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Structural and functional motor-network disruptions predict selective action-concept deficits: Evidence from frontal lobe epilepsy

Sebastian Moguilner[1,2], **Agustina Birba**[3,4], **Daniel Fino**[2,5,6], **Roberto Isoardi**[2,5], **Celeste Huetagoyena**[7], **Raúl Otoya**[5], **Viviana Tirapu**[2,8], **Fabián Cremaschi**[2,9,10], **Lucas Sedeño**[4], **Agustín Ibáñez**[1,3,4,11], **Adolfo M. García**[1,3,4,12,*]

[1]Global Brain Health Institute, UCSF, California, US, & Trinity College Dublin, Dublin, Ireland

[2]Nuclear Medicine School Foundation (FUESMEN), National Commission of Atomic Energy (CNEA), Mendoza, Argentina

[3]Center of Cognitive Neuroscience, University of San Andrés, Buenos Aires, Argentina

[4]National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

[5]Instituto Balseiro, Universidad Nacional de Cuyo, Mendoza, Argentina

[6]Fundación Argentina para el Desarrollo en Salud, Mendoza, Argentina

[7]Neuromed, Clinical Neuroscience, Mendoza, Argentina

[8]Facultad de Humanidades y Ciencias Económicas. Universidad Católica Argentina. Mendoza

[9]Neuroscience Department of the School of Medicine, National University of Cuyo, Mendoza, Argentina

[10]Santa Isabel de Hungría Hospital, Mendoza, Argentina

[11]Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile

[12]Departamento de Lingüística y Literatura, Facultad de Humanidades, Universidad de Santiago de Chile, Santiago, Chile

Abstract

[*]**Corresponding author:** Adolfo M. García, Ph. D., Universidad de San Andrés & CONICET; Vito Dumas 284, B1644BID Victoria, Buenos Aires, Argentina; Phone: (54-11) 4725-7000. adolfomartingarcia@gmail.com.

Credit Author Statement

Sebastian Moguilner: Methodology, Formal analysis, Data curation, Writing - Original draft. **Agustina Birba:** Methodology. **Daniel Fino:** Data acquisition. **Roberto Isoardi:** Resources, Data acquisition. **Celeste Huetagoyena:** Data acquisition. **Raul Otoya:** Data acquisition. **Viviana Tirapu:** Data acquisition. **Fabian Cremaschi:** Data acquisition. **Lucas Sedeño:** Methodology. **Agustín Ibáñez:** Methodology, Writing - Review & Editing, Funding acquisition. **Adolfo M. García:** Conceptualization, Validation, Methodology, Writing - Original draft, Writing - Review & Editing, Supervision, Funding acquisition, Project administration.

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Conflicts of interest

None to declare.

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Built on neurodegenerative lesions models, the disrupted motor grounding hypothesis (DMGH) posits that motor-system alterations selectively impair action comprehension. However, major doubts remain concerning the dissociability, neural signatures, and etiological generalizability of such deficits. Few studies have compared action-concept outcomes between disorders affecting and sparing motor circuitry, and none has examined their multimodal network predictors via data-driven approaches. Here, we first assessed action- and object-concept processing in patients with frontal lobe epilepsy (FLE), patients with posterior cortex epilepsy (PCE), and healthy controls. Then, we obtained structural and functional network signatures via diffusion tensor imaging and resting-state connectivity measures. Finally, we used these measures to predict behavioral performance with an XGBoost machine learning regression algorithm. Relative to controls, FLE (but not PCE) patients exhibited selective action-concept deficits together with structural and functional abnormalities along motor networks. The XGBoost model reached a significantly large effect size only for action-concept outcomes in FLE, mainly predicted by structural (cortico-spinal tract, anterior thalamic radiation, uncinate fasciculus) and functional (M1-parietal/supramarginal connectivity) motor networks. These results extend the DMGH, suggesting that action-concept deficits are dissociable markers of frontal/motor (relative to posterior) disruptions, directly related to the structural and functional integrity of motor networks, and traceable beyond canonical movement disorders.

Keywords

action semantics; diffusion tensor imaging; frontal lobe epilepsy; functional connectivity; machine learning

1. Introduction

A blooming neurocognitive framework, couched in the disrupted motor grounding hypothesis (DMGH), posits that motor-system alterations can selectively impair action comprehension –i.e., grasping of words and pictures denoting bodily movements [1–4]. Accordingly, such deficits might constitute sensitive markers of motor circuit damage [2, 5]. However, major questions remain unaddressed, limiting the clinical and theoretical relevance of this research arena. Are these deficits dissociable between frontal/motor and posterior brain disorders? What are their core neural signatures? And are they present beyond neurodegenerative movement disorders (the main target of the DMGH)? To address these questions, we obtained diffusion tensor imaging (DTI) and resting-state functional connectivity (rsFC) correlates of action-concept processing in patients with frontal lobe epilepsy (FLE), posterior cortex epilepsy (PCE) and healthy controls (HCs).

From an embodied perspective, specific concepts are grounded in sensorimotor circuits subserving the experiences they denote [6–8]. Motor circuit integrity would thus be crucial for processing words and images evoking bodily movement [9]. Therein lies the main claim of the DMGH [2]. Indeed, studies on movement disorders show that selective action semantic impairments can emerge early [10] or preclinically [11], across diverse stimuli and tasks [5], and irrespective of the patients' overall cognitive profile [12] or executive

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dysfunction [13]. Accordingly, action-concept deficits have been proposed as sensitive, systematic, and primary markers of motor-network damage [2, 5].

However, little is known about the dissociability, neural signatures, and etiological generalizability of these deficits. The limited research comparing different patient groups indicates that action semantics may be partly preserved in patients presenting mainly temporal atrophy [14] and peripheral motor disorders sparing motor-circuits [15]. This aligns with neuroscientific studies showing that action-verb processing involves altered M1 connectivity in movement disorders, like Parkinson's disease [16]. Yet, this scant evidence is devoid of data-driven reproducibility assessments and multimodal imaging analyses across patient groups with and without motor-network disruptions. Moreover, while most evidence comes from neurodegenerative motor disorders [2, 5, 16–19], findings are scant in other neurological conditions [20, 21], casting doubts on these markers' consistency across physiopathological processes. Therefore, stringent testing of the DMGH requires multimodal data-driven frameworks, such as with XGBoost machine learning regressions [22], in non-neurodegenerative conditions affecting and sparing motor networks.

To face these challenges, we examined comprehension of action and non-action concepts in FLE patients relative to PCE patients and HCs, combining DTI and rsFC metrics in a machine learning regression pipeline. FLE is a key model to this end, as it constitutes a focal neurological condition entailing hypermotor seizures [23], alterations in structural and functional motor mechanisms [24], and reduced connectivity between M1 and posterior hubs [25, 26]. Conversely, focal PCE patients rarely present motor impairments or show seizures originating or propagating through the frontal/motor regions [27, 28]. Our approach included a comparison of behavioral outcomes across groups, detection of structural and functional network signatures, and predictions of performance based on such multimodal brain measures.

We advanced three hypotheses. First, we predicted that, relative to HCs, only FLE (not PCE) patients would exhibit selective deficits in action-concept processing as well as structural and functional abnormalities along motor networks. Second, we anticipated that neural measures, across multiple structural and functional networks, would offer robust predictions of behavioral outcomes only for FLE patients in the action-concept condition. Third, we hypothesized that the networks emerging as top predictors of such deficits would be consistently involved in motor function. Briefly, this approach seeks to illuminate the scope of action-concept deficits as predicted by the DMGH.

2. Materials and methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

Our study comprised 60 participants, a sample size that conferred adequate statistical power (Supplementary material 1). These included 20 frontal lobe epilepsy (FLE) patients,

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showing stereotyped semiology with hypermotor seizures characterized by complex high-amplitude movements [23]; 20 posterior cortex epilepsy (PCE) patients (subsuming temporal, parietal, and occipital foci) not showing hypermotor seizures [27]; and 20 healthy controls. Diagnoses were made by expert neurologists following current standards of the International League Against Epilepsy [29–31]. Patients had one or more confirmed clinical seizures measured by focal epileptic electroencephalography discharges in the affected lobe. Their EEG patterns did not conform to any neurological syndrome other than epilepsy. All of them suffered from idiopathic epilepsy and had experienced their latest clinical episode up to two weeks before the neuroimaging session. All FLE patients had a motor onset, while all PCE patients presented a non-motor onset (for details, see Supplementary material 2). Signs of dyspraxia were absent in every case. Neuroradiological examination indicated that none of the patients exhibited cortical dysplasia. None of the patients had a history of other neurological or psychiatric disorders, other disease that could cause cognitive decline, or substance abuse. The healthy controls also lacked these antecedents. The three groups were matched on age, sex, education, handedness (determined via the Edinburgh test [32]), overall cognitive status (assessed with the MoCA: Montreal Cognitive Assessment [33]), executive functions (assessed with the IFS: INECO Frontal Screening [34]), and IQ (evaluated with the WASI: Weschler Abbreviated Scale of Intelligence [35]). The two patient groups did not differ significantly in terms of the nature of their epilepsy, years with symptoms or years since diagnosis. Demographic, neuropsychological, and clinical information from each group is detailed in Table 1.

All participants provided written informed consent in agreement with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board. No part of the study procedures or analyses was pre-registered prior to the research being conducted. Legal copyright restrictions prevent public archiving of the assessment tests described in this section, which can be obtained from the copyright holders in the cited references.

2.2. Picture-word association task

We employed a picture-word association (PWA) task based on stimuli from a validated picture-naming task [36]. This PWA task comprised 80 trials, each composed of a black-and-white image and an accompanying word. Half the items belonged to the action-verb condition, and the remaining half corresponded to the object-noun condition. Each condition comprised 20 congruent trials (e.g., the picture of a person swimming with the Spanish verb meaning ‘swim’, or the picture of a ball with the Spanish word meaning ‘ball’) and 20 incongruent trials (e.g., the picture of someone jumping together with the Spanish word meaning ‘kneel’, or the picture of a guitar with the Spanish word meaning ‘piano’). The pictures for the action-verb and the object-noun conditions were taken from Druks and Masterson’s action-picture set [37] and the International Picture-Naming Project Corpus [38], respectively. See Supplementary material 3 for full statistical details. No word exceeded more than three syllables. Also, the pictures in the incongruent trials were strategically chosen so that their names would not have marked phonological or semantic overlap with their accompanying words. Importantly, the actions involved in the pictures and words of incongruent trials varied randomly, varying randomly in terms of shared/

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different denoted or evoked effectors, motility level, and number of limbs involved, ruling out potential motion-related confounds.

Stimulus motility/manipulability was determined via two norming studies involving 34 respondents. Action-verb and object-noun pictures were rated in terms of how much movement they implied and how graspable they were, respectively. This was done, in both cases, on a scale from 1 (minimal) to 100 (maximal). Initially, 100 pictures of each category were pre-selected from Druks and Masterson [83] and Bates et al. [84], respectively. Stimuli with an average score below 30 were classified as having low motility/manipulability, and those with an average score above 60 were considered as having high motility/manipulability. Only 40 items were retained per category, half involving low motility/manipulability (actions: $M = 18.14$, $SD = 6.96$, range = 7.56-29.97; objects: $M = 13.75$, $SD = 6.15$, range = 4.60-29.90) and the other half involving high motility/manipulability (actions: $M = 76.56$, $SD = 14.65$, range = 60-99.12, objects: $M = 77.85$, $SD = 9.54$, range = 61.85-93.82). Therefore, items in both conditions encompassed substantial action-related variability.

Trials began with a fixation cross that remained visible for a random period of 100-300 ms, followed by a two-element display showing a picture on top and a word below it. The picture-word dyad remained on screen until a response was made. Stimuli were presented in black color in the center of the screen against a white background. Sitting comfortably at a desk with a computer, participants were instructed to view each trial and press the right arrow to indicate ‘match’ or the left arrow to indicate ‘no match’. They were also asked to perform the task as fast and accurately as possible. The exact instructions were: “You will now view slides containing a picture and word. Sometimes the picture and the word will refer to the same thing (e.g., the picture of a door and the word ‘door’). Sometimes they will refer to different things (e.g., the picture of a door and the word ‘lion’). When the picture and the word refer to the same thing, please press the right arrow. When they do not match, press the left arrow. Keep your hand in the same position and use only your fingers to respond. Try to respond correctly, as fast as you can.”

Each keystroke served to record the trial’s accuracy and response time (RT), while also triggering the following trial. In order to balance the stimuli, the same stimulus sets were used for the pre- and post-stimulation phases, but the pictures featuring a congruent word in the prestimulation phase were accompanied by an incongruent word in the post-stimulation phase, and vice versa. The action-verb and object-noun conditions were counterbalanced across participants and across sessions for each single participant. Prior to the task, four practice trials (different from the 80 ones appearing in the task) were presented for familiarization purposes. Altogether, the task lasted approximately 10 min.

2.3. Behavioral data analysis

Accuracy and RTs on the PWA task were analyzed via mixed effects models, with one between-subject factor (Group: FLE patients, PCE patients, controls) and one within-subjects factor (condition: action-verb, object-noun). RT analysis was performed considering only correct trials upon removing outliers at 2 standard deviations above or below each group’s mean for each condition separately. All analyses were covaried for the MoCA [33]

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and IFS [34] scores, and significant differences were further inspected via Tukey's HSD tests. Alpha levels were set at $P < 0.05$. Effect sizes for main and interaction effects were calculated through partial eta squared (η^2) tests, whereas those for pair-wise comparisons were obtained via Cohen's *d*. All statistical analyses were performed on IBM's SPSS Statistics (v. 23) software.

2.4. Neuroimaging methods

2.4.1. Structural networks: DTI—MRI acquisition and preprocessing steps followed the Organization for Human Brain Mapping (OHBM) guidelines [39, 40]. As in previous works [41, 42], white matter (WM) tracts were characterized via the Tract-Based Spatial Statistics software toolbox [43] (Supplementary material 4 for acquisition and preprocessing details). Local FA measures were used to perform pairwise comparisons of WM integrity between each patient group and controls as well as between both patient groups, with higher FA reflecting tracts with higher WM integrity [41]. To obtain the statistically significant differences between groups, we employed one-tailed two-sample *t*-tests using the FSL Randomise tool [44], performing 5000 permutations of Threshold-Free Cluster Enhancement. The analysis yielded significance maps corrected for multiple comparisons through the family-wise error (FWE) metric ($P < .05$), built-in in the FSL Randomise tool [44]. Global FA measures were obtained by parsing the tracts according to the Johns Hopkins ICBM DTI-based WM tract probability atlas, considering a total of 10 WM tracts [45], namely: forceps minor (Fmin), anterior thalamic radiation (ATR), cingulate gyrus cingulum (CING), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), corticospinal tract (CST), forceps major (Fmaj), uncinate fasciculus (UNC), hippocampal cingulum (CING-hipp), and inferior fronto-occipital fasciculus (IFOF).

2.4.2. Functional networks: rsFC—In the rsFC protocol, participants lied in the scanner and were asked not to think about anything in particular while remaining awake, still and with eyes closed. We performed a seed analysis to evaluate both linear and non-linear rsFC using the weighted Symbolic Dependence Metric (wSDM) [46]. This measure captures local and global temporal features of the BOLD signal by weighing a copula-based dependence measure by symbolic similarity. The method also tracks nonlinear associations, a key aspect of neural connectivity escapes linear metrics such as Pearson's R –indeed, wSDM outperforms R in identifying patients with neurological disorders based on rsFC patterns [46].

We targeted different networks, namely: (i) a motor network (MN), implicated in action planning, execution, and observation [47]; a multimodal semantic network (SemN), associated with processing of integrative, modality-neutral concepts [48]; and as a functionally unspecific control, (iii) a visual network (VN), which plays no distinctive roles in semantic processing. RsFC of each network was estimated by considering three seeds: a left and a right seed (with a size of 7x7x7 voxels each), and a bilateral seed subsuming these two (see Supplementary material 5 for acquisition and preprocessing details). For the MN, seeds were placed in the M1 region, using previously reported MNI coordinates (left: −32, −30, 68; right: 32, −30, 68) [49]. For the SemN, seeds were located in the ventral anterior temporal lobe (left: −51, 6, −39; right: 51, 6, −39) [9]. For the VN, seeds were placed in the

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primary visual area (V1) (left: −8, −92, 8; right: 8, −92, 8) [50]. Connectivity differences between group pairs (FLE patients vs. controls, PCE patients vs. controls, FLE vs. PCE patients) were calculated via one-tailed two-sample *t*-tests ($P < .05$, extent threshold = 50 voxels), corrected for multiple comparisons via the false discovery rate (FDR) metric [51], following previous fMRI studies on action-language processing [52].

2.5. Machine learning regression analysis

2.5.1. Predictor and predicted features—To establish which factors accounted for performance in the PWA task, we performed XGBoost regression analyses for each group separately. The behavioral measure yielding significant effects (namely, RT) was framed as the predicted feature. Each model was trained with several predictors, namely: the outcomes of two neuropsychological measures (MoCA and IFS), the global FA of the 10 DTI tracts described in section 2.4.1, and the rsFC of the networks obtained from the nine seeds described in section 2.4.2 (left, right, and bilateral seeds for the MN, the SemN, and the VN). For feature regularization, we employed the default XGBoost method for controlling the minimum loss reduction required to make a further partition on a leaf node [53].

2.5.2. Analysis parameters—For the training phase in all our analyses, following best practices, we employed a *k*-fold crossvalidation for hyper-parameter tuning, using 80% of the data for training and validation and 20% of the data for testing [54]. For each group, we executed a linear XGBoost machine learning regression model to predict RTs on action-verbs and object-nouns separately. A threshold of 0.26 for the R^2 coefficient of determination, indicating a large effect size [55], was used to establish the models' goodness of fit. All models yielding an R^2 equal to or above 0.26 were further subjected to a feature importance analysis to establish which variables proved most relevant for the regression. We used a GBM regressor library called XGBoost [53] (eXtreme Gradient Boosting) because of its high accuracy and robustness relative to other algorithms, while tuning its hyper-parameters by Bayesian Optimization [56, 57]. GBMs are based on the gradient boosting technique, in which ensembles of decision trees iteratively attempt to correct the classification errors of their predecessors by minimizing a loss function (i.e., a function representing the difference between the estimated and true values) while pointing in the negative gradient direction [58]. The XGBoost regressor provides parallel computation tree boosting, enabling fast and accurate predictions which have proven successful in several fields [59–61]; and also regularized boosting, helping to reduce overfitting and thus providing more generalizable results [61, 62]. To evaluate the most relevant features for predicting the target variable in the machine learning regression, we performed the feature importance analysis embedded in the XGBoost regressor. Briefly, feature importance in this algorithm is calculated by assessing how much each attribute split in the model improves the performance measure – namely, the Gini index, weighted by the number of observations the node is responsible for [63]. Feature importance is then averaged across all of decision trees within the model.

2.5.3. Data and code availability—All experimental data, as well as the scripts used for their collection and analysis, are fully available online [64].

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3. Results

3.1. Behavioral results

Accuracy was high and similar across groups and conditions, yielding non-significant main effects of group [$F(2,110) = 4.21$, $P = 0.17$, $\eta^2 = 0.71$] or condition [$F(1,110) = 2.65$, $P = 0.11$, $\eta^2 = 0.24$], as well as a non-significant interaction between both factors [$F(2,110) = 0.17$, $P = 0.84$, $\eta^2 = 0.03$)] –see Supplementary material 6 for details.

Analysis of RTs over the correct trials yielded non-significant main effects of group [$F(2,110) = 2.03$, $P = 0.14$, $\eta^2 = 0.01$] or condition [$F(2,110) = 3.52$, $P = 0.63$, $\eta^2 = 0.61$]. However, a significant interaction emerged between group and condition [$F(1,110) = 8.65$, $P = 0.04$, $\eta^2 = 0.16$], which was preserved after covariation with MoCA and IFS scores [$F(2,110) = 4.57$, $P = 0.02$, $\eta^2 = 0.68$)] (Figure 1, B2). A post-hoc analysis, via Tukey's HSD test (MSE = 0.3227, $df = 105.46$), revealed a significant selective effect in the FLE group, with action-verb trials yielding higher RTs than object-noun trials in the same group ($P = 0.002$, $d = 0.86$), action-verb trials in the control group ($P = 0.007$, $d = 0.89$), and object-noun trials in the PCE group ($P = 0.034$, $d = 0.24$). Every other pair-wise comparison within and across FLE patients, controls, and PCE patients yielded non-significant differences (all P-values > 0.08). For details, see Supplementary material 7.

3.2. Neuroimaging results

3.2.1. DTI results—Local DTI FA measurements revealed significantly lower WM integrity for FLE patients than controls in bilateral segments corresponding to the ATR tract [$t(18) = 5.41$, FWE-corrected $P = 0.03$, $d = 0.88$] (Figure 1, B1). No tract exhibited higher local FA for FLE patients than controls. Moreover, no other local FA pairwise comparison between any group pair showed significant differences in any tract. For details, see Supplementary material 8.

Global FA measures, averaged within the 10 JHU atlas tracts, showed significantly lower WM integrity for FLE patients than controls [$t(18) = 2.44$, FDR-corrected $P = 0.04$, $d = 0.84$] in the bilateral ATR tract. No other tract showed significant differences between FLE patients and controls in any direction. Also, no other global FA pairwise comparison between any group pair showed significant differences in any tract. For details, Supplementary material 9. Pearson's R correlations showed that the global FA alterations observed in FLE patients were not significantly associated with their years with symptoms or their years since diagnosis (Supplementary material 10).

3.2.2. RsFC results—Relative to controls, FLE patients exhibited MN hypoconnectivity, indexed by significantly lower (FDR-corrected $P < 0.05$) rsFC between the bilateral M1 seeds and a cluster over the left parietal operculum and supramarginal gyrus (Figure 1, B2). The cluster's peak t-score ($t(18) = 3.61$, FWE-corrected $P = 0.001$, $d = 0.76$] was located in the following MNI coordinates: −50, −42, 24. No other seed yielded significant rsFC differences in any of the remaining pairwise comparisons between FLE patients, controls and PCE patients. For details, see Supplementary material 11. Pearson's R correlations showed that the rsFC abnormalities of FLE patients were not significantly

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associated with their years with symptoms or their years since diagnosis (Supplementary material 10).

3.3. Machine learning regression results

The machine learning regression on FLE patients achieved a testing R^2 score of 0.514 for action-verbs (Figure 1, C1, first row), while the testing R^2 score for object-nouns was below the threshold for goodness of fit (Figure 1, C1, second row). The feature relevance for this model was highest for the CST: FA, followed by the ATR: FA, and the bilateral M1 rsFC network, and then by other less relevant features (see Figure 1D). In the case of both healthy controls and PCE patients, R^2 testing values fell below the threshold for goodness of fit (R^2 = 0.26) for both action-verbs and object-nouns (Figure 1, C2, C3, first and second rows).

4. Discussion

Relative to HCs, FLE (but not PCE) patients exhibited selective deficits in action-concept processing speed as well as structural and functional abnormalities along motor networks. Also, only action-concept outcomes in FLE were predicted by multimodal brain measures, with structural and functional motor networks emerging as top predictors. These results illuminate the dissociability, neural signatures, and etiological generalizability of action-concept deficits, offering new insights on the DMGH.

The selective action-concept deficits in FLE align with systematic results from disorders presenting frontal motor-network damage, such as Parkinson's, Huntington's, and motor-neuron disease as well as amyotrophic lateral sclerosis [65]. Importantly, neither MoCA nor IFS scores yielded significant differences across groups, and all results were covaried for both measures. Hence, as reported in other populations [65], their selective action-concept deficits hardly reflect domain-general cognitive dysfunctions. Crucially, no PWA impairments were observed in PCE patients. In the same vein, action-concept outcomes seem less markedly affected in patients presenting predominant temporal atrophy [14], and the same has been reported in peripheral (musculoskeletal) movement disorders with no primary compromise of motor networks [15]. Supporting the DMGH, action-concept deficits in frontal disorders (indexed by reduced processing speed) seem potentially specific relative to other brain conditions sparing motor circuits.

Importantly, object-noun skills were unimpaired in FLE patients, highlighting the specificity of their action-verb deficits. Although motor-system dysfunction may entail object-noun difficulties, these seem to occur particularly when patients manifest generalized cognitive impairment [36]. Indeed, motor-region stimulation can selectively modulate action-verb (relative to object-noun) outcomes irrespective of cognitive status or executive dysfunction [66]. In this sense, the sparing of object-noun processing skills in FLE may reflect their preserved overall cognitive profile, underscoring the sensitivity of our task for patients in non-advanced disease stages.

Note that action-verb RTs did not significantly differ between FLE and PCE patients. *Prima facie*, this might seem to challenge the DMGH. Yet, this is not necessarily the case. In addition to the putative recruitment of frontostriatal motor networks, action-verb

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processing also involves contributions from temporal and parietal regions [7, 9, 67, 68]. In fact, as acknowledged in visual cognition models, superior and inferior portions of the parietal lobe would be critically implicated in processing visuomotor information and goal-direction actions, respectively [69]. Conceivably, partial disruption of such posterior areas in PCE patients might subtly compromise action-verb mechanisms, to a point where non-impaired performance may still fail to reach significance relative to FLE patients. This hypothesis invites new studies specifically designed to explore *gradients* of deficit across lexico-semantic categories in each group.

Be that as it may, the critical link between motor mechanisms and action-verb deficits was corroborated by brain connectivity results. Only FLE (not PCE) patients showed structural and functional abnormalities, and these were exclusive to motor-related networks. The most affected functional network was seeded in M1, a critical hub for action-concept processing [7, 8, 70]; while the most affected structural network was the ATR, implicated in motor function [71, 72]. Moreover, across all groups and conditions, only action-concept outcomes in FLE were *successfully predicted* by structural and functional network results. Crucially, four of the top five predictors (the CST, ATR, and UNC, from structural results; M1-parietal/supramarginal connectivity, from functional results) were networks associated with motor processes and action semantics.

Both the CST and the ATR are specifically altered in FLE [24, 73]. CST abnormalities tracts underlie sensory-motor disability in multiple sclerosis [74] and progressive motor impairment in Huntington's disease [75], whereas ATR disruptions underpin motor-function decay in healthy adults [71] and neurological conditions [72] typified by action-language deficits [2]. The UNC, a major cortico-cortical pathway connecting fronto-temporal regions [76], contributes to semantic processing and lexical retrieval in general [77, 78], and action naming in particular [79]. Finally, aberrant functional connectivity between M1 and posterior regions has been observed in other conditions presenting selective action-verb impairments, such as Parkinson's disease [16]. In this population, in fact, resting-state motor-network connectivity is sensitive to disease progression [80] and correlates with movement symptom severity [81, 82], highlighting its sensitivity to bodily motion. More particularly, studies in FLE have also shown that decreased connectivity (and structural integrity) of motor networks, including M1-parietal integration, correlates with reduced behavioral performance in motor function [26] and action-language processing [68]. Indeed, beyond the putative role of motor regions [7, 8, 70], action concepts recruit posterior areas that subserve crossmodal semantics [9], including parietal and supramarginal hubs [8]. Briefly, in line with the DMGH, action-concept deficits seem selectively linked to multimodal disruptions along motor and semantic networks.

Interestingly, although CST integrity emerged as the principal feature for regressions in FLE patients, it did not differ between groups. This pattern aligns with previous evidence that tractographic predictors of cognitive performance in epilepsy may not necessarily be reflected in the results obtained with traditional statistics [83]. In line with this antecedent, action-verb deficits would seem related not only to significantly altered motor networks, but also to less salient abnormalities in some of them, although further work is necessary to elucidate this point.

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The lack of DTI and rsFC alterations in PCE patients might seem unexpected, but it is not necessarily so. Indeed, PCE is a diffuse construct involving different patient types with varying patterns of structural and functional network alterations [27]. This may lead to null results in group-level analyses, as noted in a review on white matter correlates of cognitive outcomes in temporal lobe epilepsy (TLE), the most frequent form of PCE [84]. Moreover, a recent study has shown that white matter alterations in FLE are more severe than in TLE [85], suggesting that they may be better captured in the former group. Accordingly, while our study does suggest that action-verb outcomes are systematically affected in patients with frontal motor-system disruptions, it does not fully exclude the possibility that similar alterations could emerge in more homogeneous patients with specific forms of PCE –in particular, parietal lobe epilepsies, given the role of this region in action-verb and action-concept processing [86–88].

Taken together, present results extend the DMGH from neurodegenerative motor disorders onto new brain conditions. Our FLE cohort had no sign of atrophy, as typically observed in the main diseases informing the hypothesis (Parkinson's and Huntington's disease). Rather, as observed here, brain abnormalities in FLE typically involve structural [24] and functional [25, 26, 89] motor-network alterations, often linked to clonic movements, uni- or bilateral tonic motor activity, and complex automatisms [73]. In line with evidence of action-concept deficits in stroke and other lesional models [20, 21], our study reinforces the etiological generalizability of the DMGH.

Our results also carry implications for FLE in particular [90]. Coarse-grained cognitive domains (e.g., attention, memory, verbal fluency) may sometimes be affected in FLE [91], but the same is true in PCE [92]. This undermines their relevance as targets for detecting *specific* signatures of FLE. Furthermore, cognitive profiles in epilepsy are heterogeneous, with diverse pathophysiological mechanisms influencing their manifestation across patients [90]. Crucially, our study shows that action-concept deficits are exclusive to FLE (relative to PCE) and can be specifically predicted by core anatomo-functional alterations of this disorder [7, 8, 79, 93]. Thus, paradigms tapping action semantics could complement cognitive tests in epilepsy and even support estimations of the course of pathology across FLE patients [2].

More generally, our results support the embodied cognition framework, which posits that action-semantic information is grounded in motor circuits [7–9]. From this perspective, beyond the contribution of crossmodal semantic hubs, such as the anterior temporal lobe [48, 94] and the angular gyrus [95], our understanding of words and concepts involves reactivations along diverse pathways mediating the bodily experiences they denote [7, 9, 13, 96]. Such reactivations, it has been argued, actually play primary roles in the construal of meaning [9, 13]. Our study reinforces this position, as the alterations in FLE could hardly prove so selective and specific if motor networks played merely epiphenomenal roles in semantic processing, as argued elsewhere [97–100]. In this sense, direct testing of the DMGH may have theoretical ramifications beyond its clinical underpinnings.

Notwithstanding, given the nature of the PWA task, our results do not reveal whether the observed deficits operated at the lexico-semantic or post-conceptual (e.g., imagery) level.

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A recent study reported impaired action imagery and spared action-verb processing upon neurosurgical removal of tumors along sensorimotor regions, challenging strong views of language embodiment [101]. However, action-verb access selectively modulates M1 activity [9] and motor-related cortical potentials [102] in shallow processing tasks. Moreover, action verbs modulate activity *within* motor regions [10] and can be selectively disturbed [67] or facilitated [66] upon direct M1 neuromodulation. These antecedents suggest that the impairment exhibited by FLE patients could be driven by both linguistic and non-linguistic conceptual alterations, inviting new research on the relative contributions of each processing level.

5. Limitations and avenues for future studies

Our work presents some limitations. First, although our sample size was similar to or larger than those of previous reports [92, 103] and it conferred high statistical power (see Supplementary material 1), it would be desirable to replicate this regression model with larger *Ns*. Second, whereas our neuropsychological protocol including several tasks and subtasks tapping diverse cognitive domains, future renditions should incorporate additional classical tests for comparison across epilepsy subtypes. Third, we lacked detailed information about the patients' medication status. Though typically absent in neurocognitive research on this population [104, 105], this factor should be considered in future studies, given that neurotransmitter bioavailability may modulate action language processing [106]. Fourth, since our task involved comparisons between action-verb and object-noun conditions, present results do not reveal whether the deficits observed in FLE patients are unique to the former category or general to verb categories at large. While evidence from motor disorders shows that action-verb deficits may occur in the absence of abstract-verb deficits [36, 65, 107–109], frontal brain regions mediating verb processing in general [110]. New studies should establish whether the reported deficits in FLE are circumscribed to the domain of action verbs. Fifth, our PCE group was composed of patients with heterogeneous foci, prompting questions on whether action-verb processing might also be impaired in specific *subsets* of patients with particular epilepsy types. Future works should replicate our study with homogeneous groups of temporal, parietal, and occipital epilepsy patients. Sixth, it is worth noting that action-verb RTs in FLE patients were longer than those of object nouns in the same group, but they did not differ from object-noun RTs in HCs. Although comparisons differing in both factors ('group' and 'condition') may not be directly informative [111], this suggests that object-noun processing may also be partly sensitive to FLE, paving the way for new studies specifically designed to investigate this category across epilepsy types. Finally, beyond our focus on FLE, our framework lays the groundwork for new embodied designs seeking specific markers of other epilepsy types.

6. Conclusion

Our study suggests that action-concept deficits emerge specifically in frontal (as opposed to posterior) brain disorders, depend directly structural and functional motor-network disruptions, and can be observed even in non-neurodegenerative conditions. These findings support and extend the DMGH as a promising translational development from the embodied

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cognition framework. Further work along these lines can inform a rich agenda at the crossing of neurology and cognitive neuroscience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Bak TH, The neuroscience of action semantics in neurodegenerative brain diseases. Current opinion in neurology, 2013. 26(6): p. 671–677. [PubMed: 24184973]
2. Birba A, et al. , Losing ground: Frontostriatal atrophy disrupts language embodiment in Parkinson's and Huntington's disease. Neurosci Biobehav Rev, 2017. 80: p. 673–687. [PubMed: 28780312]
3. Gallese V, & Cuccio V, The neural exploitation hypothesis and its implications for an embodied approach to language and cognition: Insights from the study of action verbs processing and motor disorders in Parkinson's disease. Cortex, 2018. 100: p. 215–225. [PubMed: 29455947]
4. García AM and Ibáñez A, A touch with words: Dynamic synergies between manual actions and language. Neuroscience & Biobehavioral Reviews, 2016. 68: p. 59–95. [PubMed: 27189784]
5. García AM, & Ibáñez A, When embodiment breaks down: Language deficits as novel avenues into movement disorders. Cortex, 2018. 100: p. 1–7. [PubMed: 29496261]
6. Abel TJ, et al. , Direct Physiologic Evidence of a Heteromodal Convergence Region for Proper Naming in Human Left Anterior Temporal Lobe. The Journal of Neuroscience, 2015. 35(4): p. 1513–1520. [PubMed: 25632128]
7. Pulvermuller F, How neurons make meaning: brain mechanisms for embodied and abstract-symbolic semantics. Trends Cogn Sci, 2013. 17(9): p. 458–70. [PubMed: 23932069]
8. Pulvermuller F, Neural reuse of action perception circuits for language, concepts and communication. Prog Neurobiol, 2018. 160: p. 1–44. [PubMed: 28734837]
9. Garcia AM, et al. , How meaning unfolds in neural time: Embodied reactivations can precede multimodal semantic effects during language processing. Neuroimage, 2019. 197: p. 439–449. [PubMed: 31059796]
10. Ibanez A, et al. , Motor-language coupling: direct evidence from early Parkinson's disease and intracranial cortical recordings. Cortex, 2013. 49(4): p. 968–84. [PubMed: 22482695]
11. García AM, Sedeño L, Trujillo N, Bocanegra Y, Gomez D, Pineda D, Villegas A, Muñoz E, Arias W, & Ibáñez A, Language Deficits as a Preclinical Window into Parkinson's Disease: Evidence from Asymptomatic Parkin and Dardarin Mutation Carriers Journal of the International Neuropsychological Society : JINS, 2017. 23(2): p. 150–158. [PubMed: 28205494]
12. Cervetto S, Abrevaya S, Martorell Caro M, Kozono G, Muñoz E, Ferrari J, Sedeño L, Ibáñez A, & García AM, Action Semantics at the Bottom of the Brain: Insights From Dysplastic Cerebellar Gangliocytoma. Frontiers in psychology, 2018. 9: p. 1994. [PubMed: 30515113]
13. Garcia AM, et al. , Time to Face Language: Embodied Mechanisms Underpin the Inception of Face-Related Meanings in the Human Brain. Cereb Cortex, 2020.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

14. Bak TH, Hodges JR, Kissing and Dancing - a test to distinguish the lexical and conceptual contributions to noun / verb and action / object dissociation. . J Neuroling, 2003. 16(169-181).
15. Cardona JF, Kargieman L, Sinay V, Gershanik O, Gelormini C, Amoruso L, Roca M, Pineda D, Trujillo N, Michon M, García AM, Szenkman D, Bekinschtein T, Manes F, & Ibáñez A, How embodied is action language? Neurological evidence from motor diseases. . Cognition, 2014. 132(2): p. 311–322.
16. Abrevaya S, Sedeño L, Fitipaldi S, Pineda D, Lopera F, Buritica O, Villegas A, Bustamante C, Gomez D, Trujillo N, Pautassi R, Ibáñez A, & García AM, The Road Less Traveled: Alternative Pathways for Action-Verb Processing in Parkinson's Disease. Journal of Alzheimer's disease, 2017. 55(4): p. 1429–1435.
17. García AM, Bocanegra Y, Herrera E, Pino M, Muñoz E, Sedeño L, & Ibáñez A, Action-semantic and syntactic deficits in subjects at risk for Huntington's disease. Journal of neuropsychology, 2018. 12(3): p. 389–408. [PubMed: 28296213]
18. York C, Olm C, Boller A, McCluskey L, Elman L, Haley J, Seltzer E, Chahine L, Woo J, Rascovsky K, McMillan C, & Grossman M, Action verb comprehension in amyotrophic lateral sclerosis and Parkinson's disease. Journal of neurology, 2014. 261(6): p. 1073–1079. [PubMed: 24676939]
19. Bak TH and Chandran S, What wires together dies together: verbs, actions and neurodegeneration in motor neuron disease. Cortex, 2012. 48(7): p. 936–44. [PubMed: 21924711]
20. Arevalo AL, Baldo JV, and Dronkers NF, What do brain lesions tell us about theories of embodied semantics and the human mirror neuron system? Cortex, 2012. 48(2): p. 242–254. [PubMed: 20621292]
21. Arévalo AL, Lu CC, Huang LB, Bates EA, & Dronkers NF, Action and object processing in brain-injured speakers of Chinese. Neuropsychology, 2011. 25(6): p. 792–805. [PubMed: 21728432]
22. Kaufmann T, et al. , Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat Neurosci, 2019. 22(10): p. 1617–1623. [PubMed: 31551603]
23. Lüders HA, Baumgartner J, Benbadis C, Bleasel S, Burgess A, R. et al. , Semiological seizure classification. Epilepsia, 1998. 39: p. 1006–13. [PubMed: 9738682]
24. Law N, Smith ML, and Widjaja E, Thalamocortical Connections and Executive Function in Pediatric Temporal and Frontal Lobe Epilepsy. AJNR Am J Neuroradiol, 2018. 39(8): p. 1523–1529. [PubMed: 29880477]
25. Widjaja E, Zamyadi M, Raybaud C, Snead OC, & Smith ML, Abnormal functional network connectivity among resting-state networks in children with frontal lobe epilepsy. AJNR. American journal of neuroradiology, 2013. 34(12): p. 2386–2392. [PubMed: 23868148]
26. Woodward KE, Gaxiola-Valdez I, Goodyear BG, & Federico P, Frontal lobe epilepsy alters functional connections within the brain's motor network: a resting-state fMRI study. Brain connectivity, 2014. 4(2): p. 91–99. [PubMed: 24329128]
27. Yu T, Wang Y, Zhang G, Cai L, Du W, & Li Y, Posterior cortex epilepsy: diagnostic considerations and surgical outcome. Seizure, 2009. 18(4): p. 288–292. [PubMed: 19136282]
28. Fogarasi A, Boesebeck F, & Tuxhorn I , A detailed analysis of symptomatic posterior cortex seizure semiology in children younger than seven years. Epilepsia, 2003. 44(1): p. 89–96. [PubMed: 12581235]
29. Fisher RS, et al. , ILAE official report: a practical clinical definition of epilepsy. Epilepsia, 2014. 55(4): p. 475–82. [PubMed: 24730690]
30. Berg AT, Epilepsy, cognition, and behavior: The clinical picture. . Epilepsia, , 2011. 52: p. 7–12.
31. Scheepers M, & Kerr M, Epilepsy and behaviour. Current opinion in neurology, 2003. 16: p. 183–187. [PubMed: 12644747]
32. Oldfield RC, The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 1971. 9(1): p. 97–113. [PubMed: 5146491]
33. Nasreddine ZS, et al. , The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc, 2005. 53(4): p. 695–9. [PubMed: 15817019]
34. Torralva T, Roca M, Gleichgerrcht E, Lopez P & Manes F, INECO Frontal Screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia. Journal of the International Neuropsychological Society, 2009. 15: p. 777–786. [PubMed: 19635178]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

35. Wechsler D, Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation., 1999.
36. Bocanegra Y, et al. , Unspeakable motion: Selective action-verb impairments in Parkinson's disease patients without mild cognitive impairment. Brain Lang, 2017. 168: p. 37–46. [PubMed: 28131052]
37. Druks JM, J., An object and action naming battery. . London: Psychological Press., 2000.
38. Bates EDA, S.; Jacobsen T; Székely A; Andonova E; Devescovi A, Timed picture naming in seven languages. Psychonomic Bulletin & Review, 2003. 10(2): p. 344–380. [PubMed: 12921412]
39. Nichols TE, et al. , Best practices in data analysis and sharing in neuroimaging using MRI. Nat Neurosci, 2017. 20(3): p. 299–303. [PubMed: 28230846]
40. Poldrack RA, et al. , Scanning the horizon: towards transparent and reproducible neuroimaging research. Nat Rev Neurosci, 2017. 18(2): p. 115–126. [PubMed: 28053326]
41. O'Gorman RL, et al. , Tract-based spatial statistics to assess the neuroprotective effect of early erythropoietin on white matter development in preterm infants. Brain, 2015. 138(Pt 2): p. 388–97. [PubMed: 25534356]
42. Mollink J, et al. , The spatial correspondence and genetic influence of interhemispheric connectivity with white matter microstructure. Nat Neurosci, 2019. 22(5): p. 809–819. [PubMed: 30988526]
43. Smith SM, Jenkinson M, Johansen-Berg H, et al. , Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage, 2006. 61(4): p. 1487–1505.
44. Jenkinson M, et al. , Fsl. Neuroimage, 2012. 62(2): p. 782–90. [PubMed: 21979382]
45. Hua K, et al. , Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage, 2008. 39(1): p. 336–47. [PubMed: 17931890]
46. Moguilner S, et al. , Weighted Symbolic Dependence Metric (wSDM) for fMRI resting-state connectivity: A multicentric validation for frontotemporal dementia. Sci Rep, 2018. 8(1): p. 11181. [PubMed: 30046142]
47. Sharma NB, C. J; Rowe JB, Motor imagery after stroke: relating outcome to motor network connectivity. Ann Neurol, 2009. 66: p. 604–616. [PubMed: 19938103]
48. Lambon Ralph MA, et al. , The neural and computational bases of semantic cognition. Nat Rev Neurosci, 2017. 18(1): p. 42–55. [PubMed: 27881854]
49. Vahdat S, et al. , Functionally specific changes in resting-state sensorimotor networks after motor learning. J Neurosci, 2011. 31(47): p. 16907–15. [PubMed: 22114261]
50. Saiote C, et al. , Resting-state functional connectivity and motor imagery brain activation. Hum Brain Mapp, 2016. 37(11): p. 3847–3857. [PubMed: 27273577]
51. Benjamini Y, & Hochberg Y, Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological), 1995. 57(1): p. 289–300.
52. Liljeström M, Hultén A, Parkkonen L, & Salmelin R, Comparing MEG and fMRI views to naming actions and objects. Human brain mapping, 2009. 30(6): p. 1845–185. [PubMed: 19378277]
53. Chen TG, C., Xgboost: a scalable tree boosting system. Proceedings of the 22Nd ACM SIGKDD international conference on knowledge discovery and data mining, 2016: p. 785–794.
54. Poldrack RA, Huckins G, and Varoquaux G, Establishment of Best Practices for Evidence for Prediction: A Review. JAMA Psychiatry, 2019.
55. Cohen J, Statistical Power Analysis for the Behavioral Sciences. 2nd Ed.. Hillsdale, NJ: Laurence Erlbaum Associates, 1988.
56. Zeng X and Luo G, Progressive sampling-based Bayesian optimization for efficient and automatic machine learning model selection. Health Inf Sci Syst, 2017. 5(1): p. 2. [PubMed: 29038732]
57. Feurer M, F. H, Hyperparameter Optimization. . Automated Machine Learning. The Springer Series on Challenges in Machine Learning. Springer., 2019.
58. Mason LB, J.; Bartlett PL; Frean Marcus., Boosting Algorithms as Gradient Descent in Function Space. Proceedings of the 12th International Conference on Neural Information Processing Systems, 1999.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

59. Behravan H, et al. , Machine learning identifies interacting genetic variants contributing to breast cancer risk: A case study in Finnish cases and controls. Sci Rep, 2018. 8(1): p. 13149. [PubMed: 30177847]
60. Zheng H, Yuan J, and Chen L, Short-Term Load Forecasting Using EMD-LSTM Neural Networks with a Xgboost Algorithm for Feature Importance Evaluation. Energies, 2017. 10(8): p. 1168.
61. Torlay L, et al. , Machine learning-XGBoost analysis of language networks to classify patients with epilepsy. Brain Inform, 2017. 4(3): p. 159–169. [PubMed: 28434153]
62. Xuan P, et al. , Gradient Boosting Decision Tree-Based Method for Predicting Interactions Between Target Genes and Drugs. Front Genet, 2019. 10: p. 459. [PubMed: 31214240]
63. Kingsford C, & Salzberg SL, What are decision trees? Nature biotechnology, 2008. 26(9): p. 1011–1013.
64. Moguilner S, & García AM Data for "Structural and functional motor-network disruptions predict selective action-concept deficits: Evidence from frontal lobe epilepsy". URL: https://osf.io/6ebfw/. Open Science Framework (OSF), 2021.
65. García AM, et al. , Parkinson's disease compromises the appraisal of action meanings evoked by naturalistic texts. Cortex, 2018. 100: p. 111–126. [PubMed: 28764852]
66. Suárez-García DMA, et al. , Rekindling Action Language: A Neuromodulatory Study on Parkinson's Disease Patients. Brain Sciences, 2021. 11(7): p. 887. [PubMed: 34356122]
67. Birba A, Vitale F, Padrón I, Dottori M, de Vega M, Zimerman M, Sedeño L, Ibáñez A, & García AM, Electrifying discourse: Anodal tDCS of the primary motor cortex selectively reduces action appraisal in naturalistic narratives. Cortex; a journal devoted to the study of the nervous system and behavior, 2020. 132: p. 460–472. [PubMed: 32950239]
68. Moguilner S, Birba A, Fino D, Isoardi R, Huetagoyena C, Otoya R, Tirapu V, Cremaschi F, Sedeño L, Ibáñez A, & García AM, Multimodal neurocognitive markers of frontal lobe epilepsy: Insights from ecological text processing. NeuroImage,, 2021. 235.
69. Jeannerod M and Jacob P, Visual cognition: a new look at the two-visual systems model. Neuropsychologia, 2005. 43(2): p. 301–312. [PubMed: 15707914]
70. Birba A, et al. , Motor-system dynamics during naturalistic reading of action narratives in first and second language. Neuroimage, 2020: p. 116820. [PubMed: 32278096]
71. Philp DJ, Korgaonkar MS, & Grieve SM , Thalamic volume and thalamo-cortical white matter tracts correlate with motor and verbal memory performance. . Neuroimage Clin, 2014. 91(77-83).
72. Isaacs BR, et al. , Cortico-basal white matter alterations occurring in Parkinson's disease. PLoS One, 2019. 14(8): p. e0214343. [PubMed: 31425517]
73. Kellinghaus C, & Lüders HO, Frontal lobe epilepsy. Epileptic disorders : international epilepsy journal, 2004. 6(4): p. 223–239.
74. Tovar-Moll F, Evangelou IE, Chiu AW, Auh S, Chen C, Ehrmantraut M, Ohayon JM, Richert N, & Bagnato F , Diffuse and focal corticospinal tract disease and its impact on patient disability in multiple sclerosis. Journal of neuroimaging : official journal of the American Society of Neuroimaging, 2015. 25(2): p. 200–206. [PubMed: 25318661]
75. Phillips O, Squitieri F, Sanchez-Castaneda C, Elifani F, Griguoli A, Maglione V, Caltagirone C, Sabatini El., & Di Paola M, The Corticospinal Tract in Huntington's Disease. Cerebral cortex, 2015. 25(9): p. 2670–2682. [PubMed: 24706734]
76. Hasan KMI, A., Kamali A; Kramer LA; Ashtari M; Cirino PT; Papanicolaou AC; Fletcher JM; & Ewing-Cobbs L, Development and aging of the healthy human brain uncinate fasciculus across the lifespan using diffusion tensor tractography. Brain research, 2009. 1276: p. 67–76. [PubMed: 19393229]
77. Catani M, Mesulam MM, Jakobsen E, Malik F, Martersteck A, Wieneke C, Thompson CK, Thiebaut de Schotten M, Dell'Acqua F, Weintraub S, & Rogalski E, A novel frontal pathway underlies verbal fluency in primary progressive aphasia. Brain : a journal of neurology, 2013. 136(8): p. 2619–2628. [PubMed: 23820597]
78. de Zubicaray GI, Rose SE, & McMahon KL, The structure and connectivity of semantic memory in the healthy older adult brain. 54, 2011. 2(1488-1494).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

79. Akinina Y, Dragoy O, Ivanova MV, Iskra EV, Soloukhina OA, Petryshevsky AG, Fedina ON, Turken AU, Shklovsky VM, & Dronkers NF, Grey and white matter substrates of action naming. Neuropsychologia, 2019. 131: p. 249–265. [PubMed: 31129278]
80. Olde Dubbelink KT, Stoffers D, Deijen JB, Twisk JW, Stam CJ, Hillebrand A, & Berendse HW, Resting-state functional connectivity as a marker of disease progression in Parkinson's disease: A longitudinal MEG study. NeuroImage. Clinical, 2013. 2.
81. Yoo K, Chung SJ, Kim HS, Choung OH, Lee YB, Kim MJ, You S, & Jeong Y, Neural substrates of motor and non-motor symptoms in Parkinson's disease: a resting FMRIstudy. PloS one, 2015. 10(e0125455).
82. Wu T, Wang L, Chen Y, Zhao C, Li K, & Chan P, Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. Neuroscience letters, 2009. 460: p. 6–10. [PubMed: 19463891]
83. Abbasi B, & Goldenholz DM, Machine learning applications in epilepsy. Epilepsia, 2019. 60(10).
84. Leyden KM, Kucukboyaci NE, Puckett OK, Lee D, Loi RQ, Paul B, & McDonald CR, What does diffusion tensor imaging (DTI) tell us about cognitive networks in temporal lobe epilepsy? Quantitative imaging in medicine and surgery, 2015. 5(2): p. 247–263. [PubMed: 25853083]
85. Lin Huan LX, Chunhong Qin, Wensheng Wang, Chi Zhang, Shijun Qiu, Altered White Matter Structural Network in Frontal and Temporal Lobe Epilepsy: A Graph-Theoretical Study. Frontiers in Neurology, 2020. 11: p. 561. [PubMed: 32625164]
86. Lanzilotto M, C. F, Livi A, Gerbella M, Maranesi M, Borra E, Passarelli L, Gamberini M, Fogassi L, Bonini L, Orban GA. , Anterior Intraparietal Area: A Hub in the Observed Manipidative Action Network. Cereb Cortex, 2019. 29.
87. Andersen RA, & Cui H, Intention, action planning, and decision making in parietalfrontal circuits. Neuron, 2009. 63: p. 568–583. [PubMed: 19755101]
88. Aflalo T, Zhang CY, Rosario ER, Pouratian N, Orban GA, & Andersen RA, A shared neural substrate for action verbs and observed actions in human posterior parietal cortex. Science advances, 2020. 6.
89. Cao X, Qian Z, Xu Q, Shen J, Zhang Z, & Lu G (2014). , Altered intrinsic connectivity networks in frontal lobe epilepsy: a resting-state fMRI study. Computational and mathematical methods in medicine, 2014.
90. Elger CE, Helmstaedter C, & Kurthen M, Chronic epilepsy and cognition. The Lancet. Neurology, 2004. 3(11): p. 663–672. [PubMed: 15488459]
91. Carreno M, Donaire A, and Sanchez-Carpintero R, Cognitive disorders associated with epilepsy: diagnosis and treatment. Neurologist, 2008. 14(6 Suppl 1): p. S26–34. [PubMed: 19225368]
92. Cahn-Weiner DA, Wittenberg D, & McDonald C, Everyday cognition in temporal lobe and frontal lobe epilepsy. Epileptic disorders, 2009. 11(3): p. 222–227. [PubMed: 19713170]
93. Llano DA, Functional imaging of the thalamus in language. Brain and language, 2013. 126(1): p. 62–72. [PubMed: 22981716]
94. Patterson K, Nestor PJ, and Rogers TT, Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci, 2007. 8(12): p. 976–987. [PubMed: 18026167]
95. Seghier ML, The angular gyrus: multiple functions and multiple subdivisions The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 2013. 19(1): p. 43–61.
96. Pulvermuller F, Brain mechanisms linking language and action. Nat.Rev.Neurosci, 2005. 6(7): p. 576–582. [PubMed: 15959465]
97. Hickok G, The motor system 's contribution to perception and understanding actions: clarifying mirror neuron myths and misunderstandings. Language and Cognition, 2015. 7(3): p. 476–484.
98. Papeo L and Caramazza A, When "ultrarapid" word-related motor activity is not faster than "early". Frontiers in Human Neuroscience, 2014. 8: p. 842. [PubMed: 25360104]
99. Bedny M and Caramazza A, Perception, action, and word meanings in the human brain: the case from action verbs. Ann N Y Acad Sci, 2011. 1224: p. 81–95. [PubMed: 21486297]
100. Aravena P, et al. , Action relevance in linguistic context drives word-induced motor activity. Front Hum Neurosci, 2014. 8: p. 163. [PubMed: 24744714]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

101. Argiris G, et al. , Neurosurgical lesions to sensorimotor cortex do not impair action verb processing. Scientific Reports, 2020. 10(1): p. 523. [PubMed: 31949237]
102. Cervetto S, et al. , The Neural Blending of Words and Movement: Event-Related Potential Signatures of Semantic and Action Processes during Motor–Language Coupling. Journal of Cognitive Neuroscience, 2021. 33(8): p. 1413–1427. [PubMed: 34496378]
103. Lambon Ralph MA, et al. , Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. Brain, 2012. 135(Pt 1): p. 242–58. [PubMed: 22287382]
104. Shamshiri EA, Sheybani L, & Vulliemoz S, The Role of EEG-fMRI in Studying Cognitive Network Alterations in Epilepsy. Frontiers in neurology, 2019. 10(1033).
105. Tailby C, Kowalczyk MA, & Jackson GD, Cognitive impairment in epilepsy: the role of reduced network flexibility. . Annals of clinical and translational neurology, 2017. 5(1): p. 29–40. [PubMed: 29376090]
106. Herrera E, Cuetos F, & Ribacoba R, Verbal fluency in Parkinson's disease patients on/off dopamine medication. Neuropsychologia, 2012. 50(14): p. 3636–3640. [PubMed: 22995942]
107. Fernandino L, et al. , Parkinson's disease disrupts both automatic and controlled processing of action verbs. Brain Lang, 2013. 127(1): p. 65–74. [PubMed: 22910144]
108. Fernandino L, et al. , Where is the action? Action sentence processing in Parkinson's disease. Neuropsychologia, 2013. 51(8): p. 1510–7. [PubMed: 23624313]
109. García AM, et al. , The cerebellum and embodied semantics: evidence from a case of genetic ataxia due to STUB1 mutations. Journal of Medical Genetics, 2017. 54(2): p. 114–124. [PubMed: 27811304]
110. Vigliocco G, et al. , Nouns and verbs in the brain: a review of behavioural, electrophysiological, neuropsychological and imaging studies. Neurosci Biobehav Rev, 2011. 35(3): p. 407–26. [PubMed: 20451552]
111. Vargason T, Howsmon DP, McGuinness DL, & Hahn J, On the Use of Multivariate Methods for Analysis of Data from Biological Networks. Processes (Basel, Switzerland), 2017. 5(3): p. 36.

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Highlights

- We tested action and object concepts in frontal and posterior lobe epilepsy.
- Only frontal lobe epilepsy patients showed selective action-concept deficits.
- These occurred together with structural and functional motor network abnormalities.
- Such deficits were predicted by structural and functional motor network features.
- Our results support the disrupted motor grounding hypothesis.

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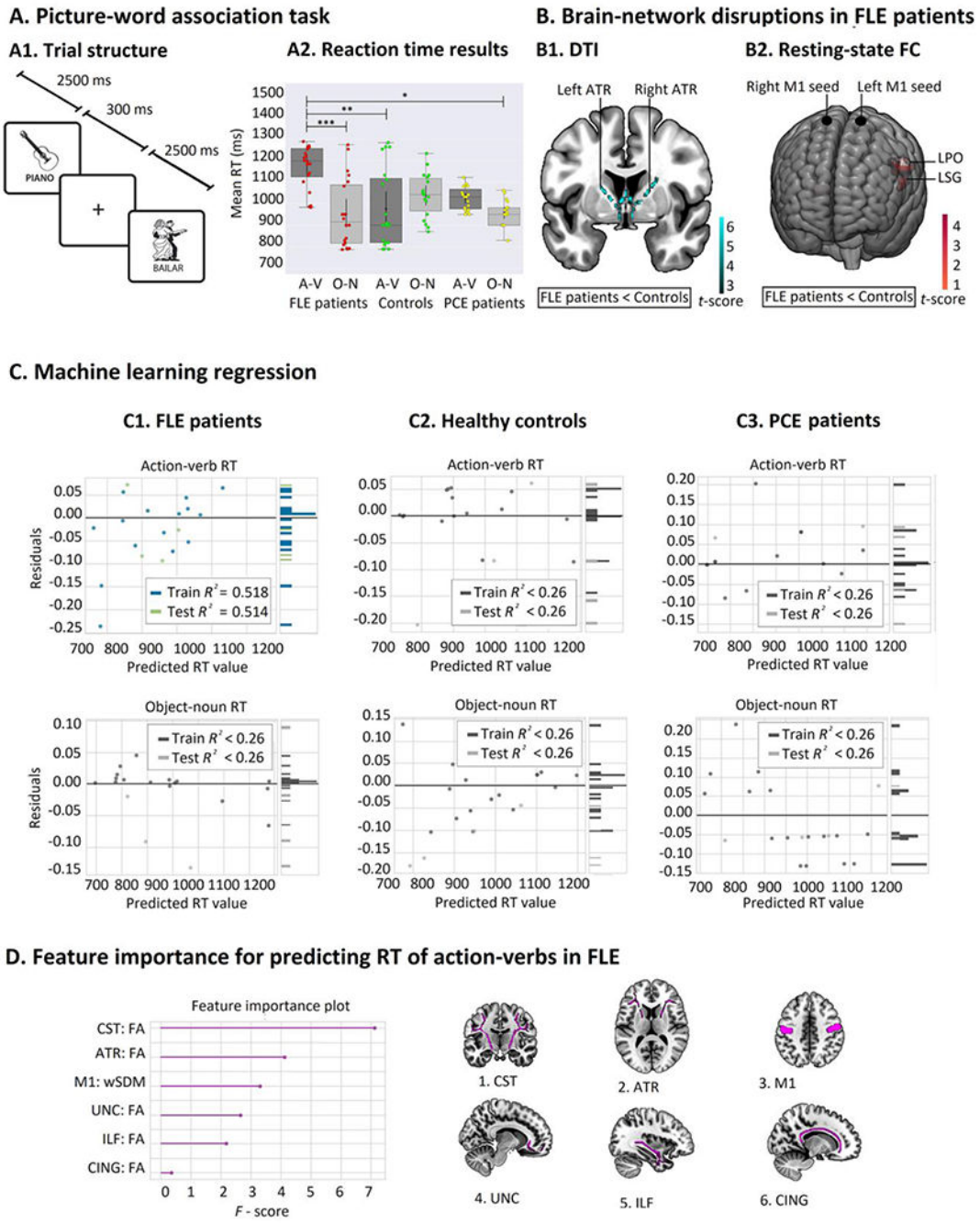

Figure 1.

Behavioral, neuroimaging, XGBoost machine learning regression, and feature importance results. **(A)** Picture-Word Association task. **(A1)** Trial structure. The task comprised 80 trials, each composed of a black-and-white image and an accompanying word. Half the items belonged to the action-verb (A-V) condition, and the remaining half corresponded to the object-noun (O-N) condition. Trials began with a fixation cross that remained visible for a random period lasting up to 300 ms. Each condition included 20 congruent trials and 20 incongruent trials (2500 ms maximum duration). **(A2)** Reaction time (RT)

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results. RTs for A-V trials in FLE patients were significantly higher than O-N trials in the same group, A-V trials in controls, and O-N trials in PCE patients. No other pairwise contrast proved significant. All results were covaried for MoCA and IFS scores. Asterisks (*) indicate significant differences. **(B)** Brain network disruptions in FLE patients. **(B1)** Local FA outcomes. Relative to controls, FLE patients exhibited reduced white matter tract integrity in the ATR. No differences were observed between PCE patients and any of the other two groups. **(B2)** Rs-FC results. Relative to controls, FLE patients showed reduced wSDM connectivity between the bilateral M1 region and the left parietal operculum and left supramarginal gyrus. **(C)** Machine learning regressions. Residual plots for FLE patients, controls, and PCE patients in the A-V and O-N conditions, showing the error for each subject's regression for the predicted RT. Only RTs for A-V trials in FLE patients yielded a significant regression. Results are shown for both the training dataset and the testing dataset, with a R^2 threshold of 0.26. **(D)** Feature importance plot for the only significant regression, namely: A-V RTs in FLE patients. Feature relevance revealed that the main predictors of A-V RTs in FLE patients were FA of the cortico-spinal tract, followed by FA of the anterior thalamic radiations, wSDM of the M1 seed, and other less important features. FLE: frontal lobe epilepsy; PCE: posterior cortex epilepsy; A-V: Action-verb; O-N: Object-noun; DTI: diffusion tensor imaging; rs-fMRI: resting-state fMRI; re-FC: resting-state functional connectivity; FA: fractional anisotropy; wSDM: weighted Symbolic Dependence Metric; ATR: anterior thalamic radiations; RT: reaction time. LPO: Left parietal operculum. LSG: Left supramarginal gyrus.

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Table 1.

Demographic, neuropsychological, and clinical characteristics of the groups.

	Group			Statistics	
	FLE patients (*n* = 20)	**Healthy controls (*n* = 20)**	**PCE patients (*n* = 20)**	***p*-values**	**Effect size**
Sex (F:M)	11:9	9:11	11:9	0.76[a]	0.01[d]
Handedness (R:L)	17:3	16:4	17:3	0.88[a]	0.01[d]
Age	27.39 (7.23)	30.21 (7.12)	28.96 (8.98)	0.37[b]	0.04[e]
Education	13.96 (1.69)	15.15 (1.82)	13.91 (1.72)	0.43[b]	0.04[e]
MoCA	26.55 (1.91)	27.84 (1.92)	26.33 (2.34)	0.19[b]	0.07[e]
IFS battery	23.46 (1.58)	26.57 (1.67)	25.12 (1.69)	0.08[b]	0.10[e]
WASI	98.59 (9.63)	106.14 (10.15)	101.17 (8.94)	0.29[b]	0.05[e]
Years with symptoms	17.32 (4.34)	----	16.27 (4.56)	0.67[f]	0.01[e]
Years since diagnosis	16.21 (5.57)	----	15.86 (4.98)	0.77[f]	0.01[c]

Descriptive statistics are shown as mean (standard deviation);

a: *p*-value calculated via a chi-squared test.

b: *p*-value calculated via an independent measures ANOVA.

d: Cramer's V.

e: Partial eta squared.

f: two-sample *t*-test.

ANOVA; FLE: frontal lobe epilepsy; PCE: posterior cortex epilepsy; MoCA: Montreal Cognitive Assessment; IFS: INECO Frontal Screening; WASI: Weschler Abbreviated Scale of Intelligence.