PARK2 (parkin) or LRRK2 (dardarin) mutation, asymptomatic first-degree relatives of the latter with similar mutations, and socio-demographically matched controls. Moreover, to detect *sui generis* language disturbances, we ran analysis of covariance tests using executive functions as covariate. **Results:** The two clinical groups showed impairments in all measures, most of which survived covariation with executive functions. However, the key finding concerned asymptomatic mutation carriers. While these subjects showed intact executive, semantic, and action-verb production skills, they evinced deficits in a syntactic test with minimal working memory load. **Conclusions:** We propose that this *sui generis* disturbance may constitute a prodromal sign anticipating eventual development of PD. Moreover, our results suggest that mutations on specific genes (PARK2 and LRRK2) compromising basal ganglia functioning may be subtly related to language-processing mechanisms. (*JINS*, 2017, 23, 150–158)

Keywords: Sporadic Parkinson's disease, Genetic Parkinson's disease, PARK2, LRRK2, Preclinical mutation carriers, language

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder in which basal ganglia (BG) deterioration progressively compromises motor function and high-level cognition (McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Samii, Nutt, & Ransom, 2004; Svenningsson, Westman, Ballard, & Aarsland, 2012). Its growing prevalence, now estimated at

1% in the elderly population (Samii et al., 2004), creates major socio-financial burdens. A need thus arises for measures enabling early (and, ideally, preclinical) detection to diminish its worldwide impact.

Linguistic tasks are promising tools in this regard (Bocanegra et al., 2015; García & Ibáñez, 2014). Indeed, executive deficits in PD (McKinlay et al., 2010) are typically accompanied by impairments of syntax, action semantics, and action-verb processing (Bocanegra et al., 2015; Cardona et al., 2013; García & Ibáñez, 2014; García et al., 2016). In line with embodied cognition models (Barsalou, 1999; Cardona et al., 2013; Gallese & Lakoff, 2005; García & Ibáñez, 2016),

Correspondence and reprint requests to: Agustín Ibáñez, Institute of Cognitive and Translational Neuroscience & CONICET; Pacheco de Melo 1860, C1126AAB, Buenos Aires, Argentina. E-mail: aibanez@ineco.org.ar

such findings indicate that networks specialized for sequencing hierarchically organized motor patterns (such as the basal ganglia) are critical for homologous linguistic operations—sequencing hierarchically organized lexical patterns, namely, syntax (Ullman, 2004, 2008)—and for processing action-related information (Bak, 2013)—as captured in recent action-language coupling models based on dynamic networks and predictive-coding principles (García & Ibáñez, 2016). In this unprecedented study, we explore whether such language disturbances are also present in asymptomatic individuals *at risk* for PD.

While most patients present sporadic forms of the disease, genome-wide association studies have identified 28 risk loci, including mutations in PARK2 or LRRK2 (Nalls et al., 2014). Since PD features prolonged prodromal stages (Braak et al., 2002), research on distinctive deficits shared by symptomatic and asymptomatic mutation carriers may reveal preclinical impairments and open opportunities for new therapeutic approaches. Here, we pursue this possibility by comparing linguistic skills among sporadic PD patients (PD-Sp), genetic PD patients with PARK2 or LRRK2 mutation (PD-Gen), asymptomatic first-degree relatives of the latter with similar mutations (PD-Rel), and healthy controls.

Our focus is on PD-Rel. Though free of motor symptoms, these individuals carried PARK2 or LRRK2 gene mutations. The latter is the main genetic determinant of PD (Goldwurm et al., 2005), and it was present in most subjects. Mutations at the LRRK2 gene present an autosomal dominant pattern and lead to substantia nigra atrophy. Yet, the expression of this gene is influenced by modifier genes which co-determine symptom severity and presentation age. Although disease onset will typically occur in late life (Goldwurm et al., 2005), individuals with this mutation will eventually manifest PD.

Accordingly, we hypothesized that PD patients would be impaired across language domains, and that at least some of those deficits would also be present in PD-Rel. Evidence of such shared deficits would highlight the relevance of verbal measures to tap motor-network integrity even in the absence of movement disorders.

METHODS

Participants

The study included 106 adult participants from Antioquia, Colombia. This region is a genetic isolate with high rates of familial dementia, in general (Acosta-Baena et al., 2011; Arcos-Burgos & Muenke, 2002), and PD, in particular (Pineda-Trujillo et al., 2001, 2006). The clinical samples comprised 33 PD-Sp patients, with no expression of any risk mutation tested; and eight PD-Gen patients, showing at least one of these risk mutations: the autosomal recessive C212Y mutation on PARK2 (caused by G to A transition at 736 position), the 321-322 GT insertion on exon 3 ($321 \pm 322\text{insGT}$) also on PARK2 (Pineda-Trujillo et al., 2001), or the autosomal dominant mutation on gene LRRK2

(G2019S) (Goldwurm et al., 2005). Clinical diagnosis of PD was made by expert neurologists (A.V. and O.B.) following current criteria (Hughes, Daniel, Kilford, & Lees, 1992). Motor impairments were assessed with the Unified Parkinson's Disease Rating Scale (section III). Disease stage was rated with the Hoehn & Yahr scale (except for five subjects from the PD-Sp group with unilateral movement disorders, all patients showed bilateral motor compromise). Functional skills were evaluated with the Barthel Index and the Lawton & Brody Index. All patients were evaluated during the “on” phase of medication.

PD-Rel comprised nine individuals unaffected by PD. All of them carried mutations on the PARK2 ($N = 3$) or LRRK2 ($N = 6$) genes, whose associated neuropathology is characterized by nigral degeneration. Homozygous (and, less often, heterozygous) expression of PARK2 mutations (Pineda-Trujillo et al., 2006) has a penetrance of 80–90% around age 40. Instead, penetrance of LRRK2 mutations varies from 17% at age 50 to 85% at age 70 (Goldwurm et al., 2005), showing that late disease onset is most typical.

The clinical and subclinical samples were matched for gender, age, and education with two groups of healthy controls ($N = 36$ and 20 , respectively) featuring no familial history of PD. Additional participant data and statistical comparisons between groups can be found in Table 1.

All participants were free of psychiatric conditions and gave written informed consent. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethical Research Committee of Antioquia University's Faculty of Medicine.

Materials

Participants completed a neuropsychological evaluation tapping executive, semantic, and linguistic domains typically compromised since early disease stages (Bocanegra et al., 2015; Cardona et al., 2013; García & Ibáñez, 2014; McKinlay et al., 2010). Executive functions were examined through the INECO Frontal Screening (IFS) battery (Torralva, Roca, Gleichgerrcht, Lopez, & Manes, 2009), which taps domains such as motor programming, conflict resolution, inhibitory control, and working memory. This battery comprises 20 items, and its maximum score is 30.

Semantic representation of objects and actions was assessed through the Pyramids and Palm Trees (PPT) test and the Kissing and Dancing Test (KDT), respectively. In both tests, participants must choose which of two pictures is most closely related to a cue picture. Each test comprises 52 trials, and the maximum score is 52. These instruments have revealed specific deficits in PD (Bocanegra et al., 2015; Cardona et al., 2014; Ibanez et al., 2013) and other motor diseases, such as Huntington's disease (Kargieman et al., 2014) and Cockayne syndrome (Baez et al., 2013). Also, action-verb processing was assessed through the Action Naming subtest of the Boston Diagnostic Aphasia Examination (BDAAE), which requires naming 12 pictures

Table 1. Demographic data and clinical evaluation

Demographic variables	Controls	PD-Sp	PD-Gen	ANOVA	Controls	PD-Rel	ANOVA
	<i>N</i> = 36	<i>N</i> = 33	<i>N</i> = 8	<i>p</i> -value	<i>N</i> = 20	<i>N</i> = 9	<i>p</i> -value
<i>Gender (F:M)</i>	17:19	17:16	4:4	.93	13:7	8:1	.15*
<i>Age (years)</i>	58.55 (8.28) [34/74]	60.36 (12.08) [33/83]	60.87 (10.85) [45/81]	.71*	56.60 (8.34) [34/74]	50.33 (18.6) [29/89]	.21*
<i>Education (years)</i>	12.02 (4.37) [5/25]	11.54 (4.9) [3/21]	10.37 (4.92) [3/17]	.65*	12.55 (4.5) [5/25]	13.67 (4) [5/17]	.53*
Clinical variables							
PD-Sp vs. PD-Gen							
<i>UPDRS-III</i>	31.27 (12.34) [8/59]	27.87 (25.64) [11/74]	.58*				
<i>H&Y</i>	2.34 (0.65) [1/3]	2.37 (0.44) [1.5/3]	.91*				

Note. Values are expressed as mean (*SD*), except for gender. Ranges are provided between brackets [Min / Max].

PD-Sp = sporadic Parkinson's disease patients; PD-Gen = genetic Parkinson's disease patients with parkin or dardarin mutation; PD-Rel = asymptomatic first-degree relatives of PD-Gen with parkin or dardarin mutation; UPDRS-III = Unified Parkinson's Disease Rating Scale, part III; H&Y = Hoehn & Yahr scale.

**p*-values were calculated through ANOVA tests.

depicting motor actions (the maximum score is 12). This skill is also differentially compromised in PD (Herrera & Cuetos, 2012).

Finally, syntactic comprehension was assessed with two BDAE subtests: Embedded Sentences and Touching A with B. In both measures, participants must choose which of four pictures best represents a given utterance. Global syntactic performance was calculated by integrating both subtests' scores (22 items, with a maximum score of 22). However, we also calculated separate scores, as each measure taps different syntactic processes. Stimuli in Embedded Sentences (10 items, maximum score = 10) include relative clauses in their subject (e.g., *The woman who is fat is kissing her husband*) or direct object (e.g., *The girl is chasing the boy who is wearing boots*). Instead, Touching A with B (12 items, maximum score = 12) features phrases with the verb *touching* and two nouns: in some cases, both nouns are coordinated direct objects (e.g., *touching the spoon and the scissors*); in others, one is a direct object and the other an instrumental adjunct (*touching the scissors with the comb*). Thus, while the former task is more crucially associated with executive (viz., working memory) skills, the latter requires identifying functional roles within predicates and depends less critically on extralinguistic mechanisms (Bocanegra et al., 2015). These tasks have revealed subtle deficits in motor disorders, including Huntington's disease (Azambuja et al., 2012), Cockayne syndrome (Baez et al., 2013), and, crucially, PD (Bocanegra et al., 2015).

Statistical Analysis

Demographic and experimental data were analyzed using analysis of variance (ANOVA) and Tukey's honest significant difference (HSD) *post hoc* tests (except for gender, which was analyzed *via* Pearson chi-square tests). Effect sizes were calculated with Eta squared (η^2). Considering the current debate on whether language deficits in PD are influenced by executive dysfunction (Bocanegra et al., 2015;

Hochstadt, Nakano, Lieberman, & Friedman, 2006), we addressed the possible influence of executive skills on language measures. To this end, the latter were also scrutinized with analysis of covariance (ANCOVA) using IFS scores as covariates. For brevity, the Results section offers only verbal descriptions of the observed differences. Full statistics are offered in Tables 2 and 3, and summarized in Figure 1.

RESULTS

Sporadic and Genetic Patients

Executive performance was significantly better for controls than PD-Sp and PD-Gen ($p < .01$). The same was true of all language measures (all $ps < .03$). Of interest, deficits in PPT, KDT, Action Naming, global syntactic performance, or Touching A with B were not influenced by executive impairment (all $ps < .05$). The only difference that disappeared for both patient groups after adjusting for IFS scores corresponded to Embedded Sentences ($p = .55$). Finally, no analysis showed differences between PD-Sp and PD-Gen (Figure 1 and Table 2). In sum, except for complex-sentence processing impairments, other language deficits in both clinical groups were independent from executive dysfunction.

Asymptomatic Mutation Carriers

Executive performance was similar between PD-Rel and controls ($p = .25$). Likewise, no between-group differences were observed in PPT ($p = .09$), KDT ($p = .10$), or Action Naming ($p = .14$). These patterns remained unchanged after covariation with IFS scores. However, global syntactic performance was significantly poorer for PD-Rel ($p = .04$). This difference was driven by the results of one specific subtest. Whereas PD-Rel did not differ from controls in the Embedded Sentences task ($p = .14$), they showed significantly lower scores in Touching A with B ($p < .01$). The latter two

Table 2. Statistical details of the performance of PD-Sp, PD-Gen, and matched healthy controls on the IFS and all semantic and language measures

Task	ANOVA						Post hoc comparison (Tukey's HSD)		
	PD-Sp	PD-Gen	Controls	F	p	n ²	PD-Sp vs controls	PD-Gen vs controls	PD-Sp vs PD-Gen
IFS	19.63 (4.16)	19.75 (2.6)	23.61 (1.9)	15.2	<.01	0.29	<.01	<.01	.99
PPT	48.33 (2.94)	48.37 (3.2)	51.02 (1.13)	12.98	<.01	0.25	<.01	.01	.99
KDT	47.54 (3.81)	47.37 (2.92)	50.88 (1.3)	13.82	<.01	0.27	<.01	<.01	.98
Action naming	10.9 (1.42)	10.87 (1.12)	11.97 (0.17)	10.88	<.01	0.22	<.01	.01	.99
Global syntactic performance	88.81 (11.9)	88.64 (11.77)	98.44 (2.96)	11.41	<.01	0.23	<.01	.01	.99
Embedded sentences	9.3 (1.21)	9.5 (1.51)	9.94 (0.23)	4.12	.02	0.1	.01	.44	.85
Touching A with B	10.15 (1.73)	9.87 (1.45)	11.69 (0.57)	14.88	<.01	0.28	<.01	<.01	.85
ANCOVA with IFS as covariate							Post hoc comparison (Tukey's HSD)		
PPT				3.63	.03	0.08	<.01	.01	.99
KDT				4.57	.01	0.1	<.01	<.01	.98
Action naming				4.18	.02	0.1	<.01	.01	.99
Global syntactic performance				3.33	.04	0.07	<.01	.01	.99
Embedded sentences				0.6	.55	0.01	—	—	—
Touching A with B				6.19	<.01	0.14	<.01	<.01	.98

Note. Values are expressed as mean (SD).

PD-Sp = sporadic Parkinson's disease patients; PD-Gen = genetic Parkinson's disease patients with parkin or dardarin mutation; IFS = INECO Frontal Screening battery; PPT = Pyramids and Palm Tress test; KDT = Kissing and Dancing Test.

Table 3. Statistical details of the performance of PD-Rel and matched healthy controls on the IFS and all semantic and language measures

Task	ANOVA					
	PD-Rel	Controls	F	p	n ²	
IFS	22.22 (4.81)	23.7 (2.1)	1.35	.25	0.05	
PPT	49.44 (3.12)	50.85 (1.18)	3.16	.09	0.1	
KDT	49.22 (4.52)	51 (1.02)	2.88	.1	0.1	
Action naming	10.77 (3.67)	12 (0)	2.32	.14	0.08	
Global syntactic performance	91.44 (15.04)	99.17 (1.7)	4.69	.04	0.15	
Embedded sentences	9.22 (2.33)	10 (0)	2.32	.14	0.08	
Touching A with B	11 (1)	11.8 (0.41)	9.57	<.01	0.26	
ANCOVA with IFS as covariate						
PPT			1.68	.20	0.03	
KDT			1.6	.21	0.05	
Action naming			1.13	.29	0.03	
Global syntactic performance			3.15	.08	0.09	
Embedded sentences			1.13	.3	0.03	
Touching A with B			8.1	<.01	0.23	

Note. Values are expressed as mean (SD).

PD-Rel = asymptomatic first-degree relatives of PD-Gen with parkin or dardarin mutation; IFS = INECO Frontal Screening battery; PPT = Pyramids and Palm Tress test; KDT = Kissing and Dancing Test.

results remained after covariation with IFS scores (Figure 1 and Table 3). In short, PD-Rel evinced selective, *sui generis* difficulties in a syntactic task which does not crucially rely on executive skills.

DISCUSSION

Both PD-Sp and PD-Gen showed pervasive language deficits. Their impairments in action semantics, object semantics, and action naming replicate previous findings in PD (Cotelli et al., 2007) and other motor disorders, such as motor neuron

disease and amyotrophic lateral sclerosis (Bak & Hodges, 2004). These deficits were not influenced by executive abilities. However, executive skills were differentially related to syntactic subdomains: whereas executive dysfunction did not influence the patients' deficits to identify functional roles within predicates, it did account for their difficulties in complex-sentence processing. These findings mirror those from a study on early sporadic PD patients (Bocanegra et al., 2015), corroborating the multidimensional role of the BG in language (Cardona et al., 2013).

The involvement of executive functions in only one of the syntactic subtests arguably reflects the latter's differential

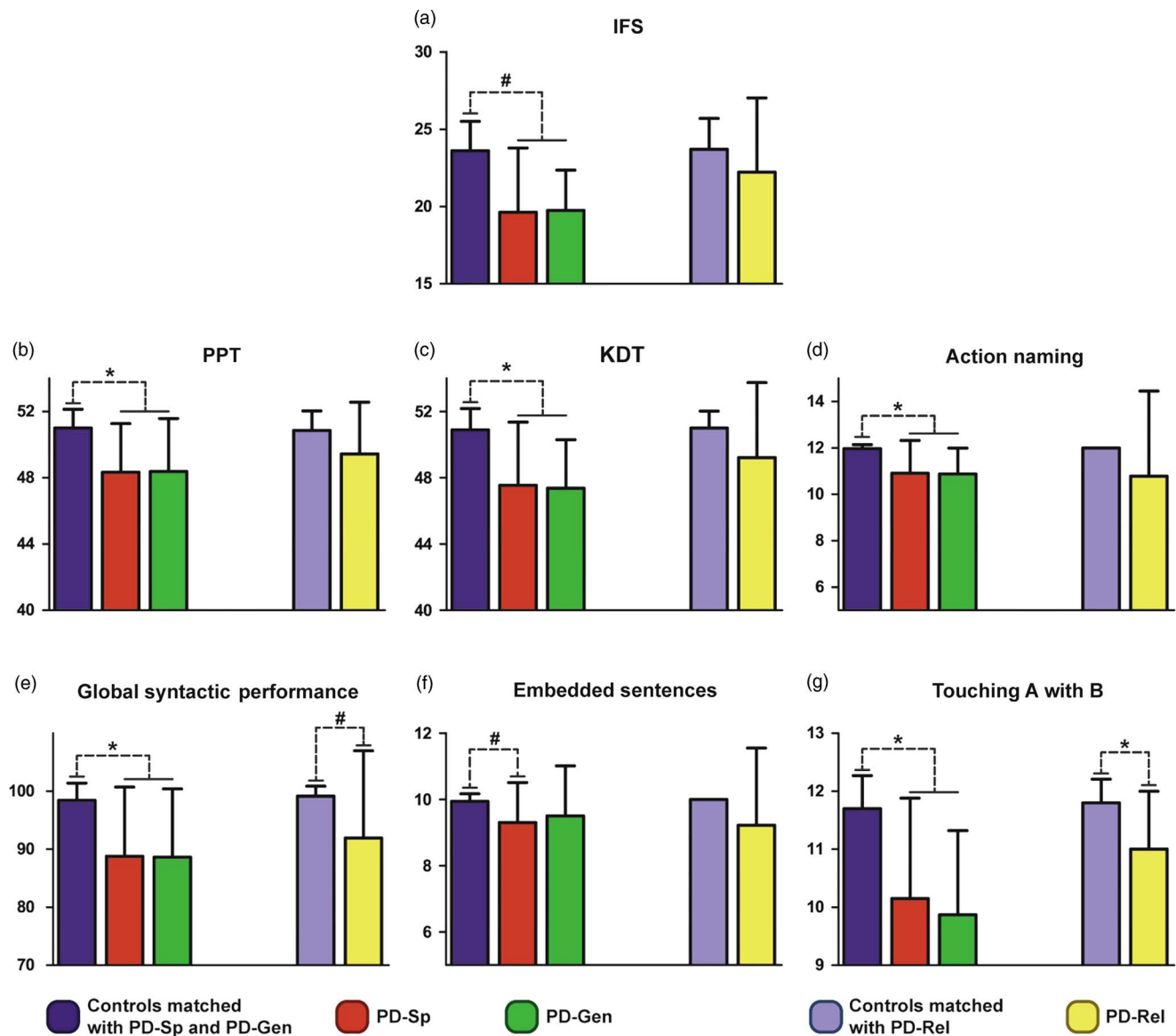


Fig. 1. Statistical analysis of executive, semantic, and linguistic tasks. # indicates statistical differences at $p < .05$. * indicates statistical differences at $p < .05$ after a covariance test adjusted for IFS scores (see statistical details in Tables 2 and 3). Black vertical bars indicate standard deviations. The y-axis in each panel shows the numerical scores of the corresponding test, except for “Global syntactic performance,” which is represented in percent values. IFS: INECO Frontal Screening battery; PPT: Pyramids and Palm Tress test; KDT: Kissing and Dancing Test; PD-Sp: sporadic PD patients; PD-Gen: genetic PD patients with parkin or dardarin mutation; PD-Rel: asymptomatic first-degree relatives of the latter with similar mutations.

demands. Parsing of embedded sentences calls on working memory mechanisms to maintain information active during processing of long-distance dependencies (Hochstadt et al., 2006). In a sentence like *The woman who is fat is kissing her husband*, subject-verb agreement cannot be established until the relative clause (*who is fat*) has been processed. Similarly, the pronoun *her* must be linked to its co-referential noun. To both ends, subject-relevant information must be kept active in working memory as new constituents are being parsed. Processing requirements are very different in *Touching A with B*. For example, the grammatical function of the phrase *the scissors in touching*

the spoon and the scissors and *touching the spoon with the scissors* is determined by 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. Thus, this task suggests negligible demands on working memory and other executive functions, as recently shown (Bocanegra et al., 2015).

Yet, our most interesting finding concerned PD-Rel. These subjects gave no signs of executive, semantic, or action-verb production difficulties. More crucially, while they were not impaired in *Embedded Sentences*, they showed a significant

disturbance in Touching A with B. This dissociation within the syntactic domain fits well with our previous interpretation. Performance on Embedded Sentences was arguably spared because the key executive mechanisms needed to parse long-distance dependencies were still operative. Thus, even if networks more specifically devoted to grammar were compromised, executive resources sufficed for task completion (Hochstadt et al., 2006).

Conversely, Touching A with B relies less crucially on domain-general skills. Indeed, as was the case with PD-Sp and PD-Gen, deficits in this task for PD-Rel were independent of executive abilities. This pattern aligns with our claim that the identification of functional roles within predicates depends on specifically grammatical mechanisms and involves minimal reliance on working memory. Despite the small size of the PD-Rel sample and the ceiling-level performance of its controls, this task yielded a large effect size (n^2 higher than 0.2; see Table 3). This result is noteworthy as effect sizes reveal the magnitude of between-group differences irrespective of sample size. Accordingly, we propose that this *sui generis* disturbance may constitute a preclinical sign of focal and incipient BG (specifically, nigral) deterioration, indexing possible development of PD. This finding also suggests that PARK2 and LRRK2 mutations compromising BG functioning have subtle disease-independent effects on syntactic mechanisms.

This explanation also accounts for why action semantics and action-verb deficits were absent in PD-Rel despite being a hallmark of PD (García & Ibáñez, 2014). While those domains share frontostriatal circuits with syntax, they depend on more widely distributed networks. Indeed, conceptual and lexical processing of action-related information is mainly associated with frontal (e.g., primary motor and premotor cortices, Broca's area) and, less crucially, temporal (e.g., Wernicke's area) hubs (Cardona et al., 2013; García & Ibáñez, 2016; Pulvermuller, 2005). Thus, although advanced atrophy in clinical PD stages preeminently disturbs such functions, complete sparing of cortical networks would support their adequate processing in asymptomatic mutation carriers.

In sum, individuals at genetic risk for PD could be characterized by impairments in language skills which focally rely on BG integrity. Deficits in other language domains could be specific to clinical stages, after cerebral atrophy has surpassed a critical threshold (Braak et al., 2002). In this sense, note that mean scores of the PD-Rel group in all other measures were below those obtained by controls. Tentatively, these results could reflect a (yet non-significant) pattern of difficulties which is likely to turn into full-blown deficits once subjects reach a clinical stage. While speculative in nature (mainly due to the sample's size), this possibility would reinforce the specificity of syntactic subdomains (in particular, functional role assignment) as key targets for the pre-clinical detection of probable PD. Indeed, effect sizes for "Touching A with B" were notably higher than those for all tasks yielding non-significant differences (see Table 3).

Implications

The worldwide spread of PD calls for tools allowing timely diagnosis and intervention. Our data suggest that specifically syntactic deficits may constitute a preclinical sign of the disease, even before other linguistic and extralinguistic domains are affected. Promisingly, the task affording this finding (Touching A with B) is an ultra-brief, robust measure which could be massively applied to patients and their asymptomatic relatives.

So far, only one study on PD has applied it, mirroring our findings in early-stage patients (Bocanegra et al., 2015). Yet, the task has also shown deficits in other autosomal dominant neurodegenerative motor disorders, such as Huntington's disease (Azambuja et al., 2012). Above and beyond this instrument, additional syntactic tasks revealing deficits in early PD patients (Cardona et al., 2013) could be applied to asymptomatic mutation carriers with the aim to develop a preclinical screening protocol. Prodromal detection of motor-network dysfunction could offer clinicians an opportunity to delay functional decline, perhaps *via* cognitive training.

However, note that these possibilities should be entertained with great caution. In addition to featuring a modest size, both genetic samples included two gene mutations with different penetrance in different age ranges: for PARK2, 80–90% around age 40 (Pineda-Trujillo et al., 2001, 2006); for LRRK2, 17% at age 50 and 85% at age 70 (Goldwurm et al., 2005). Thus, a long-term follow-up study would be indispensable to corroborate the hypothesis emerging from our results, and to clarify their specific relation to each mutation.

Our findings also have theoretical implications. First, a debate has emerged on whether syntactic deficits in PD depend on executive dysfunction (Bocanegra et al., 2015; Hochstadt et al., 2006). Rather than supporting overarching affirmative or negative answers, our data suggest that the question may have been posed at a wrong level of granularity. Indeed, syntactic sub-functions with discrepant executive demands may be differentially compromised following BG deterioration.

Second, while deficits in PD-Sp and PD-Gen confirm the cross-dimensional role of BG circuits in language functions, results from PD-Rel suggest that these subcortical structures (and, in particular, the substantia nigra) are more focally related to domain-specific syntactic skills. Such a finding fits well within the embodied cognition framework, which posits that high-order cognition is rooted in lower-level sensorimotor systems (Barsalou, 1999; Gallese & Lakoff, 2005). Accordingly, we propose that the crucial role of the BG for handling syntax (i.e., sequencing hierarchically organized patterns of linguistic information) stems from its more basic specialization for handling movement (i.e., sequencing hierarchically organized patterns of sensorimotor information). This hypothesis is compatible with multiple reports of syntactic impairments in PD (Angwin, Chenery, Copland, Murdoch, & Silburn, 2006; Friederici, Kotz, Werheid, Hein, & von Cramon, 2003; Grossman et al., 2003; Hochstadt et al., 2006; Lee, Grossman, Morris, Stern, & Hurtig, 2003; Lieberman et al., 1992; Zanini et al., 2004), and

illuminates the nature of the relationship between syntax and the procedural memory system (Ullman, 2004, 2008).

Finally, these results indicate that language-related genes may not be restricted to those classically reported, such as FOXP2 and DCDC2. Indeed, LRRK2 and PARK2, whose neuropathology is associated with nigral degeneration, may be linked to the development of (language-specific) syntactic mechanisms. In this sense, the quest for genetic determinants of language should move beyond its usual targets in an attempt to specify the subtle contributions of several (possibly myriad) genes.

Limitations and Further Research

The PD-Gen and PD-Rel groups were of moderate size, though certainly not smaller than those reported in several groundbreaking studies showing links between genetic factors and both embodied (Bak et al., 2006) and more general (Espay et al., 2011; Fujioka et al., 2014; Mercadillo et al., 2014; Renda et al., 2014) language domains. In this sense, we have aimed to minimize potential misreadings of results from these samples by adopting key methodological measures (Button et al., 2013), such as offering abundant details of the participants' profiles (including sociodemographic, clinical, and genetic data) and explicit rationales for the statistical tests we conducted.

The results from PD-Gen and PD-Rel afford novel experimental insights into the genetic basis of embodied syntactic deficits in PD. While both samples are valuable because of their uniqueness, it would be crucial to replicate our study with more participants. Such replications should also include tasks tapping other aspects of syntax (e.g., active-passive transformations, markedness) to determine the extent of syntactic impairment related to PD-relevant mutations. Also, PD-Gen and PD-Rel participants included two key genetic mutations featuring different penetrance across age groups. Further research (ideally, with these very samples) could aim to disentangle the impact of each mutation to the observed patterns and their role in syntactic skills, while offering additional insights into their relation with cortico-subcortical networks *via* electrophysiological or neuroimaging recordings—see Melloni et al. (2015).

CONCLUSION

Breakthroughs in the preclinical detection of PD are urgently needed to alleviate the socio-financial impact of the disease. Here, we offered an unprecedented report of linguistic deficits in asymptomatic carriers of mutations known to confer risk of PD. Replications and elaborations of our study could inspire valuable clinical and theoretical innovations in the quest to understand and counter this highly prevalent condition.

ACKNOWLEDGMENTS

This work was partially supported by grants from CONICET, CONICYT/FONDECYT Regular (1130920), COLCIENCIAS

(1115-545-31374 and 1115-569-33858), FONCYT-PICT 2012-0412, FONCYT-PICT 2012-1309, FONDAP 15150012, and INECO Foundation. Conflict of Interest: None to declare.

REFERENCES

- Acosta-Baena, N., Sepulveda-Falla, D., Lopera-Gomez, C.M., Jaramillo-Elorza, M.C., Moreno, S., Aguirre-Acevedo, D.C., ... Lopera, F. (2011). Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: A retrospective cohort study. *The Lancet. Neurology*, *10*(3), 213–220. doi:10.1016/s1474-4422(10)70323-9
- Angwin, A.J., Chenery, H.J., Copland, D.A., Murdoch, B.E., & Silburn, P.A. (2006). Self-paced reading and sentence comprehension in Parkinson's disease. *Journal of Neurolinguistics*, *19*(3), 239–252. doi:http://dx.doi.org/10.1016/j.jneuroling.2005.11.004
- Arcos-Burgos, M., & Muenke, M. (2002). Genetics of population isolates. *Clinical Genetics*, *61*(4), 233–247. doi:10.1034/j.1399-0004.2002.610401.x
- Azambuja, M.J., Radanovic, M., Haddad, M.S., Adda, C.C., Barbosa, E.R., & Mansur, L.L. (2012). Language impairment in Huntington's disease. *Arquivos de Neuro-psiquiatria*, *70*(6), 410–415. doi:S0004-282X2012000600006 [pii]
- Baez, S., Couto, B., Herrera, E., Bocanegra, Y., Trujillo-Orrego, N., Madrigal-Zapata, L., ... Villegas, A. (2013). Tracking the cognitive, social, and neuroanatomical profile in early neurodegeneration: Type III Cockayne syndrome. *Frontiers in Aging Neuroscience*, *5*, 80. doi:10.3389/fnagi.2013.00080
- Bak, T.H. (2013). The neuroscience of action semantics in neurodegenerative brain diseases. *Current Opinion in Neurology*, *26*(6), 671–677. doi:10.1097/wco.000000000000039
- Bak, T.H., & Hodges, J.R. (2004). The effects of motor neurone disease on language: further evidence. *Brain and Language*, *89*(2), 354–361. doi:10.1016/S0093-934X(03)00357-2
- Bak, T.H., Yancopoulos, D., Nestor, P.J., Xuereb, J.H., Spillantini, M.G., Pulvermuller, F., ... Hodges, J.R. (2006). Clinical, imaging and pathological correlates of a hereditary deficit in verb and action processing. *Brain*, *129*(Pt 2), 321–332. doi:10.1093/brain/awh701
- Barsalou, L.W. (1999). Perceptual symbol systems. *The Behavioral and Brain Sciences*, *22*(4), 577–609. discussion 610-560.
- Bocanegra, Y., García, A.M., Pineda, D., Buriticá, O., Villegas, A., Lopera, F., ... Ibáñez, A.M. (2015). Syntax, action verbs, action semantics, and object semantics in Parkinson's disease: Dissociability, progression, and executive influences. *Cortex*, *69*, 237–254.
- Braak, H., Del Tredici, K., Bratzke, H., Hamm-Clement, J., Sandmann-Keil, D., & Rub, U. (2002). Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *Journal of Neurology*, *249*(Suppl. 3), Iii/1–Iii/5.
- Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., ... Munafò, M.R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews. Neuroscience*, *14*(5), 365–376. doi:10.1038/nrn3475
- Cardona, J., Kargieman, L., Sinay, V., Gershanik, O., Gelormini, C., Amoruso, L., ... Ibanez, A. (2014). How embodied is action language? Neurological evidence from motor diseases. *Cognition*, http://dx.doi.org/10.1016/j.cognition.2014.1002.1001

- Cardona, J.F., Gershanik, O., Gelormini-Lezama, C., Houck, A.L., Cardona, S., Kargieman, L., ... Ibanez, A. (2013). Action-verb processing in Parkinson's disease: New pathways for motor-language coupling. *Brain Structure & Function*, *218*, 1355–1373. doi:10.1007/s00429-013-0510-1 [doi]
- Cotelli, M., Borroni, B., Manenti, R., Zanetti, M., Arevalo, A., Cappa, S.F., ... Padovani, A. (2007). Action and object naming in Parkinson's disease without dementia. *European Journal of Neurology*, *14*(6), 632–637. doi:ENE1797 [pii];10.1111/j.1468-1331.2007.01797.x [doi]
- Espay, A.J., Spina, S., Houghton, D.J., Murrell, J.R., de Courten-Myers, G.M., Ghetti, B., ... Litvan, I. (2011). Rapidly progressive atypical parkinsonism associated with frontotemporal lobar degeneration and motor neuron disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *82*(7), 751–753. doi:10.1136/jnnp.2009.201608
- Friederici, A.D., Kotz, S.A., Werheid, K., Hein, G., & von Cramon, D.Y. (2003). Syntactic comprehension in Parkinson's disease: Investigating early automatic and late integrational processes using event-related brain potentials. *Neuropsychology*, *17*(1), 133–142.
- Fujioka, S., Boeve, B.F., Parisi, J.E., Tacik, P., Aoki, N., Strongosky, A.J., ... Wszolek, Z.K. (2014). A familial form of parkinsonism, dementia, and motor neuron disease: A longitudinal study. *Parkinsonism & Related Disorders*, *20*(11), 1129–1134. doi:10.1016/j.parkreldis.2014.07.014
- Gallese, V., & Lakoff, G. (2005). The brain's concepts: The role of the sensory-motor system in conceptual knowledge. *Cognitive Neuropsychology*, *22*(3), 455–479. doi:714592738 [pii];10.1080/02643290442000310
- García, A. M., Carrillo, F., Orozco-Aroyave, J. R., Trujillo, N., Vargas Bonilla, J. F., Fittipaldi, S., Adolphi, F., Nöth, E., Sigman, M., Fernández Slezak, D., Ibáñez, A. & Cecchi, G. A. (2016). How language flows when movements don't: An automated analysis of spontaneous discourse in Parkinson's disease. *Brain and Language*, *162*, 19–28.
- García, A., & Ibáñez, A. (2014). Words in motion: Motor-language coupling in Parkinson's disease. *Translational Neuroscience*, *5*(2), 152–159. doi:10.2478/s13380-014-0218-6
- García, A.M., & Ibáñez, A. (2016). A touch with words: Dynamic synergies between manual actions and language. *Neuroscience & Biobehavioral Reviews*, *68*, 59–95. doi:10.1016/j.neubiorev.2016.04.022
- Goldwurm, S., Di Fonzo, A., Simons, E.J., Rohe, C.F., Zini, M., Canesi, M., ... Bonifati, V. (2005). The G6055A (G2019S) mutation in LRRK2 is frequent in both early and late onset Parkinson's disease and originates from a common ancestor. *Journal of Medical Genetics*, *42*(11), e65. doi:10.1136/jmg.2005.035568
- Grossman, M., Cooke, A., DeVita, C., Lee, C., Alsop, D., Detre, J., ... Hurtig, H.I. (2003). Grammatical and resource components of sentence processing in Parkinson's disease: An fMRI study. *Neurology*, *60*(5), 775–781.
- Herrera, E., & Cuetos, F. (2012). Action naming in Parkinson's disease patients on/off dopamine. *Neuroscience Letters*, *513*(2), 219–222. doi:http://dx.doi.org/10.1016/j.neulet.2012.02.045
- Hochstadt, J., Nakano, H., Lieberman, P., & Friedman, J. (2006). The roles of sequencing and verbal working memory in sentence comprehension deficits in Parkinson's disease. *Brain and Language*, *97*(3), 243–257. doi:10.1016/j.bandl.2005.10.011
- Hughes, A.J., Daniel, S.E., Kilford, L., & Lees, A.J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(3), 181–184.
- Ibanez, A., Cardona, J.F., Dos Santos, Y.V., Blenkmann, A., Aravena, P., Roca, M., ... Bekinschtein, T. (2013). Motor-language coupling: Direct evidence from early Parkinson's disease and intracranial cortical recordings. *Cortex*, *49*(4), 968–984. doi:10.1016/j.cortex.2012.02.014
- Kargieman, L., Herrera, E., Baez, S., García, A.M., Dottori, M., Gelormini, C., ... Ibanez, A. (2014). Motor-language coupling in Huntington's disease families. *Frontiers of Aging and Neuroscience*, *6*, 122. doi:10.3389/fnagi.2014.00122
- Lee, C., Grossman, M., Morris, J., Stern, M.B., & Hurtig, H.I. (2003). Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. *Brain and Language*, *85*(3), 347–356.
- Lieberman, P., Kako, E., Friedman, J., Tajchman, G., Feldman, L.S., & Jimenez, E.B. (1992). Speech production, syntax comprehension, and cognitive deficits in Parkinson's disease. *Brain and Language*, *43*(2), 169–189.
- McKinlay, A., Grace, R.C., Dalrymple-Alford, J.C., & Roger, D. (2010). Characteristics of executive function impairment in Parkinson's disease patients without dementia. *Journal of the International Neuropsychological Society*, *16*(2), 268–277. doi:10.1017/s1355617709991299
- Melloni, M., Sedeño, L., Hesse, E., García-Cordero, I., Mikulan, E., Plastino, A., ... Ibáñez, A. (2015). Cortical dynamics and subcortical signatures of motor-language coupling in Parkinson's disease. *Scientific Reports*, *5*, 11899.
- Mercadillo, R.E., Galvez, V., Diaz, R., Hernandez-Castillo, C.R., Campos-Romo, A., Boll, M.C., ... Fernandez-Ruiz, J. (2014). Parahippocampal gray matter alterations in spinocerebellar ataxia type 2 identified by voxel based morphometry. *Journal of the Neurological Sciences*, *347*(1-2), 50–58. doi:10.1016/j.jns.2014.09.018
- Nalls, M.A., Pankratz, N., Lill, C.M., Do, C.B., Hernandez, D.G., Saad, M., ... Singleton, A.B. (2014). Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nature Genetics*, *46*(9), 989–993. doi:10.1038/ng.3043
- Pineda-Trujillo, N., Apergi, M., Moreno, S., Arias, W., Lesage, S., Franco, A., ... Ruiz-Linares, A. (2006). A genetic cluster of early onset Parkinson's disease in a Colombian population. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *141b*(8), 885–889. doi:10.1002/ajmg.b.30375
- Pineda-Trujillo, N., Carvajal-Carmona, L.G., Buritica, O., Moreno, S., Uribe, C., Pineda, D., ... Ruiz-Linares, A. (2001). A novel Cys212Tyr founder mutation in parkin and allelic heterogeneity of juvenile Parkinsonism in a population from North West Colombia. *Neuroscience Letters*, *298*(2), 87–90.
- Pulvermuller, F. (2005). Brain mechanisms linking language and action. *Nature Reviews. Neuroscience*, *6*(7), 576–582. doi:10.1038/nrn1706 [pii];10.1038/nrn1706
- Renda, M.M., Voigt, R.G., Babovic-Vuksanovic, D., Highsmith, W.E., Vinson, S.S., Sadowski, C.M., ... Hagerman, R.J. (2014). Neurodevelopmental disabilities in children with intermediate and premutation range fragile X cytosine-guanine-guanine expansions. *Journal of Child Neurology*, *29*(3), 326–330. doi:10.1177/0883073812469723
- Samii, A., Nutt, J.G., & Ransom, B.R. (2004). Parkinson's disease. *The Lancet*, *363*(9423), 1783–1793. doi:10.1016/S0140-6736(04)16305-8

- Svenningsson, P., Westman, E., Ballard, C., & Aarsland, D. (2012). Cognitive impairment in patients with Parkinson's disease: Diagnosis, biomarkers, and treatment. *The Lancet Neurology*, *11*(8), 697–707. doi:10.1016/S1474-4422(12)70152-7
- Torralva, T., Roca, M., Gleichgerrcht, E., Lopez, P., & Manes, F. (2009). INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. *Journal of the International Neuropsychological Society*, *15*(5), 777–786. doi:10.1017/s1355617709990415
- Ullman, M. (2008). The role of memory systems in disorders of language. In B. Stemmer & H.A. Whitaker (Eds.), *Handbook of the neuroscience of language* (pp. 189–198). London: Elsevier.
- Ullman, M.T. (2004). Contributions of memory circuits to language: The declarative/procedural model. *Cognition*, *92*(1–2), 231–270. doi:10.1016/j.cognition.2003.10.008
- Zanini, S., Tavano, A., Vorano, L., Schiavo, F., Gigli, G.L., Aglioti, S.M., ... Fabbro, F. (2004). Greater syntactic impairments in native language in bilingual Parkinsonian patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(12), 1678–1681. doi:10.1136/jnnp.2003.018507