



ORIGINAL ARTICLE

A core deficit in Parkinson disease?☆



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Abstract

Introduction: Parkinson disease is a neurodegenerative condition involving motor, cognitive, and linguistic deficits. It is important to know why all these different deficits co-occur in the affected people. This paper aims to clarify whether these comorbid deficits result from the selective impairment of a computational primitive, namely, a context-sensitive computational ability according to Chomsky's Hierarchy (a well-established research tool in comparative neuroscience).

Patients and methods: A total of 15 medicated subjects with Parkinson disease and 15 controls were selected. They were matched in age and education. A battery of tasks was designed to test 3 different domains (motor capacities, cognition, and language) and 2 different computational abilities (context-free and context-sensitive operations).

Results: Significant differences between groups were observed only regarding the linguistic task involving context-sensitive computations (correferences).

Conclusions: The observed deficits in our patients with Parkinson disease cannot be explained in terms of the selective impairment of one only unspecific, low-level computational process. At the same time, differences between patients and controls are expected to be greater if the former are not medicated. Moreover, we should pursue in the search of (this kind of) computational primitives than can be selectively impaired in people with Parkinson disease, because they may help to achieve an earlier diagnosis of this condition.

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PALABRAS CLAVE

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¿Un déficit nuclear en la enfermedad de Parkinson?**Resumen**

Introducción: La enfermedad de Parkinson es un trastorno neurodegenerativo que lleva aparejados déficits motores, cognitivos y lingüísticos. Es importante esclarecer las causas de esta comorbilidad. Este trabajo tiene como objetivo determinar si dichos déficits pueden interpretarse como el resultado de la disfunción selectiva de capacidades computacionales primitivas, en particular, de una capacidad computacional sensible al contexto o de tipo 1 en la Jerarquía de Chomsky (una herramienta usada habitualmente en estudios de cognición comparada).

Pacientes y métodos: Se seleccionó a 15 sujetos con enfermedad de Parkinson medicados y a 15 controles emparejados en edad y en años de escolarización. Se diseñó una batería de pruebas específicas para el experimento que evaluaban 3 dominios diferentes (motor, lingüístico y visuoespacial) y 2 tipos de capacidades computacionales distintas (sensible e insensible al contexto).

Resultados: Se obtuvieron diferencias significativas entre ambos grupos solo en la prueba de tipo lingüístico que evaluaba la capacidad de computación sensible al contexto.

Conclusiones: Los déficits de diferente naturaleza que caracterizan a la enfermedad de Parkinson no parecen explicarse por la afectación selectiva de una capacidad computacional básica que sería funcionalmente inespecífica. Resta por ver si las diferencias entre afectados y no afectados son significativas cuando se trata de sujetos no medicados y cuando las pruebas empleadas en la evaluación se ciñen a aspectos puramente formales. Idealmente, este tipo de primitivos computacionales podría ayudar a diagnosticar precozmente el trastorno.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder caused by a selective destruction of dopaminergic neurons of the substantia nigra and the accumulation of Lewy bodies. Although degeneration initially occurs in subcortical regions, it is also observed in the cortex in more advanced stages of the disease. PD typically manifests with a wide range of motor and non-motor symptoms.^{1,2} Although psychological and cognitive disorders have traditionally been considered characteristic of later stages of the disease along with damage reaching the cortical regions,³ there is increasing evidence that PD is associated with specific neuropsychological and neuropsychiatric traits even during the preclinical stage.⁴ Language is a very good example of this. Speech impairment has traditionally been considered the main problem in this domain, and a consequence of motor impairment in PD.⁵ However, current thought suggests that other structural levels of language are also affected (lexical semantics, syntax, morphology), even when performing comprehension tasks^{6,7} and at very early stages of the disease.⁸ As a general rule, these problems are regarded as a consequence of the impairment of basic cognitive abilities, especially executive function⁹ and working memory.⁷ Several models have been proposed to explain language dysfunction in PD. Some of these are based on language processing models in which subcortical structures play an especially relevant role,¹⁰ while others regard the coexistence of language and motor problems as a result of the simultaneous impairment of parallel frontotemporal circuits which connect the basal ganglia and cortex.¹¹ Nevertheless, as stated by Bodis-Wollner and Jo,¹² "a more encompassing linguistic and functional model of PD

specific language impairments would be useful for evaluating language deficits in the context of motor dysfunction".

Today, experts in neurolinguistics are starting to support the idea that successfully implementing these models requires language to be divided into computational primitives (units and operations) whose processing is compatible with the real-time processing ability of the brain. In other words, defining language and language-related disorders in terms of syntax, semantics, or phonology is no longer applicable, since these denominations, extensively used in linguistics (at least for describing the structure of languages), refer to numerous computations and representations of general domains.¹³ Furthermore, it is to be expected that, once identified, these computational primitives would not be language-specific; instead, they would participate in other cognitive and even non-cognitive tasks. In the words of Poeppel and Embick,¹³ "the differently structured cortical areas are specialized for performing different types of computation, and that some of these computations are necessary for language but also for other cognitive functions".

In a recent attempt to find these computational primitives, some researchers have applied the formal language theory, and more specifically the Chomsky Hierarchy,¹⁴ to the characterisation of the computational processes inherent to language processing.^{15–17} This hierarchy classifies formal languages according to the computational devices (grammars) necessary for their generation. Type-3 (finite-state) grammars generate linear sequences that lack an internal structure (for example, a list of words such as a list of the Spanish provinces). Type-2 (context-free) grammars enable the (recursive) generation of hierarchically organised

structures, as in the case of complex sentences with subordinate clauses, for example, *John said that Peter washed the dishes*. Finally, type-1 (context-sensitive) grammars also enable the establishment of different classes of crossed dependencies between the elements of the organised structures; this is the case of complex sentences with 2 pronouns and 2 antecedents, for example, *John promised Peter that he (John) would help him (Peter) wash the dishes*. In fact, of all the communication systems existing in nature, only human language uses a type-1 computational device, at least to generate certain types of sentences (such as the latter example). According to some language processing models,^{18–20} such computational devices have a defined neurobiological substrate. Basically, all these devices consist of a processor (located in certain subcortical structures, including the basal ganglia) which works together with a working memory (located in different cortical areas). The more powerful the working memory, the greater the computational capacity of the device and the lower the level achieved in the Chomsky Hierarchy. Therefore, this substrate coincides with some areas affected in PD at one stage or another.^{21,22} A computational system with this organisation is expected to be functionally non-specific, meaning that it can work together with different interface devices, generating different outputs (language-related, cognitive, and motor) which would have in common certain formal properties, in particular the type of dependencies that exist between their constituent elements.^{15,17} Consequently, this model is considered valuable for making comparisons not only between different species in terms of their cognitive language-related capacities,¹⁵ but also between different cognitive domains within the same species.²³ As Heinz²³ points out, “since any pattern is a language in the sense above [as proposed by the Chomsky Hierarchy], a distinct advantage of the Chomsky Hierarchy is it allows for the comparison of patterns from different domains”. In our case, we also expect this model to help determine the comorbidities of different deficits (language-related, cognitive, and motor) in PD.

There is plenty of evidence to support the above hypothesis. For example, it is a well-known fact that the brain uses basic association mechanisms (such as chains of cortical neurons which fire synchronously) to generate complex representations at different levels and in different domains.²⁴ Particularly noteworthy is the evidence provided by neuroimaging studies, which indicates that a single central processing device performs different types of computations, as in the case of those involved in drawing.²⁵ Likewise, computationally equivalent tasks have been proven to result in substantially identical brain activation patterns. For example, an extensive neuronal network consisting of cortical and subcortical areas is activated in both hemispheres when drawing; most of these areas also participate in language processing.²⁶ Furthermore, damage to this neural substrate provokes both language-related and non language-related symptoms. Thus, focal damage to basal ganglia can result in simultaneous verbal and visual impairment along with writing problems.²⁷ Finally, several sources seem to specifically corroborate the viability of applying the Chomsky Hierarchy to the neurobiological analysis of language and cognition, particularly studies on natural language processing and artificial grammar learning.¹⁷ For example, processing of local

dependencies (ie, those operating within the same clause) activates the hippocampus and the left ventral premotor cortex, whereas the processing of hierarchically structured long-distance dependencies activates Broca’s area.²⁸

Patients and methods

Participants

Fifteen patients with PD (7 women; age, 66.7 ± 11.36 years) and 15 healthy subjects (9 women; age, 65.06 ± 7.48 years) participated in our study. Participants were paired by age and years of schooling (10.80 ± 4.32 and 9.46 ± 3.80 , respectively). The patients were diagnosed with PD by either the neurology team of the movement disorders unit at Hospital Central de Asturias or neurology teams from other hospitals, following the UK Brain Bank criteria. Mean number of years elapsed since diagnosis was 9.07 ± 5.76 . We only included patients without severe cognitive impairment or dementia according to the Mini-Mental State Examination²⁹ (mean scores were 29.22 ± 1.08 in the PD group and 29.45 ± 0.68 in the control group). All patients were taking dopaminergic drugs regularly when the test was administered. All participants were native Spanish speakers, and none of them had a history of alcohol or drug abuse, or neurological or psychiatric disorders, except for PD in the case of the study group. The patients with PD were assessed at the facilities owned by the Parkinson’s Disease Association of Asturias, in Oviedo, Spain.

Tasks

The 2 groups performed a battery of tasks aimed at determining whether PD involves a selective dysfunction at one of the levels of the Chomsky Hierarchy which may in turn explain the simultaneous presence of deficits of different types. Most of the tasks were designed ad hoc. The battery included 2 series of tests aimed at evaluating 3 different domains: motor, linguistic, and visuospatial. As will be explained further below, the visuospatial domain has been included for 2 reasons: first, it may be computationally processed in the same way as the 2 other domains, and second, there is evidence suggesting that PD is also associated with visuospatial problems, even in the prodromal stage of the disease, and these problems seem to also depend on the working memory capacity and the level of computational demand.^{30,31} The first series of tests was aimed at determining the ability to plan and perform Chomsky’s type-2 computational tasks whereas the second one evaluated the same abilities with type-1 tasks.

The first series included the following tasks:

- Type-2 motor task: the Tower of Hanoi. The most effective solution strategy for this test involves recursive processing.³² We measured the time and number of moves needed to solve the puzzle. The Tower of Hanoi has been specifically used to assess procedural memory in patients with PD as they usually apply suboptimal strategies.^{33,34}

- Type-2 linguistic task: creating complex sentences with noun or relative clauses. This task included 16 different stimuli that were processed by examining a drawing which depicted a specific action (for example, a monkey biting a dog or a thief chasing a policeman). In 8 of the exercises, patients had to complete a sentence provided by the evaluator with a noun clause (for example, the evaluator said "the dog does not want" and the patient had to complete the sentence with "the monkey to bite it"). In the remaining 8 exercises, patients had to answer a question related with the drawing using a relative clause (for example, when asked "Which policeman is scared?", the patient should answer "The policeman who is being chased by the thief"). Each verbal response was scored either 1 (correct) or 0 (incorrect). Three different criteria were used for assessing the answers: (1) the presence of recursivity in itself (the structure of the sentence could be ungrammatical at other levels, as in the case of "the one which is chased by the thief"); (2) the presence of recursivity in grammatical sentences (the generated structure is completely grammatical, as in the case of "the policeman who is being chased by the thief"); and (3) the presence of correct recursive structures which were also semantically appropriate. This type of elicited imitation tests are typically used to analyse the acquisition of this grammatical component in normal and pathological populations.^{35,36} Some studies have evaluated comprehension of these types of structures in the context of PD.³⁷
- Type-2 visuospatial task: drawing embedded geometric shapes. We used the methodology and stimuli described by Hudson and Farran.³⁸ However, we simplified the analysis by focusing exclusively on the results and not on the strategy used. Results were considered correct (and scored 1) when all the shapes were drawn in the same order as they appeared in the model, regardless of whether the drawing had defects (thin pencil lines, incomplete polygons, etc.).

The following tasks were used in the second series:

- Type-1 motor task: knot-tying. According to several authors,^{39,40} planning and tying a knot requires a Chomsky Hierarchy type-1 computational system. We used 4 knots of increasing difficulty (half-knot, overhand knot, reef or square knot, and weaver's knot). It should be noted that the processing demand required for motor planning and tying these knots is not related to the computational device, which should always be type-1, but to other factors (such as attention capacity) linked to the number of necessary steps. During the test, the evaluator provided the patient with a sheet of paper showing the steps for tying the knots. We recorded the time necessary to tie the knots. Participants taking less than 20 seconds to complete the task scored 6 points; 5 points were awarded to participants who took 20 to 40 seconds; 4 points for 40 to 60 seconds; 3 points for 60 to 80 seconds; 2 points for 80 to 100 seconds; and 1 point for 100 to 120 seconds. Participants taking more than 120 seconds to tie the knot or those who were unable to complete the task and dropped out scored 0 points.
- Type-1 linguistic task: comprehending sentences with long-distance crossed dependencies. We used complex

sentences with 2 anaphorical references in the subordinate clause (a null pronoun and an overt pronoun). To interpret these sentences correctly, the participants needed to link the 2 anaphorical references to 2 control nouns in the main clause. 16 different sentences were used: 8 of these contained a subject control verb (threat, announce, assure, say, promise) and therefore included dependencies between anaphoras and their antecedents (for example, "The man promised the woman that he [the man] would take a picture of her [the woman]"). As distractor items, we used 8 sentences with an object control verb (oblige, order, ask), which contained long-distance unbounded dependencies (for example, "the policeman ordered the doctor not to let [the doctor] him [the policeman] go"). All sentences were delivered verbally, and participants were asked to point at the picture (from 4 possible pictures) which best represented the sentence. Two of the pictures represented the 2 elements mentioned in the sentence as the antecedent of the null pronoun of the subordinate clause (ie, a man taking a picture of a woman and a woman taking a picture of a man). The other 2 pictures represented the semantic distractors (a child taking a picture of a woman and a man taking a picture of a child). This type of structure is typically used to assess the ability to process long-distance dependencies in both healthy^{41,42} and pathological populations.^{43,44}

- Type-1 visuospatial task: outlines. We designed a specific drawing test in which participants were required to complete the outline of an animal working from fragments scattered across a blank canvas. Drawing tasks such as the cube-copying test have been used to assess cognitive and motor impairment in patients with PD.⁴⁵ To complete the task correctly, participants had to mentally connect the already drawn fragments to identify the animal, and then physically join the fragments to complete the outline. This task can be considered a context-sensitive task in computational terms since participants must process a significant number of fragments simultaneously in order to mentally complete the outline and, in many cases, processing involves establishing crossed visual references between some of these fragments. Longa⁴⁶ has developed this hypothesis and applied it to the analysis of prehistoric geometric engravings (we suggest reading this article for a more detailed theoretical justification of the possibility of identifying computational processes from this type of evidence). We used the profiles of 8 well-known animals (chicken, dog, leopard, swan, rabbit, giraffe, mouse, and dolphin). The evaluator requested that the participants mentally complete the outline and say the identified animal aloud. After that, the participants were asked to draw the animal manually to reproduce the mentally evoked model. Correct results were scored 1 and incorrect results, 0.

Statistical analysis

Due to the small size of our sample and considering that our data seemed to follow a normal distribution, the results from each group were compared using the *t* test for independent samples.

Table 1 Mean scores (SD) obtained by the 2 groups in the battery of tasks.

Task	PD patients	Controls	<i>t</i>	<i>P</i>
Type-2 motor task (moves)	22.80 (11.03)	21.93 (5.86)	0.26	.79
Type-2 motor task (time)	131.33 (81.88)	98.53 (40.61)	1.39	.18
Type-2 linguistic task (recursivity)	14.4 (1.72)	15.45 (1.03)	-0.91	.36
Type-2 linguistic task (grammatical recursivity)	11.86 (1.59)	12.45 (2.11)	-2.28	.03*
Type-2 linguistic task (grammatical recursivity + plausibility)	9.86 (2.38)	11.54 (2.42)	-3.71	.001**
Type-2 visuospatial task	8 (0)	8 (0)	1	1
Type-1 motor task	15.20 (10.47)	15.83 (4.78)	-0.21	.83
Type-1 linguistic task	13.53 (1.99)	14.91 (0.70)	-2.70	.01*
Type-1 visuospatial task	4.93 (1.83)	5.20 (1.01)	-0.43	.62

* $P < .05$.** $P < .001$.

Results

Table 1 shows the task results for each group as well as *t*-test scores and statistical significance. As can be seen, none of the type-2 computational tasks showed statistically significant differences between the 2 groups. The type-2 linguistic task showed statistically significant differences only when considering grammaticality of sentences at all levels ($t_{(28)} = -2.28$; $P < .05$) and the semantic plausibility of the answers ($t_{(28)} = -3.71$; $P < .005$); no significant differences were seen when assessing the recursive nature of the generated structures ($t_{(28)} = -0.91$; $P < .05$).

No statistically significant differences were observed in type-1 visuospatial or motor tasks. In the type-1 motor task, patients with PD achieved poorer results in the most complex items (greater number of steps). However, we did find statistically significant differences between the 2 groups in the linguistic task ($t_{(28)} = -2.70$; $P < .05$). The lowest error rates for both groups were observed in stimuli of long-distance crossed dependencies (sentences with subject control verbs). However, this type of stimuli also showed the greatest differences between patients with PD and controls, nearly reaching statistical significance ($t_{(28)} = 2.00$; $P = .059$ for subject control verbs; $t_{(28)} = 1.67$; $P = .113$ for object control verbs). Most of the mistakes made by the patients with PD were the result of confusing sentences with subject control verbs for sentences with object control verbs. In contrast, in cases of long-distance crossed dependencies (sentences with object control verbs), only one third of the errors made by PD patients were due to misinterpreting object control verbs for subject control verbs. In the remaining 2 thirds, mistakes involved selecting a distractor item or misinterpreting the pronoun serving as direct object in the subordinate clause (either for a reflexive pronoun when it was not, or vice versa, or for a free reference, ie, a pronoun referring to a third entity different from those mentioned in the sentence).

Discussion

The aim of our study was to assess the utility of the Chomsky Hierarchy in characterising motor, cognitive, and linguistic dysfunctions associated with PD. Some of the elements

of the neural substrate of the language computational system are affected in PD (especially the basal ganglia); it was therefore expected that tasks susceptible of being classified within the same level of the Chomsky Hierarchy (regardless of their nature) would be simultaneously affected. In particular, we anticipated that the most complex tasks (context-sensitive or type-1 on the hierarchy) would be especially affected, for 2 main reasons: they involve a higher computational demand in terms of working memory,^{18,19} and they seem to be more sensitive to damage, since they depend on recently evolved neural networks,^{18,19} which in general show lower levels of resilience and less robust compensatory mechanisms.⁴⁷

However, our results do not allow us to conclude that there is a selective processing deficit exclusively affecting the computational capacity for type-1 tasks. In fact, only language-related tasks of this type showed statistically significant differences between groups. However, patients with PD and controls achieved similar results in visuospatial tasks. Regarding motor tasks, the most important determinant for PD patients was the number of steps necessary to complete the task successfully, rather than its computational nature. Nonetheless, this situation appears to be due to other reasons (patients need to repeat the process more times): the lack of statistically significant differences in other items of this test suggests that the computational ability to perform context-sensitive operations is preserved in patients with PD. Furthermore, the purely motor problems experienced by PD patients during task execution represent another determinant in the case of the more complex knots, as they led to a higher drop-out rate or excessively long execution times. Finally, regarding linguistic tasks, establishing long distance co-references is clearly a problem for patients with PD. Although differences between groups for these tasks did not reach statistical significance, the parameter that best distinguishes subjects from the 2 groups is the ability to correctly process long-distance crossed dependencies (ie, sentences with a subject control verb). In fact, this type of co-references is usually the most problematic in other diseases and also during language acquisition in children. The reason is that not only are these sentences more complex computationally, but also the distance between the anaphora and the antecedent is greater (and therefore its processing requires even more working memory). When processing these sentences, children employ the so-called 'minimum

distance principle'^{48,49}: they assume that the antecedent of the anaphora serving as the subject of the subordinate clause is the closest noun in the main clause. Patients with Williams syndrome, for example, seem to process sentences following the same principle,⁴⁴ and so do our patients with PD. Interestingly, the mistakes they made when processing sentences with no crossed dependencies were different: the patients either chose a distractor item (usually due to a physical resemblance which makes them mistake the drawing of a child for that of a man), incorrectly categorised the pronoun serving as the object (a non-reflexive pronoun is understood as reflexive or vice versa), or failed to detect the anaphoric function of that pronoun (the pronoun serving as the direct object is thought to be linked to an entity not mentioned in the sentence). The first of these mistakes is not linguistic. The second mistake is linguistic; however, it is not syntactic (and therefore, nor structural) but lexical (it stems from not being able to distinguish between reflexive and non-reflexive pronouns). The third mistake is not syntactic but pragmatic (in fact, all non-reflexive pronouns can be interpreted in both ways, bound and free, and whether they are correct will depend on the context).

We deem it necessary to mention 2 additional factors that may help explain the results obtained. Firstly, the patients with PD who participated in our study were taking a drug to reduce their symptoms. Considering that this drug affects dopamine levels and that the dopaminergic projections connecting the striate body and cortex play a crucial role in linguistic processing (more specifically syntactic processing, according to some models²⁰), we cannot rule out the possibility that some of the assessed computational abilities (probably type-1 abilities) may be more affected in patients who are not receiving pharmacological treatment. In fact, evidence suggests that linguistic dysfunction in patients with PD who are not taking medication is greater than in medicated patients, and not only in terms of articulation.^{50,51} Furthermore, these patients explicitly presented impaired short-term memory, which is usually reversible with medication⁵² (as we mentioned in the introduction, working memory space determines the regime reached by the computational device). Consequently, our results (especially in the linguistic domain) may be compatible with selective involvement of context-sensitive computational ability in PD patients. This study should be repeated using a non-medicated population to prove our hypothesis.

We would also like to point out that several studies have cast doubt on the potential utility of the formal language theory for the study of cognitive processes, and in particular the Chomsky Hierarchy for the analysis of natural languages.^{53–55} Possibly, the main problem in this regard is that none of the tests employed in our study can be considered strictly equivalent to the tasks administered to assess the ability to understand and use artificial grammars, which only take into account formal aspects. That is, the outlines involved in the type-1 visuospatial task represent real objects (animals) and not merely random patterns. In the same way, the type-1 linguistic task included real sentences rather than meaningless combinations of structures. In fact, when semantic cues are added to the stimuli engaged in this type of study, results improve substantially and patients are capable of learning more complex formal grammars.⁵⁶

Consequently, we cannot rule out that the results achieved by PD patients might have been worse if tasks had assessed purely formal aspects (which would support the idea that PD can be characterised as a selective impairment of a context-sensitive computational system). In any case, and although it means that we should optimise the methodological tools available to date, we feel it worthwhile to continue working on breaking down PD dysfunctions into computational primitives that may be selectively affected.

Lastly, it would be useful to assess the integrity of those primitives during the prodromal stage of the disease. In other diseases involving the basal ganglia, other domains, including language, are affected simultaneously; however, in these cases, linguistic deficits can be detected even before the disease is diagnosed. This is the case of Huntington disease, which is caused by the selective destruction of GABAergic neurons in the caudate nucleus,⁵⁷ a sub-cortical area that, according to the linguistic processing model supported in our study, represents the substrate for the sequencer device of language. Even during preclinical stages, subjects who will end up developing Huntington disease score abnormally low on tests evaluating different abilities, including language, visuospatial processing, and psychomotor speed.⁵⁸ If this was to be the case in PD, context-sensitive computational tasks might represent an endophenotype of the disease (in line with the ideas proposed by Gottesman and Gould⁵⁹), which would enable not only a more precise characterisation of the aetiology of the disease but also a more accurate early diagnosis, since this approach focuses on more biological aspects rather than exclusively on symptoms. To this end, it would also be interesting to assess patients not diagnosed with PD using the tasks employed in our study.

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Conflicts of interest

None.

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