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The Road Less Traveled: Alternative Pathways for Action-Verb Processing in Parkinson's Disease

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Abstract. Action verbs are critically embodied in motor brain networks. In Parkinson's disease (PD), damage to the latter compromises access to such words. However, patients are not fully incapable of processing them, as their performance is far from floor level. Here we tested the hypothesis that action-verb processing in PD may rely on alternative disembodied semantic circuits. Seventeen PD patients and 15 healthy controls listened to action verbs and nouns during functional MRI scanning. Using cluster-mass analysis with a permutation test, we assessed task-related functional connectivity considering seeds differentially engaged by action and non-action words (namely, putamen and M1 versus posterior superior temporal lobe, respectively). The putamen seed showed reduced connectivity within the basal ganglia in patients for both lexical categories. However, only action verbs recruited different cortical networks in each group. Specifically, the M1 seed exhibited more anterior connectivity for controls and more posterior connectivity for patients, with no differences in the temporal seed. Moreover, the patients' level of basal ganglia atrophy positively correlated with their reliance on M1-posterior connectivity during action-verb processing. PD patients seem to have processed action verbs via non-motor cortical networks subserving

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amodal semantics. Such circuits may afford alternative pathways to process words when default embodied mechanisms are disturbed. Moreover, the greater the level of basal ganglia atrophy, the greater the patients' reliance on this alternative route. Our findings offer new insights into differential neurofunctional mechanisms recruited to process action semantics in PD.

Keywords: Functional magnetic resonance imaging, language, motor cortex, Parkinson's disease, semantics

INTRODUCTION

Action verbs (i.e., verbs denoting bodily movements) are critically embodied in motor brain networks [1]. In Parkinson's disease (PD), the latter are specifically compromised by loss of dopaminergic neurons projecting from the substantia nigra to the putamen [2], leading to differential or selective difficulties to access such words [3–5]. However, patients are not fully incapable of processing them, as their performance is typically far from floor level (e.g., [6, 7]) and their ratio of occurrence in spontaneous speech is similar to that of controls [3]. Action-verb processing may then be relying on alternative semantic circuits. Suggestively, in addition to key primary motor hubs [1], action verbs also engage temporal and otherwise posterior non-motor areas implicated in noun processing [8] and amodal semantics at large [1, 9, 10]. Crucially, some of these regions are preserved in early and even advanced stages of PD [2].

Accordingly, we hypothesized that action-verb processing in PD may be differentially subserved by such non-motor circuits. To test this conjecture, we assessed functional magnetic resonance imaging (fMRI) patterns in PD patients and healthy controls while they listened to action verbs and nouns denoting non-manipulable objects. We selected seeds known to be differentially engaged by processing of action and non-action words (namely, putamen and M1 versus posterior superior temporal lobe, respectively). Evidence of alternative routes for processing action verbs in PD patients would suggest reliance on different lexico-semantic mechanisms, offering new hints into the linguistic impact of motor-network disruptions.

MATERIALS AND METHODS

Participants

Thirty-two native Spanish speakers participated in this study. Seventeen (10 female) were predemented PD patients, clinically diagnosed by at least two neurologists (O.B., A.C., A.V.) following previously reported protocols [6] (see Supplementary Material 1). Patients completed all neurological and cognitive evaluations during the "on" phase of medication (levodopa or a dopamine agonist). None of them presented other neurological disorders or chronic major psychiatric conditions and most were in early disease stages. The remaining 15 participants (8 female) were sociodemographically-matched controls with no history of psychiatric or neurological disease. Except for two patients and one control, all subjects were right-handed. Table 1 offers additional participant data and statistical comparisons between groups.

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

Data acquisition

Word listening task

Participants carried out two fMRI single-word processing studies, each lasting 12 minutes and featuring high-frequency Spanish items. In both cases, participants were instructed to attentively listen to each word. As in previous research, no overt motor responses were required [11, 12]. In the Noun Study, participants listened to non-manipulable object nouns ($n = 147$), that is, names of concrete, non-graspable entities (e.g., *casa* [*house*]) (Fig. 1A1). In the Action-verb Study, stimuli consisted of infinitive verbs ($n = 150$) denoting bodily movements (e.g., *bailar* [*dance*]) (Fig. 1B1). For details, see Supplementary Material 2.

Neuroimaging recordings

Structural and fMRI recordings were acquired through a Philips Ingenia 3.0 T with a standard 8-channel head coil. A T1-weighted spin echo sequence was used to generate 160 contiguous axial slices (TR/TE = 4.8/2.1; FOV = 240 × 180 mm^2, flip angle = 8°. 1 mm isotropic). For functional imaging analysis, 25 axial slices were acquired parallel to the plane connecting the anterior and posterior commissures and covering the whole brain (TR/TE = 2000/30; voxel size = 2.5 × 2.5 × 4.5 mm^3; FOV = 240 × 240 mm^2; flip angle: 90°). For details, see Supplementary Material 3.

Table 1
Demographic data and clinical evaluation

		PD $n = 17$	Controls $n = 15$	Statistical comparison p-value*
Demographic variables	Gender (F:M)	10:7	8:7	$0.75^{\#}$
	Age (years)	55.29 (11.67)	52.53 (11.71)	0.51^{*}
	Education (years)	11.18 (5.59)	11.67 (5.92)	0.81^{*}
Clinical variables	UPDRS-III	28.35 (13.57)		
	H&Y	2.38 (0.65)		
	Years since diagnosis	6.85 (5.38)		

Note: Values are expressed as mean (SD) with the exception of gender. PD, Parkinson's disease patients; UPDRS-III, Unified Parkinson's Disease Rating Scale, part III; H&Y, Hoehn &Yahr scale. $^{\#}p$-value calculated with a chi-square test. $^{*}p$-values calculated with t-tests for independent samples.

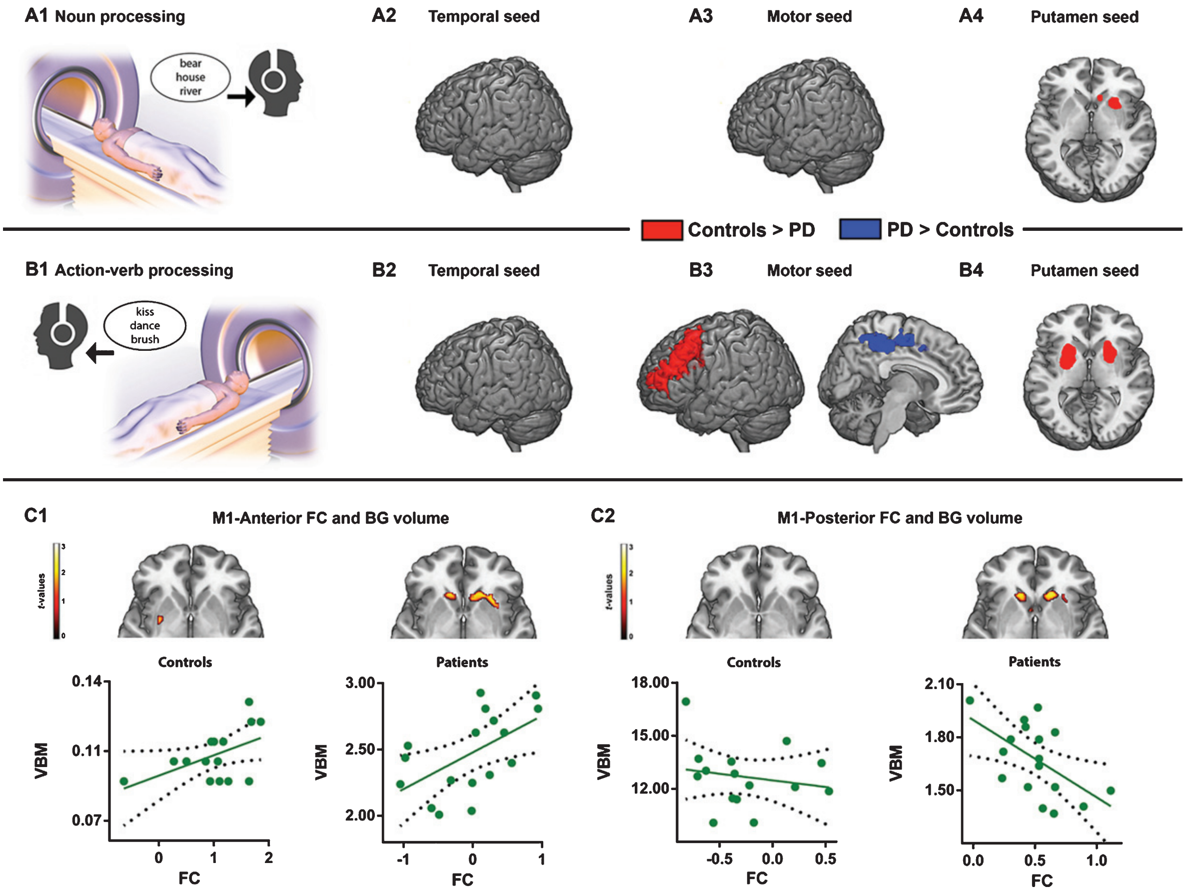

Fig. 1. A1) Subjects listened to non-manipulable concrete nouns inside the MRI scanner. A2–A4) Seed analysis differences between controls and patients during noun processing. B1) Subjects listened to action verbs inside the MRI scanner. B2–B4) Seed analysis differences between controls and patients during action-verb processing. Red colors indicate clusters where connectivity with the respective seed was significantly higher ($p < 0.05$, FWE corrected at cluster level) for controls than for patients. Blue colors indicate clusters where connectivity with the respective seed was significantly higher ($p < 0.05$, FWE corrected at cluster level) for patients than for controls. C1-C2) Correlations between BG volume and M1 functional connectivity during action-verb processing, for controls and patients. Scatterplots depict the dispersion of correlation results. PD, Parkinson's disease patients; FC, functional connectivity; BG, basal ganglia; VBM, voxel-based morphometry.

Data analysis

Seed analyses. We used seed analysis to explore between-group differences in each study separately. We selected seeds differentially related to action verbs and concrete nouns. First, we chose a temporal seed, located in a subregion more critically related to noun than verb processing (posterior superior temporal gyrus) [8]. Second, we considered a frontal seed more critically associated with action verbs, located in M1 [1]. Finally, given the association between basal ganglia (BG) disruptions and action-verb deficits in PD [4–6], we established a mask in this structure and placed a seed in the putamen [13], whose dynamics are compromised by alterations of substantia nigra projections in PD patients [2]. All seeds were located in the left hemisphere, which is dominant for language in over 95% of right-handers [14, 15].

To identify key circuits recruited by the groups during the tasks, we calculated the functional connectivity (FC) of these seeds in each study. For each participant, we extracted the BOLD signal time-course from the voxels within each seed region. FC maps were obtained by correlating these data to every voxel in the brain via Pearson's correlation coefficient. The ensuing maps were then recalculated by reference to their z scores. We applied a cluster mass analysis to compare each FC map between groups. Statistical analyses were performed via a permutation test on FSL's randomize tool. For details, see Supplementary Material 4.

Correlations between FC patterns and BG volume. We also evaluated the association between FC results and gray matter differences in the BG, the key target of atrophy in early PD [2]. First, using SPM12 software, we calculated differences in BG volume between groups via voxel-based morphometry (VBM) –for details, see Supplementary Material 5. Then, given our focus on the role of motor regions in action-verb processing, we performed regression analyses of results from the Action-verb Study to assess correlations between BG volume and FC patterns from the M1 seed in each group. For details, see Supplementary Material 7.

RESULTS

Seed analysis

Noun study

During noun listening, no connectivity differences emerged between groups in either the temporal (Fig. 1A2) or the motor (Fig. 1A3) seeds. However, the putamen seed showed reduced FC with the right caudate and pallidum nucleus for patients (Fig. 1A4). For details, see Supplementary Material 6.

Action-verb study

Action-verb processing yielded no differences in the temporal seed (Fig. 1B2). However, FC from the motor seed was markedly different between groups. Whereas patients showed greater long-range FC between M1 and bilateral posterior areas (median cingulate and paracingulate gyri), controls exhibited higher connectivity between M1 and left anterior regions – in particular, the inferior frontal gyrus, IFG (Fig. 1B3). Finally, results from the putamen seed showed reduced connectivity within the BG for patients (Fig. 1B4). For details, see Supplementary Material 6.

Correlations between BG volume and between-group differences in FC for action verbs

For both groups, BG volume was positively associated with FC between M1 and IFG during action-verb processing (Fig. 1C1). Conversely, correlations between BG volume and FC between M1 and posterior regions differed between groups. The correlation was not significant for controls, but it was significant and negative for patients (Fig. 1C2). For details, see Supplementary Material 7.

DISCUSSION

We explored whether action-verb processing in PD relies on alternative, disembodied pathways. Unlike non-manipulable concrete nouns, action verbs engaged different cortical networks in controls and patients, with greater frontal connectivity between motor hubs in the former and increased reliance on posterior non-motor regions in the latter. Notably, the engagement of this alternative pathway was proportional to the level of BG atrophy in patients. It appears, then, that action verbs in this population could be processed through amodal circuits, a possibility which offers new insights into possible compensatory lexico-semantic mechanisms after frontostriatal disruptions.

Noun processing in PD

Although PD involves frontostriatal damage, M1 connectivity did not discriminate between groups during processing of non-manipulable concrete nouns. Abundant research indicates that these words are mainly subserved by temporal and otherwise posterior hubs [8], which are typically preserved in early

PD [2]. This could probably account for the absence of between-group differences in our temporal seed analysis and, more generally, for the finding that verbal skills in this population are better preserved for nouns than action verbs [4, 5].

However, connectivity within the BG was significantly reduced in patients during noun processing. This aligns with evidence that frontostriatal damage may also compromise object-related information [6]. Note, however, that BG integrity is much less critical for nouns than action verbs, as activation increases for the former over the latter are mainly triggered in posterior cortical regions [8].

In short, cortical mechanisms specialized for processing non-manipulable concrete nouns were similar in both groups, despite marginal differences in the role of BG circuits.

Action-verb processing in PD

Relative to patients, controls exhibited greater connectivity between anterior (M1 and IFG) and within subcortical (BG) motor regions during action-verb processing. This corroborates the crucial involvement of movement-related networks for embodied action semantics [1, 9]. Conversely, PD patients showed radically different patterns. FC from M1 involved posterior brain areas (median cingulate and paracingulate gyri) implicated in amodal lexical semantics [16]. This suggests that action-verb processing in PD involves alternative, non-motor pathways.

Amodal semantic systems have been acknowledged as secondary contributors to action-verb processing [9, 10]. We propose that these disembodied networks are taking over the task at large in PD patients, given that their default embodiment mechanisms are dysfunctional. This interpretation finds support in our correlation results. First, BG volume in controls positively correlated with the recruitment of anterior motor regions for action verbs, corroborating the crucial role of frontostriatal networks for grounding this word class [5–7]. This was also true in PD patients, which indicates that as BG atrophy progresses, action-verb processing depends less on connectivity between frontal motor hubs (M1 and IFG). Moreover, BG volume negatively correlated with reliance on nonmotor circuits for action-verb processing in PD. Thus, the larger the damage within the BG, the greater the reliance on amodal circuits for processing these words. Importantly, the latter pattern was specific to PD patients, which could suggest a compensatory role for the amodal pathway we have identified.

Note that the patients performed the tasks during the "on" phase of medication, as is typically done in fMRI research to prevent their movements from spoiling the data [17, 18]. This circumstance created more stringent testing conditions for our hypothesis, given that levodopa has been observed to differentially improve action-verb processing in PD patients [19, 20]. The fact that alternative pathways were selectively recruited for this word class despite pharmacological compensation speaks to the robustness of our finding.

Our results give rise to new perspectives on alternative mechanisms subserving action verbs when relevant embodied systems are disrupted by physiopathology. It seems that if the default motor pathway for action verbs is compromised, less fine-grained semantic networks are called upon in a manner proportional to motor network atrophy.

A new option for clinical interventions in PD?

The present results have clinical implications. Unlike what happens in healthy subjects [21], stimulation of motor hubs in PD does not facilitate processing of specific types of action verbs [22]. Such null results may reflect the functional irrelevance of motor structures for action-verb processing in the patients. Future stimulation studies could assess the conjecture that action-verb processing in PD may improve upon stimulation of *posterior* regions affording alternative, disembodied pathways. This hitherto untested hypothesis could inspire new approaches to cognitive intervention for PD and other motor disorders.

Limitations and avenues for further research

Our work has limitations. First, our sample was relatively small. However, robust findings have been obtained with similar or smaller samples [4]. Second, our protocol lacked behavioral lexical tasks, which should be included in future replications to correlate with fMRI results and thus obtain anatomo-clinical correlations. Note, however, that our hypothesis is independent from behavioral performance, and that previous research has also shed light on lexical mechanisms through passive listening tasks (e.g., [12]). Third, neuropsychological assessments could also add important insights, especially since object and action semantics are differentially related to extralinguistic impairments in PD [6].

Finally, it would be important to assess whether our results were influenced by the distinctive morphological properties of Spanish verbs. Whereas verb-processing studies in this language must necessarily use morphologically complex words (since verb stems, also called roots, have no lexical status on their own), similar studies in other languages, like English, usually employ morphologically simple words (English infinitive verbs typically coincide with verb stems). Thus, although the dependence of action verbs on motor circuits is well established for English-speaking neurotypicals [1], replications of the present study in English would be useful to determine whether the recruitment of alternative pathways for action verbs in our Spanish-speaking PD patients was influenced by the role of (disrupted) frontostriatal circuits in morphological processing [23, 24].

CONCLUSION

Unlike healthy subjects, PD patients seem to process action verbs via a non-motor pathway involved in coarse-grained, amodal lexical semantics. Reliance on this alternative network was directly associated with the level of BG atrophy, suggesting that the recruitment of disembodied mechanisms is proportional to the disruption of embodied ones. These results could shed new light on alternative pathways operative during language processing in PD, paving the way for clinical innovations.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-160737.

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