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Received 18 April 2014
accepted 29 May 2014

WORDS IN MOTION: MOTOR-LANGUAGE COUPLING IN PARKINSON'S DISEASE

Abstract

A growing body of evidence indicates that neurodegenerative motor disorders involved high-order cognitive dysfunctions. Crucially, evidence obtained in multiple behavioral, neuroimaging, and electrophysiological studies points to selective impairments of action language –that is, processing of linguistic stimuli denoting motor actions, including idioms (e.g., *cut a rug*) and action verbs (e.g., *clap*). Action-verb deficits (with relative preservation of noun processing) have been repeatedly documented in Parkinson's disease (PD). However, research on relevant biomarkers is still scant, and clinical implications of these findings have not yet been formally discussed. Relevant insights may be obtained through the assessment of motor-language coupling (i.e., the behavioral and neural integration of action-verb processing and ongoing motor actions). We propose that motor-language coupling deficits, as indexed by a cortical-subcortical network, may constitute an early neurocognitive marker of PD. Specifically, deficits in this domain at the prodromal stage may be detected through the action-sentence compatibility (ACE) paradigm, which induces a contextual coupling of ongoing motor actions and action-verb processing. Our translational proposal is supported and illustrated by recent studies demonstrating the sensitivity of the ACE technique as well as its potential to assist in differential diagnosis and intervention-program design.

Keywords

• motor-language coupling • Parkinson's disease • verb-processing • neurolinguistics

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The emergence of motor-language approaches in the study of neurodegenerative diseases

In recent years, the disruption of non-motor functions in motor disease has emerged as a promising topic for both basic and translational neuroscience. Impairments of movement and cognition were long regarded as separate phenomena [1]. However, a growing body of evidence indicates that neurodegenerative motor disorders also involve high-order cognitive dysfunctions, ranging from working memory, attention, and executive processing deficits [2-4], to impairments of language [4-10] and action knowledge [11]. Further data comes from studies showing that the same genes (e.g., C9orf72) are involved in diseases once perceived as purely motor or purely cognitive, such as motor neuron disease (MND) and frontotemporal dementia, respectively [12].

A cognitive domain which seems to be specifically compromised in motor diseases is

action language, that is, processing of linguistic stimuli denoting motor actions, including idioms (e.g., *cut a rug*) and action verbs (e.g., *clap*). A pioneering report of selective action-language deficits in MND [6] was corroborated in subsequent clinical [13-15] and neuroimaging [16] studies. Additional imaging evidence obtained from neurotypical samples indicates that the processing of linguistic stimuli related to specific body parts (e.g., the word *kick*) activates motor content-specific regions (e.g., cortical areas engaged by leg movement) [17-19, but see 20, 21]. The involvement of motor areas in the execution, comprehension, and mental enactment of actions has been dubbed 'motor cognition' [22].

In this paper, we review recent findings on motor cognition in an attempt to set forth relevant translational proposals. Specifically, our focus is on early detection of Parkinson's disease (PD) through the assessment of motor-language coupling (i.e., the behavioral and neural integration of action-verb processing

and ongoing motor actions). Converging evidence obtained in varied PD studies supports a neurocognitive model of the network underlying such impaired processes, and motivates the postulation of specific biomarkers. The latter, we propose, may allow for prodromal detection of the disease and timely application of rehabilitation strategies.

Action-language impairments in Parkinson's disease

The exploration of motor cognition has been boosted by multiple reports of selective action-verb impairments in PD. PD is primarily caused by the degeneration of dopaminergic neurons in basal ganglia structures, especially the substantia nigra [23]. The main clinical feature of this disorder is the loss of voluntary movement control, with marked signs of resting tremor and bradykinesia [24,25]. Given this symptom profile, PD offers an appropriate framework to examine the relation between bodily motion and action language.

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Several clinical studies have documented selective action-verb deficits with relative preservation of noun processing in PD. This was observed in varied linguistic tasks, requiring either action-verb identification (e.g., lexical decision [26]) or generation (e.g., picture naming [27,28], verbal fluency [29], related-word production [30]). Other reports have found that PD patients exhibiting difficulties in both action-verb and noun processing were more impaired in the former during word naming [31] and word generation [32], and that they improved action naming more than object naming upon stimulation of the subthalamic nucleus [33]. Moreover, lexical decision and semantic similarity judgment experiments have shown that verb-processing deficits in PD compromised action (e.g., *squeeze*) but not abstract (e.g., *improve*) verbs [34]. Finally, a study comparing motor-language coupling in early PD, neuromyelitis optica, and acute transverse myelitis, indicated that deficits in the integration of action verbs and manual actions result from atrophy of cortico-subcortical motor network system, and not from peripheral (musculoskeletal) motor system affection [35].

A double dissociation may be postulated between PD patients and those exhibiting selective object-word deficits with relative preservation of action words and action semantics subsequent to posterior atrophy, as observed in Alzheimer's disease [36] and semantic dementia [37,38]. Furthermore, differential activations of frontal/prefrontal regions for verbs, and middle/posterior temporal regions for nouns, have been reported in neuroimaging studies with neurotypical native speakers of English [39,40], German [41], Italian [42], and Japanese [43].¹ Note, however, that the latter findings refer to motor action verbs in general, and only to verbs. In other words, the noun/verb dissociation, as predicated in these studies, fails to cover the full scope of action-language and is, in principle, blind to the differences between action and abstract verbs.

¹ Interestingly, no such anatomical dissociation was observed in three separate fMRI studies with native Chinese speakers [44-46]. Unlike the other Indo-European languages considered, Chinese lacks explicit word-class contrasts in its grammatical morphology, which suggests that neural noun-verb dissociations may be influenced by structural properties of the individual's native language.

In brief, PD patients feature impairments of action verbs (including action semantics) without comparable deficits in other aspects of language, such as noun processing. The neural dissociation between action verbs and nouns, in fact, has been corroborated in studies with neurotypical participants. Moreover, the observed dysfunctions may occur even when other cognitive domains are relatively spared. Given this peculiar pattern, PD affords a promising framework to test neurolinguistic theories, identify possible biomarkers, and delineate novel intervention strategies.

Motor-language coupling as a possible neurocognitive biomarker of Parkinson's disease

While the evidence for selective action-verb deficits in PD has accrued steadily, research on relevant biomarkers is still scant. In an fMRI study, Péran *et al.* [47] found that right-handed non-demented PD patients, during the 'on' phase of their medication, made more errors in action-verb generation than in action naming (Figure 1). This finding suggests that action verbs may not be homogeneously compromised across linguistic functions. Crucially, their imaging data revealed that the former task preferentially engaged an extended cortical network involving aspects of the prefrontal cortex, Broca's area, and the anterior cingulate cortex.

A new, promising neurocognitive biomarker has been proposed in a recent study by Ibáñez *et al.* [48], based on the action-sentence compatibility effect (ACE) paradigm. The ACE "taps the ability" to integrate action-verb comprehension with manual actions. In the ACE task (Figure 2), participants listen to sentences involving actions typically performed with an open hand (OH, e.g., *clapped*) or a closed hand (CH, e.g., *hammered*), as well as neutral sentences denoting non-manual actions (e.g., *visited*). Immediately upon comprehension of each sentence, participants press a button with a pre-assigned hand-shape (open or closed). The combination of response type and sentence type generates compatible (OH sentence and OH response, or CH sentence and CH response), incompatible (OH sentence and CH response, or vice versa), and neutral (neutral sentence with either response) trials. The ACE is defined as shorter reaction times in the compatible than in the incompatible conditions [49-51].

In a first experiment, Ibáñez *et al.* [48] used this paradigm with a sample of 17 (11 male) right-handed early PD patients (mean age = 62.71, *SD* = 7.34) and 15 controls matched for age, gender, education, and handedness. All participants were native Spanish speakers. The patients were tested during the 'on' phase of levodopa or a dopamine agonist. Both groups featured a preserved general cognitive repertoire, as assessed by the Spanish version of the Addenbrooke's Cognitive Examination-

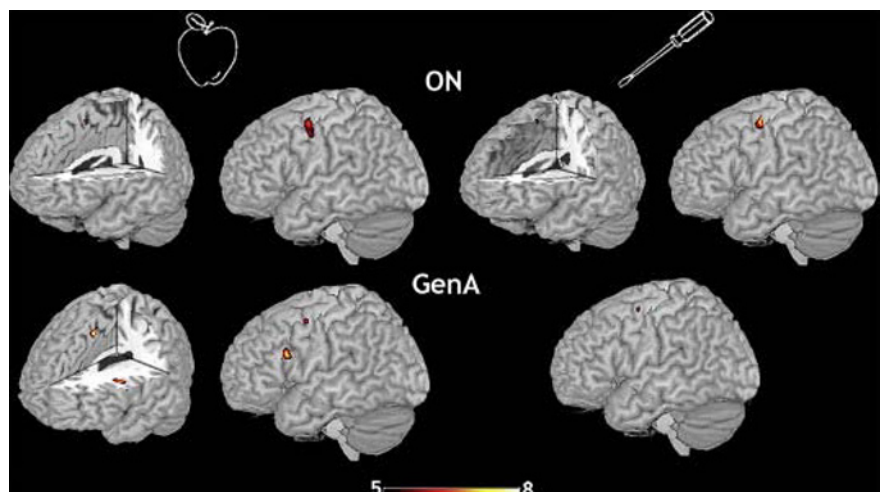


Figure 1. Object naming vs generation of action verbs in Parkinson's disease. Activation maps of positive correlations between each condition (object naming: ON; generation of action verbs: GenA) and the motor deficit of Parkinsonian patients. Reprinted with permission from [47].



Figure 2. ACE: Response button and pre-assigned hand-shapes. (A) OH motor response during sentence comprehension task. (B) CH motor response during sentence comprehension task. (C) Custom-made response button. A commonly available USB joystick with analogue sticks was adapted to detect when a participant initiated a response. Reproduced with permission from [49].

Revised [52] and the INECO Frontal Screening battery [53]. Relative to controls, early PD patients exhibited a significantly reduced ACE, a result which could not be attributed to general cognitive deficits or impaired executive functioning. Deficits in action semantics were also revealed by the patients' scores on the Kissing and Dancing Test (KDT) [37], which taps retrieval of conceptual information from pictures depicting (mainly motor) actions. Furthermore, ACE performance was strongly correlated with KDT scores. In brief, this study showed that deficits in motor-language coupling and action semantics precede the onset of executive dysfunction in PD (Figure 3 A-C).

In a second experiment, with patients suffering from drug-resistant epilepsy, Ibáñez *et al.* [48] employed the ACE paradigm in combination with direct electrocorticography (Figure 3 D-G). During the task, intracranial recordings were obtained of primary motor and premotor cortices as well as cortical regions involved in semantic processing (left inferior frontal and middle/superior temporal gyri). The results showed simultaneous bidirectional effects: on the one hand, motor preparation affected language processing (as indexed by an N400 at the above mentioned gyri); on the other, language processing modulated activity in movement-related areas (as indexed by a motor potential at primary motor and premotor cortices).

Taken together, these experiments motivate two important conclusions. First, motor and language processes seem to influence each other in the above brain areas. Second, the

network supporting motor-language coupling appears to extend beyond somatotopically defined neocortical regions; specifically, the abolished ACE in early PD suggests that the basal ganglia play a crucial role in this integration. The authors propose that this network would involve loops projecting from cortical areas to basal-ganglia/thalamic structures and back to the cortex (Figure 4).

Consistent with embodied cognition views [54-56], this model posits that activation of action/motor routines through the basal ganglia would prime action-verb simulation in frontal areas, leading to further processing of more abstract conceptual relations in temporal regions. Unlike homuncular explanations in embodied language theories, the model aligns with current network approaches to action-language and social cognition suggesting an orchestrated coordination of several brain regions indexing different processes [57,58] (for further discussion of the model, see [48,59]). Crucially, this proposal implies that motor-language coupling deficits following damage to the above network could constitute a potential neurocognitive biomarker of PD.

A translational perspective: early detection and enhanced assessment of Parkinson's disease through motor-language coupling

From a translational perspective, the model and data presented above have important clinical implications. Motor-language coupling deficits may be conceived as an early marker

of PD in non-demented patients, enabling the design of timely intervention techniques.

Admittedly, several reports have documented selective action-verb impairments in other neurodegenerative diseases, such as progressive supranuclear palsy [13,15], amyotrophic lateral sclerosis [14,60], corticobasal degeneration [61,62], and frontotemporal dementia [63,64]. This evidence has been afforded by (non-motor) linguistic tasks, such as action naming. Instead, the ACE paradigm taps *motor-language integration* by inducing a contextual coupling of ongoing motor actions and action-verb processing. Therefore, this task may offer more sensitive, discriminatory measurements of motor cognition deficits in early PD relative to other neurodegenerative diseases.

A first step in this direction has been taken by Cardona *et al.* [35], who showed that ACEs are abolished in PD, but not in neuromyelitis optica and acute transverse myelitis. Furthermore, a recent study on Huntington's disease (an autosomal dominant neurodegenerative disorder which affects the neostriatum and the basal ganglia) revealed ACE impairments in both patients and their relatives [65]. Additional comparative studies could reveal which pathologies involve impaired or spared motor-language interactions to hone the effectiveness of the ACE task in differential diagnosis. Moreover, the assessment of the patients' family groups could be critical for early detection of motor disease genetic subtypes. The prospective research program thus implied should include further behavioral

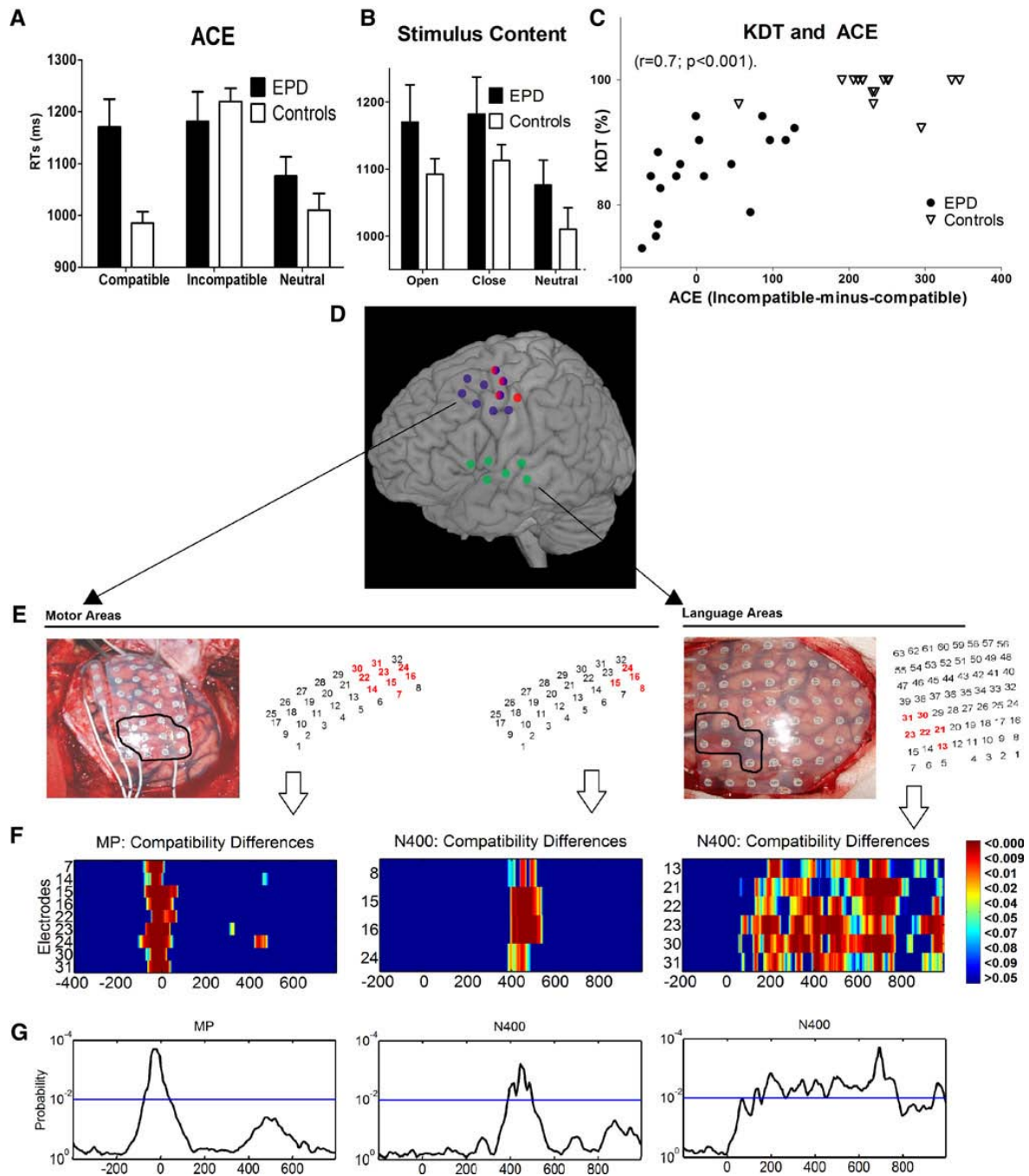


Figure 3. ACE in early Parkinson's disease (EPD) and intracranial recordings. (A) Mean RTs from compatible, incompatible, and neutral trials for PD and control participants. A classic ACE (compatible facilitation and incompatible delay of RTs) was observed for controls, but no ACE was observed in early PD participants. (B) Preserved motor response discrimination for early PD participants. In both groups, OH and CH sentences produced longer RTs than neutral sentences due to a higher frequency effect of neutral sentences. (C) Verbal processing (KDT) is associated with the ACE. The ACE is computed as the subtraction between incompatible and compatible trials (the higher the time interval, the stronger the ACE). KDT scale denotes percentage of correct responses. In panels A and B, the bars depict the SD. (D) Motor and language areas producing an ACE. Normalized position of the electrodes showing a significant ACE (compatibility effect) superimposed in a render 3D map of the canonical CH2bet from MRICron software. The figure depicts the position of electrodes evincing an ACE from both patients' grids in a common space showing the activation of IFG, STG, and MTG (language-related areas) and the MFG, PM, and M1 (motor-related areas). Electrode color is indicative of ERP modulation: MP (Blue); M-N400 (Red); L-N400 (Green). (E) Pictures of subdural grids and electrode arrays. In the three schematic grids, numbers in red are indicative of significant compatibility effects observed at those sites for MP, M-N400, and L-N400 (from left to right). (F) Time-probability charts showing the significant effects at MP in premotor/motor (M1, ventral, and dorsal PM) areas and N400 windows (M-N400 localized in premotor/motor areas including M1 and ventral-dorsal PM area; and a L-N400 localized in STG, MTG, and inferior frontal gyrus). (G) Point-by-point p -value waveform of the compatibility effect for MP, M-N400, and L-N400. The blue lines highlights the $p < 0.01$ threshold. Modified with permission from [48 and 59].

and neuroimaging studies to establish inter-pathological differences in the shared and distinct neural substrates supporting motor cognition.

The translational potential of neurocognitive research through the ACE paradigm is further underscored by the results of Ibáñez *et al.* [48]. These authors demonstrated that motor-language coupling may be affected before executive functions in early PD. In cases of genetic familial PD (identifiable, for example, by a homozygote PARK8 mutation), the assessment of this interactive domain during prodromal stages may lead to early detection, prior to the onset of clinical manifestations. Importantly, although the results surveyed have been obtained by testing multi-patient samples, the ACE task may also reveal motor-language coupling deficits in individual cases, provided that normative data are duly established.

The observation of deficits in action-semantics alone (as opposed to impairments in motor-language interaction) may also serve as an early marker of PD. It has been argued that linguistic deficits in this disease are not *sui generis*, but a result of executive dysfunction [32]. However, using the KDT, Ibáñez *et al.* [48] found that early PD patients also exhibited impaired action-semantics in the absence of executive deficits. For their own part, Fernandino *et al.* [34] showed that deficits in processing action-semantics, as compared to other forms of abstract cognition, involve lower processing demands on executive functioning. Such results suggest that action comprehension (as assessed by the KDT) in PD may also occur before executive domains are compromised, although additional studies must be conducted to confirm this hypothesis.

More generally, assessment of PD through the ACE task and the KDT may offer new insights to develop rehabilitation and stimulation programs. Prodromal detection of the disease may allow for timely intervention with a view to delaying cognitive decline. In fact, cognitive training has been shown to reduce executive dysfunction in this population [66]. The possibility that cognitive stimulation may also impact on motor-language interactions suggests potential innovations in the design

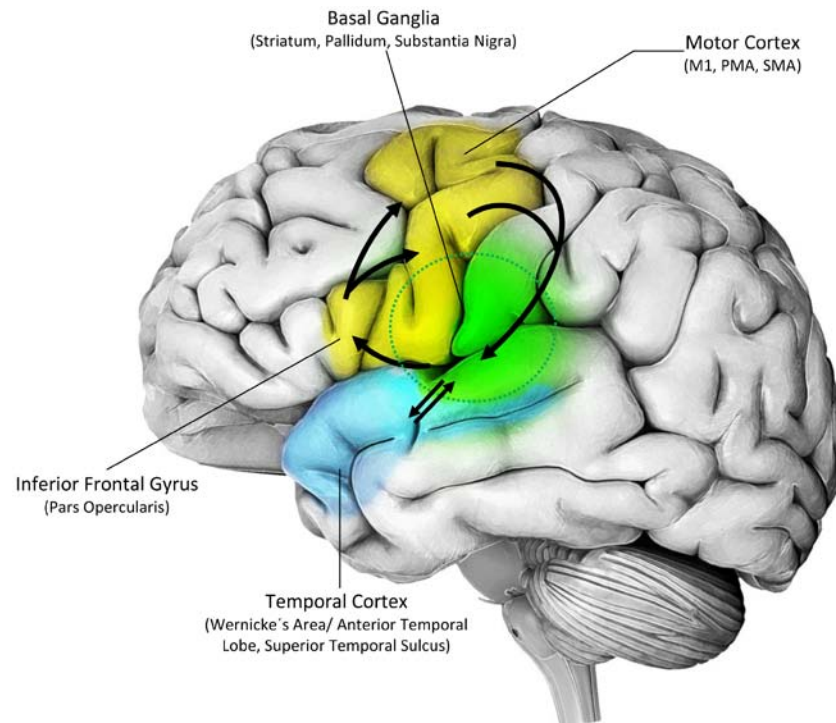


Figure 4. Neuroanatomical model of motor-language coupling. Coronal and lateral view of the left hemisphere showing the proposed frontotemporal basal ganglia-thalamocortical network (light yellow, blue, and green regions of interest, respectively). The arrows indicate the suggested principal flow of information involved in action-verb processing through two main overlap subcircuits. The frontal lobe, the basal ganglia, and the thalamus (frontal-basal ganglia-thalamocortical component) comprise loops which integrate motor simulation and action programming. These cortical regions play a complementary role in action-verb processing. The temporal lobe, the basal ganglia, and the thalamus (temporal-basal ganglia-thalamocortical component) comprise loops that would play a central role in the grounding of abstract conceptual knowledge involved in words referring to motor concepts. Modified with permission from [59].

of rehabilitation strategies and calls for further research.

Note that our proposal is rooted in the ACE task and the KDT, thus being limited to the domain of action and action-verb *comprehension*. Future studies should also explore whether PD can be detected at a prodromal stage through tasks tapping other language skills, such as action-verb identification (e.g., lexical decision), generation (e.g., picture naming), or reading (e.g., word naming). The ensuing findings could reveal whether selective verb affectation in early PD generalizes to all language functions (e.g., comprehension vs. production) and to all levels of action-language processing (e.g., semantics vs. phonology).

Clearly, detection of early PD through action-language performance, while possible, does not yet constitute a concrete tool for clinicians. A major difficulty is that PD diagnoses are

established upon observation of motor symptoms. The conundrum is, how to identify *candidates to develop the disease*. In this sense, the assessment of patients' relatives, with special emphasis on genetic factors, represents a promising avenue.

Conclusion

Deficits in action-verb processing and motor-language coupling have been empirically determined in PD research. Clinical, neuroimaging, and electrocorticography evidence indicates that these domains are supported by a cortico-subcortical network which would be partially damaged in PD prior to clinical manifestation or executive dysfunction. The assessment of the above domains may allow for early detection of the disease, paving the way for successful intervention strategies.

In summary, the interplay between basic and translational research on motor-language interactions can offer significant contributions to both embodied cognition models and PD rehabilitation programs.

Acknowledgments

This work was partially supported by grants from CONICET, CONICYT/FONDECYT Regular (1130920 and 1140114), COLCIENCIAS (1115-

545-31374, contract: 392), FONCyT-PICT 2012-0412, FONCyT-PICT 2012-1309, and the INECO Foundation.

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