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Original Article

Multimodal neurocognitive markers of naturalistic discourse typify diverse neurodegenerative diseases

Agustina Birba[1,2], Sol Fittipaldi[1,2], Judith C. Cediel Escobar[3,4], Cecilia Gonzalez Campo[1,2], Agustina Legaz[1,2], Agostina Galiani[5], Mariano N. Díaz Rivera[1,6], Miquel Martorell Caro[2], Florencia Alifano[2], Stefanie D. Piña-Escudero[7], Juan Felipe Cardona[3], Alejandra Neely[8], Gonzalo Forno[9,10,11], Mariela Carpinella[12,13], Andrea Slachevsky[9,14,15,16], Cecilia Serrano[17], Lucas Sedeño[2], Agustín Ibáñez[1,2,8,18], Adolfo M. García[1,2,18,19]

[1]Centro de Neurociencias Cognitivas, Universidad de San Andrés, B1644BID Buenos Aires, Argentina,
[2]National Scientific and Technical Research Council (CONICET), C1425FQD Buenos Aires, Argentina,
[3]Facultad de Psicología, Universidad del Valle, Santiago de Cali 76001, Colombia,
[4]Departamento de Estudios Psicológicos, Facultad de Derecho y Ciencias Sociales, Universidad Icesi, Cali 1234567, Colombia,
[5]Institute of Cognitive and Translational Neuroscience (INCyT), INECO Foundation, Favaloro University, CONICET, C1060AAF Buenos Aires, Argentina,
[6]National Agency of Scientific and Technological Promotion, C1425FQD Buenos Aires, Argentina,
[7]Sandler Neurosciences Center, UCSF Global Brain Health Institute, San Francisco, CA 94158, USA,
[8]Latin American Brain Health Institute (BrainLat), Universidad Adolfo Ibáñez, 8320000 Santiago, Chile,
[9]Neuropsychology and Clinical Neuroscience Laboratory, Physiopathology Department, ICBM, Neurosciences Department, Faculty of Medicine, University of Chile, 8380000 Santiago, Chile,
[10]School of Psychology, Universidad de los Andes, 7620001 Santiago, Chile,
[11]Alzheimer's and other cognitive disorders group, Institute of Neurosciences, University of Barcelona, 8007 Barcelona, Spain,
[12]Unidad de Neurociencias, Instituto Conci Carpinella, 5000 Córdoba, Argentina,
[13]Facultad de Medicina, Universidad Católica de Cuyo Sede San Luis, 5700 San Luis, Argentina,
[14]Gerosciences Center for Brain Health and Metabolism, 7800003 Santiago, Chile,
[15]Memory and Neuropsychiatric Clinic (CMYN) Neurology Department, Hospital del Salvador & University of Chile, 7500000 Santiago, Chile,
[16]Servicio de Neurología, Departamento de Medicina, Clínica Alemana-Universidad del Desarrollo, 7690000 Santiago, Chile,
[17]Unidad de Neurología Cognitiva, Hospital César Milstein, C1221AC Buenos Aires, Argentina,
[18]Global Brain Health Institute, University of California, San Francisco, CA 94158, US; and Trinity College, Dublin D02 DP21, Ireland,
[19]Departamento de Lingüística y Literatura, Facultad de Humanidades, Universidad de Santiago de Chile, 8431166 Santiago, Chile

*Address correspondence to Adolfo M. García, PhD, Universidad de San Andrés & CONICET, Vito Dumas 284, B1644BID Victoria, Buenos Aires, Argentina. Email: adolfo.garcia@gbhi.org; Agustín Ibáñez, PhD, Universidad de San Andrés & CONICET, Vito Dumas 284, B1644BID Victoria, Buenos Aires, Argentina. Email: agustin.ibanez@gbhi.org.

Neurodegeneration has multiscalar impacts, including behavioral, neuroanatomical, and neurofunctional disruptions. Can disease-differential alterations be captured across such dimensions using naturalistic stimuli? To address this question, we assessed comprehension of four naturalistic stories, highlighting action, nonaction, social, and nonsocial events, in Parkinson's disease (PD) and behavioral variant frontotemporal dementia (bvFTD) relative to Alzheimer's disease patients and healthy controls. Text-specific correlates were evaluated via voxel-based morphometry, spatial (fMRI), and temporal (hd-EEG) functional connectivity. PD patients presented action–text deficits related to the volume of action–observation regions, connectivity across motor-related and multimodal-semantic hubs, and frontal hd-EEG hypoconnectivity. BvFTD patients exhibited social–text deficits, associated with atrophy and spatial connectivity patterns along social-network hubs, alongside right frontotemporal hd-EEG hypoconnectivity. Alzheimer's disease patients showed impairments in all stories, widespread atrophy and spatial connectivity patterns, and heightened occipitotemporal hd-EEG connectivity. Our framework revealed disease-specific signatures across behavioral, neuroanatomical, and neurofunctional dimensions, highlighting the sensitivity and specificity of a single naturalistic task. This investigation opens a translational agenda combining ecological approaches and multimodal cognitive neuroscience for the study of neurodegeneration.

Key words: embodied cognition; fMRI/hd-EEG functional connectivity; naturalistic texts; neurodegeneration; voxel-based morphometry.

Introduction

The multiscalar impact of neurodegeneration encompasses behavioral, anatomical, and connectivity levels (Arvanitakis et al. 2019). These dimensions are differentially affected depending on the disease and its higher-order impairments (García-Cordero et al. 2016; Melloni et al. 2016). In particular, Parkinson's disease (PD) and behavioral variant frontotemporal dementia (bvFTD) patients exhibit deficits in grasping action-related and social verbal meanings, respectively, together with

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structural and functional brain abnormalities (Gregory et al. 2002; Birba et al. 2017). However, no existing framework captures such disease-specific patterns via naturalistic stimuli, creating a gap between ecological neurocognitive models and translational research on neurodegeneration. Here we combined behavioral, neuroanatomical (voxel-based morphometry [VBM]), and resting-state functional connectivity (rsFC) measures (derived from fMRI and high-density EEG [hd-EEG]) to examine core signatures of naturalistic action- and social-discourse comprehension in PD and bvFTD, vis-à-vis healthy controls and Alzheimer's disease (AD) patients.

Beyond dominant motor symptoms and diverse neurocognitive dysfunctions (Helmich et al. 2012), PD involves deficits in processing action language—verbal materials denoting bodily movement (Boulenger et al. 2008; Fernandino et al. 2013; Gallese and Cuccio 2018; Cervetto et al. 2021). Indeed, comprehension of actions is affected early, selectively, and primarily in PD (Birba et al. 2017). These deficits entail alterations in movement-related circuits, such as atrophy of motor regions (Birba et al. 2017), altered activation (Péran et al. 2009) and connectivity (Moguilner et al. 2021a) patterns along motor networks, and motor-related temporal (hd-EEG) rsFC abnormalities (Melloni et al. 2015). Thus, verbal tasks evoking bodily actions could afford sensitive multidimensional signatures of PD (Birba et al. 2017).

Regarding bvFTD, patients exhibit various social cognition disorders (Piguet et al. 2011), including early difficulties in linguistic tasks taxing emotional, empathic, and mentalizing skills (Hsieh et al. 2012; Ibáñez et al. 2018), as well as faux pas detection (Gregory et al. 2002) and social coordination (McMillan et al. 2012). These domains are subserved by fronto-insulo-temporal networks and frontotemporal oscillatory (hd-EEG) dynamics that are specifically affected in bvFTD (Piguet et al. 2011; Ibáñez et al. 2017) and underpin processing of verbal social stimuli (Perdikis et al. 2017; Rice and Hoffman 2018). Therefore, linguistic paradigms tapping social information comprehension may provide multiscalar markers of bvFTD.

Yet, these antecedents mainly rely on single-item tasks. Though critical to capture selective disruptions and potential markers of neurodegenerative disorders (Hardy et al. 2016; Birba et al. 2017; Geraudie et al. 2021), such paradigms neglect the contextual and cohesive richness of real-life discourse, offering low ecological validity (Hasson et al. 2018). Importantly, those alterations cannot be a priori assumed to hold in discourse-level materials, as contextual information influences category-specific word processing (Van Dam et al. 2010), favors the retrieval of task-relevant information (Ledoux et al. 2006), and facilitates performance in persons with brain disorders (Aviezer et al. 2009; García et al. 2018). Furthermore, findings of category-specific deficits in PD and bvFTD lack an integrated theoretical rationale enabling their joint conceptualization. Promisingly, action-related deficits in PD (García et al. 2018) and sociocognitive difficulties in bvFTD (McMillan et al. 2012) can be synergistically interpreted via *embodied cognition models*, which posit that language understanding depends on reactivations of sensorimotor and affective networks (Pulvermüller 2013). Strategically, our framework uses a naturalistic embodied paradigm including an action text (AT), a nonaction text (nAT), a social text (ST), and a nonsocial text (nST). This allows tackling differential patterns of deficit in each disorder. To further test for specificity, we also included AD patients, whose broad memory impairments and widespread neural alterations would potentially affect all text categories (Piguet et al. 2011; Melloni et al. 2015; García-Cordero et al. 2016; Melloni et al. 2016). This way, we aimed to ascertain the ecological validity, nosological specificity, and neurobiological signatures of these disturbances.

Considering previous findings, we raised three predictions. First, PD patients would exhibit selective action comprehension deficits related to atrophy and spatial rsFC alterations along action-related circuits, together with altered connectivity signatures. Second, bvFTD patients would be selectively impaired in grasping social information, with this pattern being linked to disruptions of areas and networks subserving social cognition, as well as frontotemporal hd-EEG hypoconnectivity. Finally, AD should entail cross-categorical deficits associated to widespread neural disturbances and memory deficits. Briefly, our naturalistic framework aims to track discriminatory embodied signatures of PD and bvFTD across multiple neurocognitive dimensions.

Materials and Methods

Participants

The study comprised 109 native Spanish speakers: 25 PD patients, 20 bvFTD patients, 23 AD patients, and 41 controls. This sample size reaches a power of 0.96 (Supplementary Material 1). Participants were recruited in three centers from the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) (Ibáñez, Pina-Escudero, et al. 2021b; Ibáñez, Yokoyama, et al. 2021c). Unified procedures ensure consistency across sites so that participants can be reliably framed as an integrated multicentric sample (Ibáñez, Pina-Escudero, et al. 2021b; Ibáñez, Yokoyama, et al. 2021c). These same procedures have been reported in previous works (Baez et al. 2014; Melloni et al. 2016; García et al. 2017; Donnelly-Kehoe et al. 2019; Moguilner et al. 2020; Legaz et al. 2021; Salamone et al. 2021; Ibáñez, Fittipaldi, et al. 2021a). All participants had normal or corrected-to-normal hearing. Patients were diagnosed by expert neurologists following UKPD-SBB standards for PD (Hughes et al. 1992), current criteria for probable bvFTD (Rascovsky et al. 2011), and NINCDS-ADRDA clinical criteria for AD (McKhann et al. 2011). Diagnoses were supported by extensive neurological, neuropsychiatric, and neuropsychological examinations (Piguet et al. 2011)

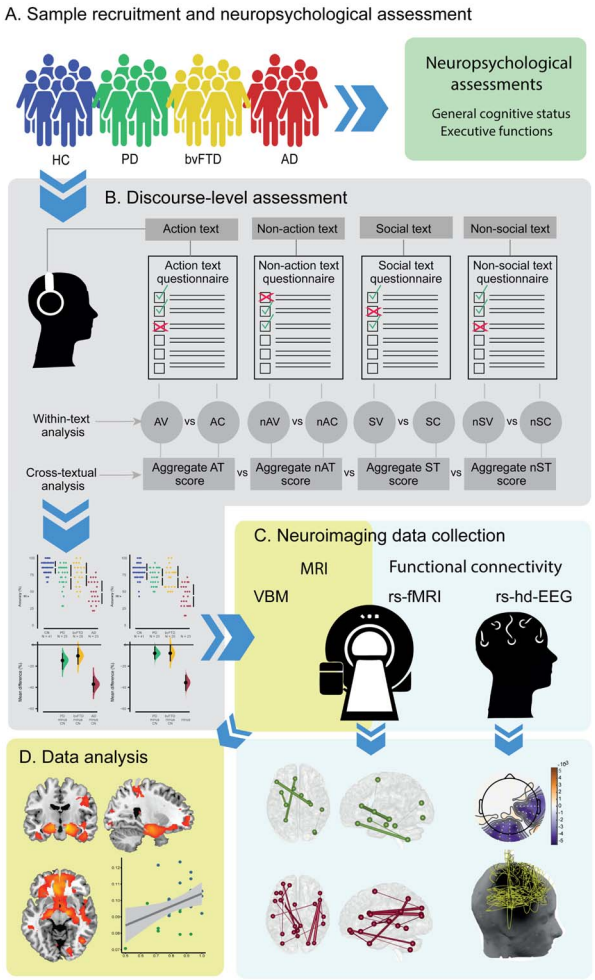

Fig. 1. Experimental design and data analysis. (*A*) Sample collection and neuropsychological assessment. PD patients, bvFTD patients, AD patients, and healthy controls were included in the study upon completion of a neuropsychological assessment that complemented their clinical evaluation. (*B*) Discourse-level assessment. In the discourse-level task, participants listened to four naturalistic texts, namely an action text (AT), a nonaction text (nAT), a social text (ST), and a nonsocial text (nST). After each one, they answered a 14-item multiple-choice comprehension questionnaire tapping on verb-related and circumstantial information. Results were first subjected to within-text analyses, to evaluate whether a specific condition (verbs or circumstances) in each text yielded impairments in each patient sample compared with controls. Then, we performed a cross-textual analysis, including "text" as a factor and evaluating all its possible interactions with "group" and "condition." After checking that the variable "condition" did not interact with "group," we averaged the two conditions per text and generated four aggregate scores (AT, nAT, ST, nST), thus reducing dimensionality while increasing variance across texts for the regressions with MRI, fMRI, and hd-EEG data. (*C*) Neuroimaging data collection. Participants underwent a resting-state MRI and fMRI session. Then, a subsample of participants completed a 10-min resting-state protocol while hd-EEG signals were recorded. (*D*) Data analysis. The aggregate text scores were regressed in a VBM analysis and associated with the functional connectivity metrics derived from the resting-state fMRI and hd-EEG sessions. HCs: healthy controls; PD: Parkinson's disease patients; bvFTD: behavioral variant frontotemporal dementia patients; AD: Alzheimer's disease patients; MoCA: Montreal Cognitive Assessment; IFS: INECO Frontal Screening battery; AV: action verbs; AC: action circumstances; nAV: nonaction verbs; nAC: nonaction circumstances; SV: social verbs; nSV: nonsocial verbs; MRI: magnetic resonance imaging; VBM: voxel-based morphometry; fMRI: functional magnetic resonance imaging; hd-EEG: high-density electroencephalography.

(Fig. 1A). No patient reported a history of other neurological disorders, psychiatric conditions, primary language deficits, or substance abuse.

PD patients had no symptoms of Parkinson-plus or significant atrophy patterns (Supplementary Material 2). They were assessed during the "on" phase of antiparkinsonian medication. Available UPDRS-III scores fell below the cutoff for mild/moderate symptoms. BvFTD exhibited sociobehavioral impairments as defined by caregivers (Piguet et al. 2011) and predominantly frontotemporal atrophy (Supplementary Material 2). AD patients presented executive dysfunction and working memory (WM) deficits, as established through the INECO Frontal Screening (IFS) battery (Torralva et al. 2009), as well as predominant temporohippocampal atrophy (Supplementary Material 2). Available CDR scores for bvFTD and AD patients fell slightly below and above the cutoff for mild dementia, respectively. All patient groups had mild cognitive impairment, based on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005). Controls were cognitively preserved, functionally autonomous, and had no background of neuropsychiatric disease or alcohol/drug abuse.

All groups were matched for age and education. A significant difference in sex emerged between bvFTD patients and controls. Thus, although no other group pair exhibited differences, all analyses were covaried for sex. For demographic and neuropsychological details, see Table 1.

All participants provided written informed consent pursuant to the Declaration of Helsinki. The study was approved by the Ethics Committees of the involved institutions.

Experimental Protocol

All participants completed a multidimensional protocol involving neuropsychological and discourse-level assessments, as well as MRI, fMRI, and hd-EEG recordings (Fig. 1).

Discourse-Level Task

Naturalistic Texts

All narratives were created through a systematic protocol (Trevisan and García 2019) for establishing semantic distinctions between text sets Table 2; García et al. 2018). The number of critical items manifesting the semantic contrasts between AT, nAT, ST, and nST was statistically controlled across texts, and so were relevant linguistic variables (Table 3). For details, see Supplementary Material 3.

Comprehension Questionnaires

Each text had a 14-item multiple-choice questionnaire featuring wh- questions (Trevisan and García 2019). Half the questions pointed to verb-related information and half to circumstances, realized by adverbial or prepositional phrases. Questions were presented following the stories' sequence of events. Successive questions

Table 1. Demographic and neuropsychological information

	HC N = 41	PD N = 25	bvFTD N = 20	AD N = 23	Main effect	Pairwise comparisons		
						Groups	estimate	*P*-value
Demographic data								
Sex (F:M)	30:11	12:13	6:14	16:7	$\chi^2 = 12.64$ $P = 0.005$[a]	HC-PD	3.23	0.07[b]
						HC-bvFTD	8.65	0.003[b]
						HC-AD	0.0004	0.98[b]
Years of age	72.05 (5.84)	7.40 (7.00)	68.20 (9.41)	73.30 (4.94)	$F = 2.40$ $P = 0.07$[a]	HC-PD	0.98	0.33[c]
						HC-bvFTD	1.67	0.15[c]
						HC-AD	-0.91	0.36[c]
Years of education	13.37 (3.56)	13.32 (4.54)	14.95 (5.18)	11.87 (4.38)	$F = 1.83$ $P = 0.14$[a]	HC-PD	0.04	0.96[c]
						HC-bvFTD	-1.23	0.22[c]
						HC-AD	1.40	0.17c
Neuropsychological data								
MoCA (cutoff: 21[e])	25.65 (3.3)	23.32 (5.19)	21.79 (5.38)	17.43 (4.19)	$F = 16.17$ $P < 0.001$[a]	HC-PD	2.00	0.05[c]
						HC-bvFTD	2.87	0.008[c]
						HC-AD	7.77	<0.001[c]
IFS battery (cutoff: 25[f])	21.26 (4.07)	20.16 (5.22)	18.89 (5.56)	14.50 (5.29)	$F = 9.68$ $P < 0.001$[a]	HC-PD	0.89	0.81[c]
						HC-bvFTD	1.61	0.12[c]
						HC-AD	5.27	<0.001[c]
UPDRS-III[d] (cutoff: 32[g])	–	20.41 (14.70)	–	–				
CDR[d] (cutoff: 1[h])	–	–	0.84 (0.85)	1.14 (0.65)				

Notes: Data presented as mean (*SD*), with the exception of sex. HC: healthy controls; PD: Parkinson's disease; bvFTD: behavioral variant frontotemporal dementia; AD: Alzheimer's disease; MoCA: Montreal Cognitive Assessment; IFS: INECO Frontal Screening battery; UPDRS-III: Unified Parkinson's Disease Rating Scale, part III; CDR: Cognitive Dementia Rating. [a]*P*-values calculated via independent measures ANOVA. [b]*P*-values calculated via chi-squared test (χ^2). [c]*P*-values calculated via unpaired *t*-test. [d]Data from patients who completed the full clinical protocol. [e]Cutoff for MCI (Delgado et al. 2019). [f]Cutoff for mild effects (Torralva et al. 2009). [g]Cutoff for moderate effects (Martinez-Martin et al. 2015). [h]Cutoff for mild dementia (Morris 1991).

Table 2. General features of the texts

	AT	nAT	ST	nST
Theme	A day at the playground	A nightly outing	Two neighbors interacting	A peaceful day at home
Content	High action content	Low action content	High social content	Low social content
Verbs	Mostly motor processes	Mostly nonmotor processes	Mostly social nonmotoric processes	Mostly nonsocial motor process
Verb example	*Running*	*Waiting*	*Accepting (a request)*	*Exercising*
Circumstances	General circumstantial information	General circumstantial information	Socially laden circumstantial information	Nonsocially laden circumstantial information
Circumstance example	*Saturday afternoon*	*The street*	*Kindly*	*On his nightstand*

were independent from each other. Each question was accompanied by five options: a correct response, three incorrect responses, and "I don't remember." The latter option always appeared last; the other three were randomized across questions. Correct responses received one point; incorrect responses received zero. Each questionnaire had a maximum of 14 points (7 for verb-related questions, 7 for circumstantial questions). See Supplementary Material 4.

Procedure

First, a different narrative was administered for familiarization purposes. Each text was presented via stereo headphones. Subjects were instructed to close their eyes and listen attentively to answer some questions. Following each narration, the examiner overtly read each question and its options. When necessary, questions were read twice; if additional repetitions were requested, the item received zero points. Participants answered orally. The texts were counterbalanced across participants (Fig. 1B, top).

Discourse-Level Task Analyses

We performed two types of hypothesis-driven analyses. Based on the results of García et al. (2018), we first predicted specific deficits in action verbs for PD and, by extension, anticipated selective social language impairments in bvFTD. As in previous multimodal text-level research with multiple patient groups (Moguilner et al. 2021b), we carried out a within-text analysis via 4 × 2 mixed-effects ANOVAs, with a between-subject factor ("group") and a within-subject factor ("condition": verbs, circumstances). Second, to increase stringency, we implemented a cross-textual analysis via a 4x4x2

Table 3. Linguistic features of the texts

	AT	nAT	ST	nST	Statistic	P-value*	Pairwise comparisons**
Characters[a]	936	974	959	949	$X^2 = 0.81$	0.85	
Words	207	203	199	199	$X^2 = 0.21$	0.97	
Nouns	48	44	43	40	$X^2 = 0.74$	0.86	
Verbs	**32**	**32**	**32**	**32**	$X^2 = 1$	0.00	
Action verbs	**24**	**1**	**7**	**15**	$X^2 = 25.42$	<0.001	**AT-nAT**: $X^2 = 21.16$, $P < 0.001$ **AT-ST**: $X^2 = 9.33$, $P = 0.002$ **nST-nAT**: $X^2 = 12.25$, $P < 0.001$ **nAT-ST**: $X^2 = 4.5$, $P = 0.03$.
Nonaction verbs	**8**	**31**	**25**	**17**	$X^2 = 14.75$	0.002	**AT-nAT**: $X^2 = 13.56$, $P < 0.001$ **AT-ST**: $X^2 = 8.75$, $P = 0.003$ **nST-nAT**: $X^2 = 4.1$, $P = 0.04$.
Social verbs	**5**	**6**	**24**	**0**	$X^2 = 37.8$	<0.001	**ST-AT**: $X^2 = 12.48$, $P < 0.001$ **ST-nAT**: $X^2 = 1.8$, $P = 0.001$ **ST-nST**: $X^2 = 24$, $P < 0.001$ **nST-AT:** $X^2 = 5$, $P = 0.02$ **nST-nAT**: $X^2 = 6$, $P = 0.01$.
Nonsocial verbs	**27**	**26**	**8**	**32**	$X^2 = 13.13$	0.004	**ST-AT**: $X^2 = 1.31$, $P = 0.001$ **ST-nAT**: $X^2 = 9.5$, $P = 0.002$ **ST-nST**: $X^2 = 14.4$, $P < 0.001$.
CAs	**27**	**22**	**28**	**30**	$X^2 = 1.29$	0.72	
Social CAs	**4**	**2**	**15**	**0**	$X^2 = 25.67$	<0.001	**ST-AT**: $X^2 = 6.36$, $P = 0.01$ **ST-nAT**: $X^2 = 9.9$, $P = 0.001$ **ST-nST**: $X^2 = 15$, $P < 0.001$.
Nonsocial CAs	**23**	**20**	**13**	**30**	$X^2 = 6.93$	0.07	**ST-nST**: $X^2 = 6.72$, $P = 0.009$.
Frequency[b]	1.64	1.79	1.73	1.82	$F = 1.23$	0.29	
Familiarity[b]	6.17	6.28	6.33	6.23	$F = 0.85$	0.46	
Imageability[c]	5.17	4.96	4.85	5.00	$F = 0.82$	0.48	
Syllabic length[c]	2.50	2.45	2.59	2.42	$F = 0.76$	0.52	
Graphemic length[c]	5.95	6.03	6.29	5.81	$F = 1.09$	0.35	
Sentences	22	22	22	23	$X^2 = 0.03$	0.99	
Minor sentences	3	3	3	4	$X^2 = 0.23$	0.97	
Simple sentences	8	8	8	8	$X^2 = 1$	0.99	
Compound sentences	3	4	4	5	$X^2 = 0.05$	0.91	
Complex sentences	8	7	7	6	$X^2 = 0.28$	0.96	
Grammaticality[d]	4.45	4.24	3.74	4.24	$F = 1.90$	0.12	
Coherence[d]	4.00	4.00	3.74	4.00	$F = 0.65$	0.63	
Comprehensibility[d]	4.50	4.38	4.25	4.38	$F = 0.37$	0.83	
Readability[e]	77.30	79.92	74.81	72.26			
Reading difficulty[f]	Fairly easy	Fairly easy	Fairly easy	Fairly easy			
Emotional valence[g]					Main effect of text: $F = 0.03$, $P = 0.99$.		Tukey's HSD tests showed no significant between-text effects in any emotion ($P > 0.05$).
Positive	55.45	56.06	6.71	61.18			
Negative	5.61	11.97	1.62	.31	Text-by-emotion interaction: $F = 2.98$, $P = 0.008$		
Neutral	39.09	31.97	36.04	39.29			

Notes: AT: action text; nAT: nonaction text; ST: social text; nST: nonsocial text; CAs: circumstantial adjuncts. [a]Character count was performed without counting spaces. [b]Data extracted from the LEXESP database, through B-Pal (Davis and Perea 2005). Results based on the mean of all content words in each text. [c]Data extracted from B-Pal (Davis and Perea 2005). Results based on the mean of all content words in each text. [d]Data collected from a panel of 13 Spanish-speaking undergraduates, based on Likert scales ranging from 1 (very low) to 5 (very high). [e]Based on the Szigriszt-Pazos Index (Szigrist Pazos 1993). [f]Based on the Inflesz scale rating (Barrio-Cantalejo et al. 2008). [g]Data collected from a panel of 17 native Spanish speakers, who rated each sentence in the texts in terms of overall emotional content (positive, negative, or neutral). *Alpha level set at $P < 0.05$. **Only significant differences are shown (omitted contrasts were all nonsignificant).

mixed-effects ANOVA, adding "text" as a within-subject factor. Since no group-by-condition interaction emerged, we averaged the two conditions per text and generated four aggregate scores (Fig. 1B, bottom), thus reducing dimensionality while increasing variance for brain–behavior associations. All analyses were covaried for sex. Contrasts of groups were inspected via Tukey's HSD tests. Note that, although our naturalistic stimuli are matched for multiple variables, comparisons across texts are not recommended for this paradigm, given that other important aspects were not controlled among narratives (e.g., mean utterance length, propositional density, and metaphoricity, as well as articulatory, phonetic, and prosodic aspects of the recordings) (García et al. 2018; Moguilner et al. 2021b). To control for mnesic skills, all text-level analyses were replicated covarying for the IFS WM index (added scores of the backward digits span, verbal WM, and spatial WM subtests). Alpha was set at $P < 0.05$. Effect sizes were calculated through partial eta squared (η^2) for ANOVA results and Cohen's d for pairwise comparisons. Analyses were performed on R (v.3.5.2).

MRI/fMRI Methods

Data Acquisition and Preprocessing

MRI/fMRI acquisition and preprocessing steps are reported following OHBM recommendations (Nichols et al. 2017). We acquired three-dimensional volumetric and 10-min-long resting-state MRI sequences (Fig. 1C, left). Twenty dimensional volumetric images (from eight controls and four patients per pathological group) and twenty-four functional images (from eight controls, five PD patients, six bvFTD patients, and five AD patients) were excluded due to artifacts. The resulting samples remained demographically matched (Supplementary Material 5). For specific parameters and MRI preprocessing details, see Supplementary Material 6.

VBM Analysis

For each control–patient tandem, we examined associations between whole-brain GM volume and the four aggregate text scores (AT, nAT, ST, nST) via SPM12's multiple regression module (Fig. 1D, left). As this is an exploratory study with a modest sample size per group, statistical significance was set to $P < 0.001$, uncorrected, with an extent threshold of 50 voxels, as in previous imaging studies (Melloni et al. 2016; Santamaria-García et al. 2017; Sedeño et al. 2017; de la Fuente et al. 2019). These parameters match recommended limits for the study's power levels (Woo et al. 2014), circumventing biases of liberal primary thresholds on false positives and achieving good balance between Type-I and Type-II errors (Lieberman and Cunningham 2009). See Supplementary Material 7.

fMRI rsFC Analysis

Based on the resting-state fMRI recordings, we examined positive associations between each text's aggregate score and rsFC patterns (Fig. 1C, middle). See Supplementary Material 6.

We used Pearson's correlations (García-Cordero et al. 2016) to establish rsFC between each pair of areas from the adjacency matrix, and then, for each control–patient set, we examined Spearman's correlations between connectivity patterns and each text's aggregate score. We used an uncorrected threshold of $P < 0.001$ (Jabbi et al. 2008; Kanske et al. 2016), which avoids detrimental effects of liberal primary thresholds on false positives (Fig. 1D, middle; Lieberman and Cunningham 2009). See Supplementary Material 8.

hd-EEG Methods

Data Acquisition and Preprocessing

Sixty-three participants (21 controls, 12 PD patients, 15 bvFTD patients, 15 AD patients) completed a 10-min-long hd-EEG rsFC protocol (Fig. 1C, right). These subsamples remained sociodemographically matched. See Supplementary Material 9.

hd-EEG rsFC Analysis

hd-EEG rsFC analysis was performed through the weighted symbolic mutual information (wSMI) metric, which captures nonlinear information sharing during cognitive operations (Hesse et al. 2016), including embodied semantic processes (Melloni et al. 2015). See Supplementary Material 9.1.

To identify disease-specific wSMI patterns, we performed nonparametric cluster-based permutations (1000 iterations) for independent samples (Maris and Oostenveld 2007), comparing controls to each patient group (Fig. 1D, upper right). Significant connections were plotted on a 3D head model (Fig. 1D, lower right). See Supplementary Material 10.

Next, for each control–patient set, we tested Pearson's correlations between the significant cluster's mean connectivity and the participants' aggregate scores in each text. Multiple comparisons among the four texts in each set of correlations were corrected via the false discovery rate (FDR) method. See Supplementary Material 10.

Results

Behavioral Results

Within-Text Analyses

The AT revealed a group-by-condition interaction (Fig. 2A, first inset) [$F_{(3,105)} = 3.1$, $P = 0.03$, $\eta^2 = 0.08$]. PD patients exhibited action verb deficits ($P < 0.001$, $d = 5.94$) and preserved outcomes on circumstances ($P = 0.76$, $d = 2.33$; Fig. 2A, second inset). The nAT yielded significant effects of group [$F_{(3,104)} = 31.5$, $P < 0.001$, $\eta^2 = 0.48$]. ST outcomes revealed significant effects of group [$F_{(3,104)} = 26.50$, $P < 0.001$, $\eta^2 = 0.43$], with controls outperforming bvFTD ($P = 0.01$, $d = 4.11$) but not PD ($P = 0.25$, $d = 2.74$) patients (Fig. 2A, third inset). The nST yielded a significant group effect [$F_{(3,104)} = 15.43$, $P < 0.001$, $\eta^2 = 0.31$], with controls performing similar to bvFTD patients ($P = 0.10$, $d = 4$) and better than PD patients ($P < 0.005$, $d = 5.33$; Fig. 2A, fourth inset). AD patients were outperformed by all three groups in the four texts (all P-values < 0.05). For full results, see Supplementary Material 11. All significant results remained so after covariation with WM outcomes. See Supplementary Material 12.

Cross-Textual Analysis

The cross-textual analysis (Fig. 2B) revealed a significant group-by-text interaction [$F_{(9,735)} = 2.36$, $P = 0.01$, $\eta^2 = 0.06$]. The group-by-condition and the group-by-text-by-condition interactions were nonsignificant (P-values > 0.18). Post hoc comparisons (Tukey's HSD: MSE $= 0.02$, $df = 223.4$) showed that, compared with controls, PD patients were selectively impaired in the AT ($P < 0.005$, $d = 4$ 0.31) and the nST ($P < 0.005$, $d = 5.88$), while bvFTD patients presented selective deficits in the ST ($P = 0.005$, $d = 5.88$)—with no significant differences between these pathological groups. AD patients

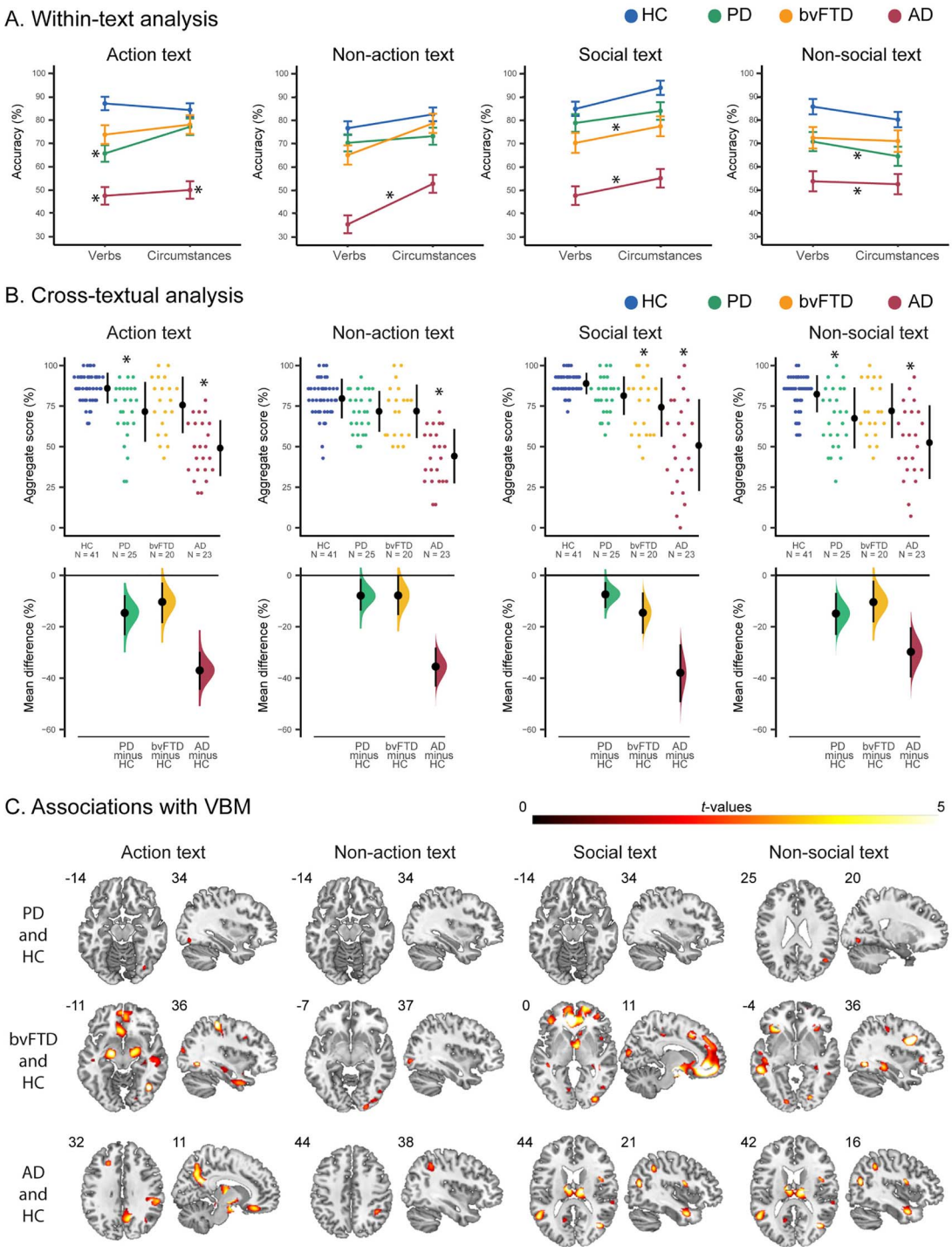

Fig. 2. Behavioral results and associations with VBM outcomes. (A) Within-text analyses. Results from the action text showed that, relative to controls, PD patients were impaired in verbs but not in circumstances; no such deficit was observed in bvFTD patients. Neutral text outcomes showed similar performance among controls and PD and bvFTD patients. Social text scores revealed a specific deficit for bvFTD patients relative to controls, in both conditions; no such deficit was observed in PD patients. Outcomes in the nonsocial text yielded a significant impairment of PD patients relative to controls; no such deficit was observed in bvFTD patients. AD patients were impaired in the two conditions of each text compared with all three other groups. Lateral asterisks denote condition-specific deficits relative to controls. Midline asterisks indicate significant differences for an entire text relative to controls. (B) Cross-textual analyses. Aggregate text scores confirmed the patterns observed in the within-text analyses. Relative to controls, PD patients were selectively impaired in the action and nonsocial texts, while bvFTD patients showed a selective impairment in the social text. AD patients were impaired in all four texts. Asterisks indicate significant differences relative to controls. (C) Associations with VBM. Each patient group was analyzed in tandem with controls to identify regions associated with the aggregate score of each text ($P < 0.001$ uncorrected, extent threshold = 50 voxels). For PD, significant associations were found for the action and nonsocial texts with action observation areas. For bvFTD, the social text was mainly associated with frontotemporal hubs of the so-called social network, whereas the action text was associated with action-related and multimodal semantic regions—the other two texts yielded sparser, unspecific associations. For AD, all four texts were associated with temporohippocampal regions typically underlying memory deficits in this disorder. HC: healthy controls; PD: Parkinson's disease; bvFTD: behavioral variant frontotemporal dementia; AD: Alzheimer's dementia. VBM: voxel-based morphometry.

were outperformed by all groups in all texts (all *P*-values < 0.05). For full results, see Supplementary Material 13. All significant results remained so after covariation with WM outcomes (Supplementary Material 14), and they were not driven by category-specific patterns of forgetfulness or fatigue (Supplementary Material 15).

Briefly, relative to controls, PD patients showed difficulties in the AT (and in the nST, which features high motility) and bvFTD patients presented ST deficits, whereas AD patients were impaired in all texts.

MRI/fMRI Results

Associations between VBM and Performance

In the PD–control tandem (Fig. 2C, top), AT scores were associated with extrastriate body area (EBA) regions (e.g., right FG). Performance on nST outcomes was associated with regions subserving body-motion imagery (e.g., LG). No significant associations emerged for nAT or ST scores (Supplementary Material 16.1).

In the bvFTD–control tandem (Fig. 2C, middle), ST scores were associated with frontal (e.g., OFC), temporoparietal (e.g., MTG), and occipital regions. Second, nST scores were related to frontostriatal (caudate), temporoparietal, occipital, paracentral, and right hippocampal areas. A similar pattern emerged for AT scores, associated with frontal (e.g., OFC), temporoparietal (precuneus), and occipital regions. Finally, nAT scores were associated with the right inferior temporal and occipital cortices (Supplementary Material 16.2).

In the AD–control tandem (Fig. 2C, bottom), a significant association emerged between AT scores and temporohippocampal (e.g., MTG), parietal (e.g., IPG), frontal (e.g., SFG), and occipital regions, as well as the right cerebellum. The nAT was associated with the left hippocampus as well as the right parahippocampus, MTG, amygdala, and IPG. ST scores were associated with temporohippocampal, parietal (IPG), and frontal (insula) regions, as well as the left cerebellum. Finally, the nST was associated with temporohippocampal (e.g., MTG), parietal, and frontal (e.g., OFC) regions, as well as the right occipital cortex (Supplementary Material 16.3).

Associations between Spatial (fMRI-Derived) rsFC and Performance

In the PD–control tandem (Fig. 3A, top), AT scores correlated with rsFC across frontostriatal (piriform cortex), and occipital regions, as well as the cerebellum. No significant association emerged for nAT outcomes. ST scores correlated with rsFC between the right hippocampus and posterior (e.g., STG) hubs, and between the piriform cortex and the right cerebellum. Finally, nST scores were associated with rsFC between the hippocampus and the left STG and right inferior occipital cortex, as well as between the left cuneus and vermis (Supplementary Material 17.1).

In the bvFTD–control tandem (Fig. 3A, middle), ST scores were associated with rsFC between frontal (e.g., amygdala) and right hippocampal/parahippocampal hubs. Also, AT scores correlated with rsFC between frontostriatal (e.g., piriform) and posterior (e.g., cerebellar) regions. No significant associations emerged for either nST or nAT scores (Supplementary Material 17.2).

In the AD–control tandem (Fig. 3A, bottom), AT scores were associated with rsFC across multiple default-mode-network (DMN) hubs, as well as the SMA and the occipital cortex. Also, nAT outcomes were associated with rsFC between bilateral OFC, cerebellar, and occipital hubs. An association also emerged between ST scores and rsFC between the right insula and the bilateral STG, and between the right angular gyrus and the left precuneus. Finally, nST outcomes correlated with rsFC across DMN hubs, among others (Supplementary Material 17.3).

hd-EEG Results

Disease-Specific wSMI Clusters

Relative to controls, PD patients presented bilateral frontal hypoconnectivity ($P = 0.04$, cluster-corrected; Fig. 3B1, left), whereas bvFTD patients featured right frontotemporal hypoconnectivity ($P = 0.04$, cluster-corrected) (Fig. 3B1, middle) and AD patients presented higher right occipitotemporal connectivity ($P = 0.04$, cluster-corrected; Fig. 3B1, right).

Associations between Temporal (hd-EEG-Derived) rsFC and Performance

In the PD–control tandem (Fig. 3B2, left), mean frontal-cluster connectivity correlated positively with AT ($r = 0.41$, $P = 0.04$, FDR-corrected) and ST ($r = 0.41$, $P = 0.04$, FDR-corrected) scores. In the bvFTD–control tandem (Fig. 3B2, middle), the right frontotemporal cluster's mean connectivity correlated with ST outcomes ($r = 0.45$, $P = 0.02$, FDR-corrected). For the AD–control tandem (Fig. 3B2, right), the right occipitotemporal cluster correlated negatively with AT ($r = 0.56$, $P < 0.001$, FDR-corrected), nAT ($r = -44$, $P = 0.01$, FDR-corrected), and ST ($r = -.39$, $P = 0.03$, FDR-corrected) scores. Every other association was nonsignificant (all *P*-values > 0.06). These patterns were specific to each patient group, as shown by null results in most control correlations—except for AD (Supplementary Material 18).

Discussion

Our multidimensional framework tracked discriminatory markers of PD, bvFTD, and AD via a naturalistic language paradigm. PD and bvFTD presented selective deficits in action-related and socially laded texts, respectively, associated with putative motor and social regions and networks, respectively. Instead, AD patients were impaired in all discourse types, with outcomes related to unspecific and widespread neural alterations. Below we discuss these findings in turn.

PD patients were impaired in the AT, with no deficits in the nAT or the ST. This replicates evidence of action–language difficulties for PD with preservation of

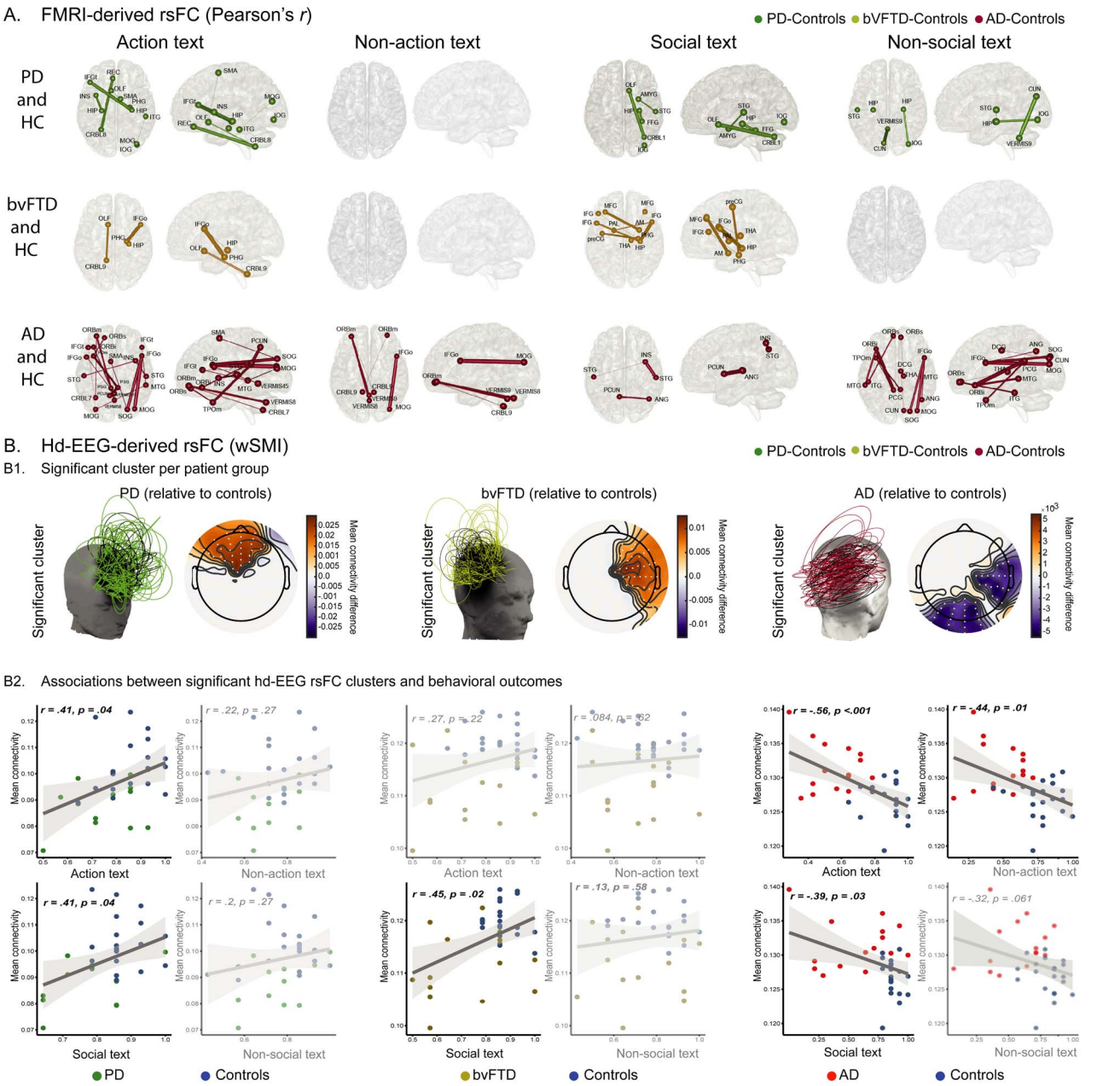

Fig. 3. rsFC results. (*A*) fMRI-derived rsFC. A whole-brain analysis, over 116 regions of interest, at $P < 0.001$ (uncorrected), was performed to test the association between the functional connectivity of each pair of brain areas and each of the four aggregate text scores. Link thickness indicates connectivity strength. ANG: angular gyrus; AMYG: amygdala; CRBL: cerebellum; CUN: cuneus; FFG: fusiform gyrus; HIP: hippocampus; IFG: inferior frontal gyrus; INS: insula; IOG: inferior occipital gyrus; ITG: inferior temporal gyrus; MFG: middle frontal gyrus; MOG: middle occipital gyrus; OLF: olfactory cortex; ORB: orbitofrontal; PAL: pallidus; PCUN: precuneus; PHG: parahippocampal gyrus; preCG: precentral gyrus; PSG: posterior cingulum; REC: rectus gyrus; SMA: supplementary motor area; SOG: superior orbital gyrus; STG: superior temporal gyrus; THA: thalamus; TPO: temporoparietal occipital junction. For better visualization, see Supplementary material 17.4. (*B*) hd-EEG-derived rsFC. (*B1*) Significant clusters per patient group. The three insets show the topographic wSMI patterns of the subtracted connectivity between each group of patients and controls (in a range of 4–10 Hz). Between-group comparisons were performed via cluster-based nonparametric permutation tests, at $P < 0.05$. The panel shows reduced connectivity for PD (left inset) and bvFTD (middle inset) patients relative to controls, as well as enhanced connectivity for AD patients (right inset). The color map indicates ranges from orange (indicating lower connectivity for the patient group) to violet (indicating lower connectivity for controls). The 3D head model represents the links of the cluster, with the arc size indicating connectivity strength. (*B2*) Associations between significant hd-EEG rsFC clusters and behavioral outcomes. Pearson's correlations between the mean connectivity of each significant cluster and the four aggregate scores. Significant correlations are highlighted. All *P*-values are FDR-corrected. HC: healthy controls; PD: Parkinson's disease; bvFTD: behavioral variant frontotemporal dementia; AD: Alzheimer's disease; rsFC: resting-state functional connectivity; wSMI: weighted symbolic mutual information.

multiple categories in single-word (Bocanegra et al. 2015) and discourse-level (García et al. 2018) tasks, corroborating that this domain distinctively recruits motor mechanisms (Pulvermüller 2013). The specificity of action-related difficulties in PD patients is strengthened by their deficits in the nST (which depicted an individual's bodily actions), alongside preserved AT (and nST) comprehension in bvFTD. Accordingly, this domain

may discriminate between PD and nonmotor disorders, as surmised in recent embodied accounts (Birba et al. 2017).

VBM results reinforce the embodied nature of such selective difficulties, which were associated with the volume of core EBA hubs subserving observation and imagery of body parts and their motion (Astafiev et al. 2004). Indeed, damage to these regions in PD (Potgieser et al. 2014) entails motion perception deficits (Weil et al. 2016). Moreover, the association with such posterior areas supports the view that, unlike controls (Pulvermüller 2018), PD patients over-rely on alternative (nonmotor) areas for action–language (Birba et al. 2017) and action–imagery (Helmich et al. 2007) processes.

These impairments did not depend solely on the disruption of motion-related networks, but also on their cross-regional connections. For the AT, frontostriatal hubs comprised within (e.g., SMA; Morris et al. 2016) or projecting to (e.g., GR, PC; Diodato et al. 2016) motor regions subserving action language (Pulvermüller 2013) were distinctively connected with temporo-(para)hippocampal hubs implicated in general semantic (Binder et al. 2009) and motor imagery (Vingerhoets et al. 2002) skills—some of which play secondary roles during action–language processing (Hauk et al. 2004). Compatibly, reduced motor imagery in PD has been associated with connectivity between motor and temporal (EBA) regions (Helmich et al. 2007). Together, these findings endorse the interplay of embodied and multimodal systems for action–language processing in PD.

Additionally, AT outcomes correlated with frontal hd-EEG hypoconnectivity. Crucially, the topography of this cluster (and, partially, its frequency range) has been linked to signatures of action-related processes, like event-related beta desynchronization during object grasping (Ewen et al. 2016); oscillatory abnormalities during motor imagery (Pfurtscheller et al. 2006); and mu-rhythm desynchronization (Vukovic and Shtyrov 2014); and rsFC modulations (Melloni et al. 2015) during action–language processing. Moreover, this pattern was distinctive of PD, as AT outcomes were not associated with the significant hd-EEG cluster of bvFTD. Therefore, hd-EEG signatures of action–discourse outcomes may also constitute nosologically specific markers of PD.

Unlike PD, bvFTD was characterized by selective difficulties in grasping social-related discourse (ST). Conceivably, this deficit stems from broader social cognition impairments in these patients (Piguet et al. 2011), who typically fail at inferring others' thoughts and interpreting social cues (Hsieh et al. 2012; Ibáñez et al. 2018). Indeed, bvFTD patients exhibit poor faux pas detection (Gregory et al. 2002) and social coordination (McMillan et al. 2012) in text-level tasks, suggesting that social-discourse skills are grounded in more general sociocognitive mechanisms.

In fact, whereas preserved nST outcomes in bvFTD yielded volumetric associations across functionally unspecific sites, ST deficits correlated with core social-network regions. These areas are affected in bvFTD (Piguet et al. 2011), leading to undesirable social behavior (Mychack et al. 2001), theory-of-mind deficits (Gregory et al. 2002), and impaired social-concept processing (Rice and Hoffman 2018). The relation between specific ST deficits and the integrity of these areas further supports the reliance of socially laden language on more basic sociocognitive systems.

Also, whereas nST outcomes yielded no associations with spatial rsFC in bvFTD, ST outcomes correlated with the coupling between frontoamygdalar hubs subserving social cognition (Hesse et al. 2016) and hippocampal/-parahippocampal hubs acknowledged by social cognition (Tavares et al. 2015) and multimodal semantic (Binder et al. 2009) models. Given that disrupted frontotemporal connectivity underpins interpersonal coordination outcomes in bvFTD (Melloni et al. 2016), this ST-specific pattern also seems grounded in sociocognitive alterations.

Furthermore, ST outcomes in bvFTD correlated with hd-EEG hypoconnectivity over right frontotemporal sites. Topographically and frequentially similar clusters differentiate bvFTD patients from controls (Dottori et al. 2017) and capture signatures of sociocognitive processes, like delta–theta synchronization during facial emotion recognition (Perdikis et al. 2017) and oscillatory abnormalities during interpersonal cooperation in bvFTD (Melloni et al. 2016). Indeed, atypical frontotemporal oscillations constitute a hallmark of social inappropriateness in this disease (Ibáñez 2018). Since no other group showed frontotemporal hypoconnectivity and selective ST deficits, this pattern seems distinctive of bvFTD.

The nosological specificity of the patterns in PD and bvFTD is supported by results from AD. As in previous works, this group provides a more specific (neurodegenerative) benchmark than healthy participants (Piguet et al. 2011; Melloni et al. 2015; García-Cordero et al. 2016; Melloni et al. 2016). Such patients were outperformed in all texts by every other group, with widespread, unspecific neuroanatomical and spatial connectivity correlates involving all four lobes and the cerebellum. This could reflect pervasive semantic memory, working memory, and long-term declarative memory deficits in AD, related to early temporohippocampal atrophy as well as parietal, insular, and perisylvian degeneration (Whitwell et al. 2012). Moreover, AD patients exhibited hd-EEG hyperconnectivity within a temporooccipital cluster, which correlated negatively with performance in three texts and nearly reached significance for the remaining one. Compatibly, posterior hyperconnectivity in AD (Knyazeva et al. 2010) correlates negatively with domain-general cognitive skills (Knyazeva et al. 2010) underlying processing of any stimulus type.

Although results from the AD sample prove less informative because of their nonselectivity, they emphasize the disease specificity of the patterns observed in PD and bvFTD. Moreover, this contrast reinforces the sensitivity of embodied deficits for disease stages that spare

higher-order domains, given that the AD patients were more cognitively impaired (even in mnesic aspects). Indeed, previous evidence indicates that action semantic deficits are selective in cognitively preserved PD patients, but that they are accompanied by general semantic difficulties in cognitively impaired patients (Bocanegra et al. 2017; García et al. 2018). Briefly, the distinctively nonselective nature of these patterns verifies the specificity of the multidimensional signatures observed in PD and bvFTD.

Yet, although our task reveals differential patterns of deficit for each patient group relative to HCs, direct comparisons among the patient groups only revealed significantly lower performance across texts for AD than both PD and bvFTD, without discriminating between the latter two groups. Potentially, this might reflect the fact that nonprimary but moderate alterations in action semantics and social semantics may occasionally emerge in bvFTD (Silveri et al. 2003; Cotelli et al. 2006) and PD (Baez et al. 2020), respectively. Nevertheless, note that behavioral performance on the AT for PD and the ST for bvFTD was selectively correlated with anatomofunctional alterations in each group. Though indirectly, this attests to the potential disease discriminability of the deficits observed in each disorder, although more specific studies with more items, and more controlled texts, would be necessary to better address this issue.

Our findings bear clinical implications. Most linguistic assessments target general, isolated aspects of phonology, morphosyntax or lexicosemantics, which often reveal similar deficits in PD, bvFTD, and AD (McMillan et al. 2012; García et al. 2018). Though certainly useful to inform disease characterization and delineate intervention areas, these approaches rarely reveal fine-grained signatures that could differentiate among disorders. Our framework seems to circumvent this limitation employing context-rich, cohesive, coherent narratives that capture key properties of everyday discourse and target sensitive embodied domains (Halliday et al. 2014).

Limitations and Avenues for Further Research

Yet, our work features some limitations. First, the patient samples had moderate sizes. Nevertheless, we matched or surpassed the sample size of other robust multimodal studies (García-Cordero et al. 2016; Melloni et al. 2016), with a strict control clinical variables, detailed diagnostic procedures, systematic assessments, and power estimations that corroborated the adequacy of our Ns. Looking forward, however, this approach should be tested with more participants per site to tackle novel questions hinging on cross-center comparisons. Second, while we focused on patients with relatively preserved cognitive status, our protocol could be run on bvFTD and PD patients with more advanced cognitive impairment. This would be useful to establish whether observed deficits remain selective under higher cognitive dysfunction thresholds. Third, testing items were limited to 14 questions per text. Although previous versions of this paradigm yielded robust condition-specific effects with similar numbers of trials (García et al. 2018), future studies should increase this figure. Fourth, given the multimodal nature of our work, we only focused on specific, hypothesis-driven metrics for each neuroscientific technique. However, future studies could implement different measures, such as cortical thickness or surface-based morphometry for structural imaging (Fischl 2012), weighted symbolic dependence metric for fMRI (Moguilner et al. 2018), and weighed symbolic phase index for hd-EEG (Imperatori et al. 2019). In this sense, our hd-EEG analyses targeted hypothesis-driven frequencies known to capture distinct patterns in neurodegenerative diseases (Melloni et al. 2015; Dottori et al. 2017) and embodied language domains (Melloni et al. 2015; García et al. 2020). Still, future studies could explore other frequency ranges and additional connectivity features, such as network distance—as in (García-Cordero et al. 2016). Finally, although our findings provide a multimodal picture across behavioral, anatomic, electrophysiological, and FC dimensions, all brain–behavior correlations were based on offline neural measures. Further works should replicate this protocol with online recordings during text-level processing, as in Birba et al. (2020).

Conclusion

In conclusion, the potential of multidimensional approa ches to discriminate among neurodegenerative diseases can be boosted through the use of simple, theoretically driven naturalistic tasks. As shown here, deliberate semantic manipulations in ecological narratives can reveal behavioral, neuroanatomical, and neurofunctional signatures of PD and bvFTD relative to controls and AD patients. This study thus lays the groundwork for establishing discriminatory embodied markers across neurodegenerative subtypes.

Author contributions

Agustina Birba: Methodology, Formal analysis, Validation, Investigation, Writing—original draft preparation, Visualization. Sol Fittipaldi: Software, Formal analysis, Data curation, Writing—original draft preparation, Visualization. Judith C. Cediel Escobar: Formal analysis, Data curation. Cecilia Gonzalez Campo: Software, Formal analysis, Data curation, Visualization. Agustina Legaz: Formal analysis, Data curation. Agostina Galiani: Formal analysis, Data curation. Mariano N. Díaz Rivera: Data curation, Writing—review & editing. Miquel Martorell Caro: Resources, Data curation. Florencia Alifano: Resources, Data curation. Stefanie D. Piña-Escudero: Resources, Data curation. Juan Felipe Cardona: Resources, Data curation. Alejandra Neely: Resources, Data curation. Gonzalo Forno: Resources, Data curation. Mariela Carpinella: Resources, Data curation. Andrea Slachevsky: Resources, Data curation. Cecilia Serrano: Resources, Data curation. Lucas Sedeño: Investigation,

Writing—review & editing. Agustín Ibáñez: Conceptualization, Methodology, Resources; Writing—review & editing, Project administration, Funding acquisition. Adolfo M. García: Conceptualization, Methodology, Resources, Writing—original draft preparation, Writing—review & editing, Visualization, Supervision.

Data Availability

All experimental data and the scripts used are available online via the Open Science Framework at https://osf.io/vb4tf/?view_only=ced6492ca7d749a996733b213d82d9b2 (data from "Discourse markers of neurodegeneration").

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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Notes

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