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Can sex influence the neurocognition of language? Evidence from Parkinson's disease

Jana Reifegerste [a,b,c,*], Ivy V. Estabrooke [b,d], Lauren E. Russell [b], João Veríssimo [e], Karim Johari [f], Barbara Wilmarth [g,h], Fernando L. Pagan [g,h], Charbel Moussa [g], Michael T. Ullman [b,**]

[a] Department of Psychology, Westfälische Wilhelms-Universität Münster, Münster, Germany
[b] Brain and Language Laboratory, Department of Neuroscience, Georgetown University, Washington, DC, USA
[c] Potsdam Research Institute for Multilingualism, University of Potsdam, Potsdam, Germany
[d] Center for Science and Technology Policy, Salt Lake City, UT, USA
[e] Department of Linguistics, University of Potsdam, Potsdam, Germany
[f] Department of Psychology, University of South Carolina, Columbia, SC, USA
[g] Translational Neurotherapeutics Program, Laboratory for Dementia and Parkinsonism, Department of Neurology, Georgetown University Medical Center, Washington, DC, USA
[h] Movement Disorders Clinic, Department of Neurology, MedStar Georgetown University Hospital, Washington, DC, USA

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ABSTRACT

Parkinson's disease (PD), which involves basal ganglia degeneration, affects language as well as motor function. However, which aspects of language are impaired in PD and under what circumstances remains unclear. We examined whether lexical and grammatical aspects of language are differentially affected in PD, and whether this dissociation is moderated by sex as well as the degree of basal ganglia degeneration. Our predictions were based on the declarative/procedural model of language. The model posits that grammatical composition, including in regular inflection, depends importantly on left basal ganglia procedural memory circuits, whereas irregular and other lexicalized forms are memorized in declarative memory. Since females tend to show declarative memory advantages as compared to males, the model further posits that females should tend to rely on this system for regulars, which can be stored as lexicalized chunks. We tested non-demented male and female PD patients and healthy control participants on the intensively studied paradigm of English regular and irregular past-tense production. Mixed-effects regression revealed PD deficits only at regular inflection, only in male patients. The degree of left basal ganglia degeneration, as reflected by right-side hypokinesia, predicted only regular inflection, and only in male patients. Left-side hypokinesia did not show this pattern. Past-tense frequency effects suggested that the female patients retrieved regular as well as irregular past-tense forms from declarative memory, whereas the males retrieved only irregulars. Sensitivity analyses showed that the pattern of findings was robust. The results, which are consistent with the declarative/procedural model, suggest a grammatical deficit in PD due to left basal ganglia degeneration, with a relative sparing of lexical retrieval. Female patients appear to compensate for this deficit by relying on chunks stored in declarative memory. More generally, the study elucidates the neurocognition of inflectional morphology and provides evidence that sex can influence *how* language is computed in the mind and brain.

1. Introduction

The neurocognition of language can be elucidated by examining patterns of impaired and spared abilities in populations with neural disorders. One such disorder is sporadic Parkinson's disease (PD), a late-onset progressive disease involving the degeneration of dopaminergic neurons in the basal ganglia. Although PD has historically been associated mainly with motor deficits, research has increasingly revealed that

* Corresponding author. Potsdam Research Institute for Multilingualism, University of Potsdam, Potsdam, Germany.
** Corresponding author.
E-mail addresses: jana.reifegerste@gmail.com (J. Reifegerste), michael@georgetown.edu (M.T. Ullman).

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language and other aspects of cognition can also be impacted, including in the well-studied paradigm of regular/irregular inflectional morphology (Grossman et al., 1999; Johari et al., 2019b; P. Lieberman et al., 1992; Longworth et al., 2005; Macoir et al., 2013; Ullman et al., 1997).

However, the pattern of impairment of inflectional morphology in PD has varied across studies (see below). This has confused not only the status of this important aspect of language in PD, but also its neurocognition more generally. We argue that two important factors that might contribute to the observed variability of inflectional morphology in PD, and that could elucidate the neurocognition of inflectional morphology more generally, are the degree of (left) basal ganglia degeneration and sex—that is, whether the PD patients are male or female. In the remainder of the Introduction we first provide a theoretical background for this perspective, and then examine the existing literature on inflectional morphology in PD, before turning to an overview of the present study.

1.1. The declarative/procedural model: predictions for Parkinson's disease and sex differences

This paper focuses on the declarative/procedural (DP) model of language and its predictions regarding PD and sex differences, since this model is arguably the best developed neurocognitive theory of inflectional morphology, particularly regarding sex differences, and forms the basis of our predictions.

1.1.1. The DP model

According to the DP model, the learning, storage, and processing of language depend importantly on two general-purpose learning and memory systems in the brain, declarative and procedural memory (Ullman, 2004, 2016; Ullman et al., 2020). Declarative memory, which is conceptualized as the learning and memory that rely on the medial temporal lobe and associated circuits, underlies both explicit and implicit knowledge (Eichenbaum, 2012; Henke, 2010; Squire and Wixted, 2011; Ullman et al., 2020). It subserves knowledge of facts and events (semantic and episodic knowledge), and may be necessary for learning arbitrary bits of information and binding them together. Accordingly, the model predicts that (at least) idiosyncratic aspects of language, including simple words and the conceptual/semantic knowledge they refer to (e.g., *cat* and what it means), as well as representations of irregular morphological forms (e.g., *dug*), must rely at least in part on declarative memory. Procedural memory, which is conceptualized as the learning and memory that rely on the basal ganglia and associated circuitry, involves dopaminergic processes, and underlies the implicit learning, storage and processing of a wide range of motor and cognitive skills and habits, including those involving sequences, categories, and rules (Ashby and Crossley, 2012; Doyon et al., 2009; Eichenbaum, 2012; Squire and Wixted, 2011; Ullman et al., 2020). Rule-governed composition in grammar, including in syntax and morphology (e.g., for regularly inflected forms, such as *soar* + *-ed*), is posited to depend importantly on procedural memory.

The two memory systems interact (Packard, 2008; Poldrack and Packard, 2003; Ullman, 2004; Ullman et al., 2020). Most importantly for our purposes here, they can complement each other by learning analogous functions, such as knowledge of a given sequence or rule. That is, they play at least partly redundant roles, though they generally learn (and process) the knowledge in different ways (e.g., see just below for grammar). Additionally, functions learned in declarative memory can apparently inhibit (block) analogous functions learned in procedural memory, and vice versa, depending on which is predominant; the two systems can therefore also be thought of as being in competition. As a consequence of system redundancy, the DP model predicts that grammatical functions that tend to rely on procedural memory can also depend on declarative memory. For example, complex forms such as regularly inflected forms can be not only composed (e.g., *soar* + *-ed*) by rule-governed processes in procedural memory, but also stored as whole words, that is, as chunks, in declarative memory (e.g., *soared*). The extent to which grammar depends on procedural or declarative memory is predicted to be modulated by multiple item-, task-, input-, and participant-level factors (Ullman, 2016; Ullman et al., 2020). For example, the processing of higher frequency regular forms is more likely to rely on the retrieval of stored (lexicalized) chunks in declarative memory than on compositional processes in procedural memory, as compared to low frequency words, simply because the stored representations of higher frequency forms are stronger (Alegre and Gordon, 1999; Morgan-Short and Ullman, 2020; Prado and Ullman, 2009). Crucially for our purposes here, the relative dependence of grammar on the two systems should also be influenced by which system is more available for learning or use (Ullman, 2016; Ullman et al., 2020). For example, if the procedural system is impaired, declarative memory may take over in a compensatory role (Ullman and Pullman, 2015). Conversely, individuals or populations with better declarative memory abilities should rely more on this system for grammatical functions, for example, by storing complex forms as chunks (Ullman, 2016; Ullman and Pullman, 2015).

1.1.2. The DP model and Parkinson's disease

According to the DP model, the degeneration of dopaminergic neurons in the basal ganglia in Parkinson's disease should lead to impairments of rule-governed combinatorial aspects of grammar, including of composed regularly inflected forms (e.g., *soar* + *-ed*) (Ullman, 2004; Ullman et al., 1997). Left basal ganglia degeneration should be particularly likely to lead to grammatical impairments, given the left lateralization of grammar and its procedural memory underpinnings (Tyler et al., 2011; Ullman et al., 1997; Ullman and Pierpont, 2005; Wright et al., 2012). (Here we discuss only first/native language; for discussion of second language, including in PD, see Ullman, 2020).

However, not all PD patients are expected to show grammatical impairments. At early stages of the disease, when basal ganglia degeneration has not progressed much, any impairments should of course be milder, and may not be detectable. Moreover, the extent of the grammatical deficits in PD caused by basal ganglia dysfunction should depend at least in part on which portions of the basal ganglia are affected. Motor circuits, which mainly pass through the putamen, are primarily affected in PD, in particular at earlier stages of the disease (Cheng et al., 2010; Rodriguez-Oroz et al., 2009). However, increasing evidence suggests that grammar (as well as other language and cognitive functions) depends heavily on circuits that pass through the caudate nucleus (Moro et al., 2001; Rodriguez-Oroz et al., 2009; Ullman, 2016). Thus, earlier stages of PD may not be associated with observable grammatical deficits. Rather, such impairments should emerge as the disease progresses, in particular, to the point of also affecting the relevant circuits in the caudate nucleus.

Therefore, marked impairments of aspects of grammar that depend on procedural memory, including regular morphology, are expected particularly in PD patients at more advanced stages, especially those with greater degeneration of the left basal ganglia. Moreover, across patients, such grammatical impairments should correlate with left basal ganglia degeneration, for example, as reflected by the degree of right-side hypokinesia, which primarily reflects degeneration of the left basal ganglia (Berardelli et al., 2001; Mazzoni et al., 2012).

Crucially, since aspects of grammar can also be learned in declarative memory, this system could play an important compensatory role for grammar in PD (Ullman, 2016; Ullman and Pullman, 2015). Indeed, evidence suggests that PD patients compensate with declarative memory for procedural memory deficits in a variety of tasks, such as category and sequence learning (Beauchamp et al., 2008; Dagher et al., 2001; Moody et al., 2004; Shohamy et al., 2004; Ullman and Pullman, 2015). The degree of such compensation should depend on various factors, including declarative memory abilities. In particular, those individuals or populations with PD who have better declarative memory should

compensate more effectively, and so should show fewer grammatical deficits.

In contrast, the DP model predicts that lexical memory (unlike grammar), including irregular morphological forms, should remain relatively spared in PD. This should hold especially for individuals who are not demented, since declarative memory is particularly impaired in dementia in PD (Piatt et al., 1999). Note that irregulars may be somewhat impaired even in non-demented PD patients. First, declarative memory can also be affected in non-demented PD patients (Muslimovic et al., 2005). Moreover, since frontal/basal-ganglia circuits appear to underlie lexical recall (though probably somewhat different circuits than underlie grammar, in particular those that involve BA 45/47 rather than BA 44/6 in frontal cortex; Ullman, 2006), tasks involving the recall of lexical items may also show some impairments. Nevertheless, such impairments should be relatively mild in tasks with cues for recall, such as in the prompted production of irregular past-tense forms.

1.1.3. The DP model and sex differences

Evidence suggests that girls and women generally have better learning abilities in declarative memory than boys and men, in particular – but not only – for verbal material (Guillem and Mograss, 2005; Herlitz and Rehnman, 2008; Kaushanskaya et al., 2011; Maitland et al., 2004; McGivern et al., 1997; McGregor et al., 2020; Reifegerste et al., 2020; Ullman et al., 2008). This sex difference is found not just in traditional tasks of episodic memory such as remembering if one saw a known word a few minutes ago (which are thought to rely on episodic knowledge of personally-experienced time and place), but also in tasks involving learning new items or associations such as novel faces, patterns, or words (whose learning need not depend on such personally-experienced episodes). This female advantage appears to extend even into old age, though the size of the advantage in older adults has varied across studies (Bleecker et al., 1988; De Frias, Nilsson and Herlitz, 2006; Gale et al., 2007; Herlitz et al., 1997; Jack et al., 2015; Maitland et al., 2004; Pauls et al., 2013; Reifegerste et al., 2020; Rodríguez-Aranda and Martinussen, 2006).

Consequential to the female advantage at learning in declarative memory, the DP model predicts that females should on average be more successful than males at remembering grammatical knowledge in declarative memory, such as chunks (e.g., *soared*) (Ullman, 2004, 2016; Ullman et al., 2008). (Note that the DP model as it was originally proposed, in Ullman et al. (1997), did not address sex, though this factor has been discussed and examined in the years following this initial publication.) Therefore, females should rely more on declarative memory for aspects of grammar than males. This should hold even among older adults, not only because older females should on average still show more successful learning of chunks than males, but also because this advantage is decades old, and thus the cumulative memorization of chunks should be much greater for females than males. Additionally, these stronger female representations should tend to inhibit (block) the application of the regular rule by procedural memory, further strengthening the female dependence on declarative memory-based chunking.

Converging evidence increasingly supports the view that females rely more than males on declarative memory for grammar, in particular for regular inflection. That is, evidence from multiple approaches, including the examination of 'past-tense frequency effects' (see section 3.4), suggests that females (girls and women) rely more than males (boys and men) on regularly inflected forms stored as wholes (e.g., *soared*) in declarative memory, while males rely correspondingly more on rule-governed composition (e.g., *soar* + *-ed*) rooted in procedural memory (Babcock et al., 2012; Dye et al., 2013; Hartshorne and Ullman, 2006; Morgan-Short and Ullman, 2020; Prado and Ullman, 2009; Steinhauer and Ullman, 2002; Ullman et al., 2002, 2008). Thus, males and females appear to differ at least to some extent in *how* they process grammar in the mind and brain.

If regulars depend more on frontal/basal-ganglia-based composition in males, and more on declarative memory-based storage in females, then left basal ganglia degeneration in PD should affect regulars in males more than in females (Johari et al., 2019b; Ullman et al., 2008; Ullman and Pullman, 2015). This prediction holds whether the increased female dependence on declarative memory for regulars occurred before and/or after the onset of PD. That is, if females rely less than males on basal-ganglia-based composition prior to disease onset (as evidence suggests; see just above), then basal ganglia degeneration in PD should not affect regular inflection in females as much as in males. Alternatively, or in addition, basal ganglia degeneration in PD could lead to the subsequent (compensatory) memorization of regulars, which would be expected to take place to a greater extent in female than in male patients. Indeed, evidence suggests that the female advantage in declarative memory also holds in PD, at least in non-demented patients, and possibly in demented patients as well (Augustine et al., 2015; Fengler et al., 2016; Liu et al., 2015). Thus, the prediction that regulars should be less affected by basal ganglia degeneration in female than male PD patients could be due to greater female memorization of regulars both before onset (which may be termed 'pre-compensation') and/or after onset (compensation).

1.1.4. Predictions for regular and irregular inflectional morphology in PD

Thus, the DP model makes the following predictions regarding regular and irregular inflectional morphology in PD. First of all (as also laid out in Ullman et al., 1997), because impairments of combinatorial inflectional morphology are expected at higher levels of left basal ganglia degeneration, PD patients at higher levels of such degeneration should show particular impairments of regular versus irregular inflection, as compared to healthy controls. Moreover, since male PD patients should depend more than female PD patients on basal-ganglia-based composition, this relative impairment of regulars should be more pronounced in males. In contrast, at lower levels of left basal ganglia degeneration, these impairments of regulars might be weaker or perhaps not detectable at all. It is important to keep in mind that even at higher levels of basal ganglia degeneration in males, regular inflection may still show better or similar performance as compared to irregular inflection, simply because performance at irregulars is worse than at regulars in healthy individuals, including the elderly, and thus this pattern constitutes the baseline (Clahsen and Reifegerste, 2017; Prado and Ullman, 2009; Ullman, 2004; Ullman et al., 1997). Therefore, *reversing* this trend, with worse performance at regulars than irregulars, would require a substantial selective impairment of regular inflection. In sum, a *relative* impairment of regulars versus irregulars, as compared to controls, should be observed in PD, particularly at higher levels of left basal ganglia degeneration, especially in males.

It also follows that with increasing left (but not right) basal ganglia degeneration – for example as reflected in increasing right-side (but not left-side) hypokinesia across PD patients – an increasing deficit of composed regulars, but not or less of stored irregulars, should be observed. However, this association should only be found to the extent that regulars depend on frontal/basal-ganglia circuits. Thus, an association between right-side hypokinesia and regular inflection should be observed in male PD patients, while this association should not be found, or should be weaker, in female PD patients. In contrast, no association between right-side hypokinesia and irregulars is expected, in either sex. In sum, the DP model predicts a highly specific pattern, with right-side (not left-side) hypokinesia predicting worse performance at regulars (but not irregulars) in males (but not females).

1.2. Regular and irregular inflectional morphology in Parkinson's disease

Here we summarize the existing empirical literature on regular/irregular inflectional morphology in PD. We are aware of nine studies that have examined this topic in patients with Parkinson's disease and healthy controls. Three of these studies tested the regular/irregular distinction in English past-tense or plural inflection (Almor et al., 2002;

Longworth et al., 2005; Ullman et al., 1997) and two examined the distinction in Greek past-tense inflection (Stavrakaki et al., 2010; Terzi et al., 2005), while the others probed Dutch past-tense inflection (Colman et al., 2009), German past-participle and plural inflection (Penke and Wimmer, 2012), French future-tense inflection (Macoir et al., 2013), and Farsi past-tense inflection (Johari et al., 2019b).

1.2.1. The status of regular/irregular inflection in patients with PD for whom there is no evidence for high levels of left basal ganglia degeneration

Of the nine studies, seven examined regular and irregular morphology in PD patients for whom there was no evidence for high levels of left basal ganglia degeneration—that is, studies in which either a) behavioral measures did not suggest generally high levels of left basal ganglia degeneration, or b) there were no reported relevant measures reflecting such degeneration. Specifically, four of the seven studies (Colman et al., 2009; Longworth et al., 2005; Macoir et al., 2013; Penke and Wimmer, 2012) tested patients at mild to moderate stages of disease progression (Goetz et al., 2008; Hoehn and Yahr, 1967), while in the other three studies disease stage was not specified or was unclear (Almor et al., 2002; Stavrakaki et al., 2010; Terzi et al., 2005). Hypokinesia was reported across all patients for only one of these seven studies (Colman et al., 2009), in which the patients showed a wide range of both right-side and left-side hypokinesia rather than mainly high levels of hypokinesia.

None of these seven studies reported a clear PD deficit at regulars versus irregulars, as compared to controls. Not surprisingly, in several studies the PD patients showed better performance at regulars than irregulars, with a similar pattern in controls (Almor et al., 2002; Macoir et al., 2013; Penke and Wimmer, 2012), consistent with the more general pattern of worse performance at irregulars than regulars in the literature (see above). Crucially however, most of the seven studies did not directly compare regular and irregular inflection between patients and controls, for instance by examining a group-by-regularity interaction (Almor et al., 2002; Colman et al., 2009; Longworth et al., 2005; Penke and Wimmer, 2012; Stavrakaki et al., 2010; Terzi et al., 2005). Therefore, in these studies the exact pattern of PD performance at regular and irregular inflection, compared to controls, remains unclear. Additionally, several studies included a fair number of female patients (Colman et al., 2009; Macoir et al., 2013; Penke and Wimmer, 2012; Terzi et al., 2005), or did not report sex at all (Almor et al., 2002; Stavrakaki et al., 2010), leaving open the possibility that the (apparent) absence of a relative deficit at regulars might have been partly due to the inclusion of female patients.

1.2.2. The status of regular/irregular inflection in PD as a function of measures of left basal ganglia degeneration

Of the nine studies that examined regular/irregular inflection in PD, three tested whether higher levels of left basal ganglia degeneration in PD patients, as reflected by right-side hypokinesia, are associated with greater deficits at regular versus irregular inflection. Two of these studies examined this issue without taking into account the factor of sex (Longworth et al., 2005; Ullman et al., 1997), while one specifically contrasted male and female patients (Johari et al., 2019b). Note that although Colman et al. (2009) examined correlations between past-tense inflection and both right-side and left-side hypokinesia, this study did not examine regular and irregular inflection separately.

Ullman et al. (1997) examined English past-tense production in non-demented PD patients who showed a wide range of hypokinesia levels, as well as in healthy controls. Thus, this study did not examine only PD patients with high levels of hypokinesia. Right-side hypokinesia correlated with patients' production of regularly inflected forms, for both existing regulars (e.g., *soar-soared*) and novel regulars (novel verbs such as *plag-plagged*), but not with the production of irregularly inflected forms (e.g., *dig-dug*). This pattern held even when left-side hypokinesia was covaried out. In contrast, left-side hypokinesia did not correlate with past-tense production for either regularly or irregularly inflected forms, with or without right-side hypokinesia covaried out. Additionally, PD/control group comparisons were performed in a subset of patients with the highest levels of right-side hypokinesia. In this analysis significant interactions were found between PD/controls and regular/-irregular inflection; in follow-up analyses, the PD subset was marginally worse at regulars (and significantly worse at novel regulars) than irregulars. No PD/control regular/irregular analysis was reported for the full sample of participants. Overall, the study suggests that left (but not right) basal ganglia degeneration is associated with impairments of regular (but not irregular) inflection in PD. Given that the majority of both the full group (22 of 28) and the subset (4 of 5) of PD patients were male, the observed patterns may have been driven primarily by males, and thus females might show a different pattern. However, sex differences were not examined.

A weaker association between right-side hypokinesia and regular inflection was reported by Longworth et al. (2005), who also probed English past-tense production in non-demented PD patients. In addition to their analyses examining regular/irregular morphology in the full sample of PD patients (for which hypokinesia levels were not reported; see above), the study tested associations between right-side hypokinesia and inflection. They reported a marginally significant association between right-side hypokinesia and novel regulars, with no such association found for irregulars. Unlike Ullman et al. (1997), no association was found between right-side hypokinesia and the production of regular past-tense forms. The majority of patients were male, though sex was not examined as a factor (Longworth et al., 2005). Associations with left-side hypokinesia were not reported.

The one study examining regular versus irregular inflection separately in male and female PD patients tested Farsi past-tense production in non-demented patients with moderate-to-severe PD and relatively *high* levels of right-side hypokinesia (Johari et al., 2019b). As compared to healthy controls, the male PD patients showed past-tense production deficits at existing regular and novel regular verbs, relative to irregulars, whereas the females did not show this pattern. Indeed, the female patients' impairment was mildest at the production of existing regular past-tense forms, consistent with the storage of such forms by females in declarative memory. Additionally, across the PD patients, right-side hypokinesia correlated with the production of regularly inflected forms (for both existing and novel regulars) but not irregularly inflected forms, even with left-side hypokinesia covaried out. In contrast, left-side hypokinesia did not correlate reliably with any of the three verb types.

Thus, as expected by the DP model, higher levels of left basal ganglia degeneration in PD (as reflected by right-side hypokinesia) have shown associations with deficits at regular but not irregular inflection. In contrast, right basal ganglia degeneration (as reflected by left-side hypokinesia) does not appear to reliably affect either regular or irregular inflection. Importantly, sex may modulate the effect of left basal ganglia degeneration on regular inflection. In particular, some evidence suggests that higher levels of right-side hypokinesia are associated with impairments of regular inflection in males but not (or less so) in females, specifically in the production of existing regular inflected forms (Johari et al., 2019b). In contrast, no such sex difference seems to be found for irregular inflection, and left-side hypokinesia has no effect on either type of inflection in either sex.

However, the evidence regarding the relation between hypokinesia and regular/irregular inflection is variable and still sparse, in particular with respect to potential sex differences. Indeed, only one study has directly examined the effect of hypokinesia separately in males and females, in an inflectional system whose neurocognition has not been well-studied (i.e., in Farsi). Thus, the further investigation of the role of right-side (and left-side) hypokinesia on regular (and irregular) inflection in males and females seems warranted. The examination of such potential sex differences in English regular/irregular past-tense production in PD may be especially informative, since this inflectional system and task have been so well-studied. Such an approach has the potential not only to further clarify the neurocognition of regular and

irregular inflection across the sexes in PD, but also to elucidate the neurocognition of inflectional morphology more generally, including a potential role for sex.

1.3. The present study

The present study was designed to address the gaps and weaknesses of previous research on regular/irregular inflection in PD, in particular regarding the predicted modulatory roles of sex as well as left basal ganglia degeneration, as reflected by right-side hypokinesia. Our study tested English regular and irregular past-tense production in male and female non-demented PD patients with a wide range of right-side hypokinesia, from low to high levels, and age- and education-matched male and female healthy controls. Our predictions were based on the DP model, as laid out above. We performed two sets of analyses.

First, in a *group comparison* between the PD patients and controls, we tested for effects of group (PD/control), sex (male/female), verb type (regular/irregular), and their interactions. We expected some degree of PD impairment at the task as compared to controls, particularly for regulars, especially in males. However, given that the patients were not selected to have only high levels of right-side hypokinesia, we did not predict strong deficits. Moreover, we did not expect to find worse performance at regular than irregular verbs in the PD group, even in male patients, given the general pattern of worse performance at irregulars than regulars.

Second, *within the PD patients* we tested associations between right-side (and left-side) hypokinesia and regular (and irregular) inflection. We predicted that right-side (but not left-side) hypokinesia would be associated with the production of regular (but not irregular) past-tense forms in males, with no such (or much less of an) association in females. That is, right-side (but not left-side) hypokinesia should specifically affect regular inflection in males.

2. Methods

2.1. Participants

Forty-eight patients diagnosed with Parkinson's disease were recruited from Massachusetts General Hospital (MGH) or Georgetown University Medical Center (GUMC). Diagnosis of PD was performed at each site by neurologists specializing in movement disorders. We tested all patients who appeared to meet our criteria, on the basis of information in their most recent medical records. Testing subsequently revealed the presence of exclusionary criteria for some patients. First, four patients with scores greater than three on the Information, Memory and Concentration subtest of the Blessed Dementia Scale (Blessed et al., 1968) were excluded from all analyses, in order to minimize the influence of dementia (see Introduction). Second, two patients were excluded from analysis due to the presence of drug-induced dyskinesia (see Ullman et al., 1997). One additional patient was excluded from the main analyses because his performance on the past-tense production task was more than two standard deviations below the mean; sensitivity analyses with this participant included yielded the same pattern of results as the main analyses (see section 3.3).

Therefore, the main analyses were performed over 41 patients (21 men, 20 women). All were right-handed. Thirty-six patients were receiving levodopa (Sinemet, Sinemet-CR, Rytary, Inbrija) (18 males and 18 females), of whom 23 (9 females and 14 males) were also taking additional drugs for the treatment of Parkinson's disease, including Eldepryl, Deprenyl, Artane, Permax, Lodosyn, Parlodel, Azilect, Mirapex, Nuplazid, and/or Symmetrel. Three patients (1 male, 2 female) were taking only non-levodopa PD medications, including Eldepryl, Artane, Permax, and/or Symmetrel. There were no sex differences in the number of patients receiving any sort of PD medication (19 males, 20 females), or, more specifically, in the number of patients taking levodopa (18 males, 18 females).

Forty-one normal control (NC) participants (19 men, 22 women) were also recruited. None had any known neurological or neuropsychiatric disorders. All but four were right-handed; these four were ambidextrous (one male, three females). Sensitivity analyses (section 3.3) excluding the ambidextrous control participants yielded the same pattern of results as the main analyses.

All participants were native speakers of English. The NC participants and the PD group did not differ in age or years of education (age $t(80) = -0.04$, $p = .968$; education $t(80) = 1.45$, $p = .150$), and did not differ in their sex ratios ($\chi^2(1) = 0.0488$, $p = .825$). See Table 1.

The men and women did not differ significantly in age or education within either the PD group (age: $t(39) = 0.34$, $p = .733$; education: $t(37) = 1.44$, $p = .159$) or the NC group (age: $t(39) = 1.18$, $p = .245$; education: $t(39) = 0.23$, $p = .817$), or within the PD group on the Information, Memory and Concentration subtest of the Blessed Dementia Scale ($t(39) = 0.48$, $p = .634$), right-side hypokinesia ($t(39) = -0.01$, $p = .995$), or left-side hypokinesia ($t(39) = 0.27$, $p = .792$). Hypokinesia was measured with the four hand and foot movements tests (each given on both the left and right side) of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987). The right-side hypokinesia score for each patient was computed as the sum of their scores for the four right-side tests, and similarly for left-side hypokinesia (Ullman et al., 1997). Each test is scored as 0 (normal), 1 (slight), 2 (mild), 3 (moderate), or 4 (severe). Thus, the possible range of scores for both right-side and left-side hypokinesia was 0–16. Both the male and female PD patients showed a wide range of both right-side hypokinesia (male: 0.5–10; female: 0.5–13.5) and left-side hypokinesia (male: 0.7–11.5; female: 0–10); these ranged between normal and moderate-to-severe.

Data from a portion of the participants reported in Ullman et al. (1997) are included in our analyses here. Whereas that paper examined regular/irregular inflection in PD (and several other disorders), without examining sex differences, the present paper focuses on the effect of sex. Thus, none of the sex effects examined here have been previously published for any of the participants. The combined data from patients tested at GUMC and those tested at MGH (i.e., reported in Ullman et al., 1997) provided a relatively large sample of PD patients – larger than any other PD study of inflection described in section 1.2 –, decreasing the likelihood of false negative results. About half of the 41 PD patients were reported in Ullman et al. (1997) (n = 23, or 56% of the 41 patients), while about a third of the NC participants were included in that paper (n = 14, or 34% of the 41 controls). Note that the 23 PD patients included here from Ullman et al. (1997) is smaller than the number reported in that paper (n = 28) due to more stringent exclusionary criteria used here (Blessed Dementia Scale > 3 here vs. > 5 in the prior paper). Sensitivity analyses including testing site (MGH vs. GUMC) as a covariate did not change the pattern of results (section 3.3).

2.2. Past-tense production task

This task has been described elsewhere in detail (e.g., Ullman et al., 1997, 2005). In brief, participants were asked to read out loud a sentence containing a present-tense verb form, and a subsequent sentence requiring the past tense, which they were asked to also produce aloud (e.g., "Every day I *dig* a hole. Just like every day, yesterday I ___ a hole"). This constitutes a more naturalistic task than producing inflected forms from stems alone, and is easier for patients to perform. Following Ullman et al. (1997), each sentence pair was printed on one sheet of paper. Responses were audio recorded, and were transcribed by the experimenter during testing. The audio recording was then also transcribed by another trained researcher, and this was compared to the original transcription to resolve any discrepancies. An item was scored as correct if the correct response was given without any prompting from the experimenter. Accuracy (correct, incorrect) constituted the dependent variable for all analyses (see below). The nature of the task (i.e., in which participants read aloud both sentences) precluded collection of valid response times for the production of past-tense forms.

Table 1
Demographic and clinical data.

Group	Sex	N	Age (years)	Education (years)	Blessed Dementia Scale	Right-side hypokinesia	Left-side hypokinesia
PD	Men	21	68.2 (8.0)	16.6 (2.9)	0.9 (1.2)	3.82 (3.22)	4.33 (3.30)
	Women	20	67.2 (10.3)	15.3 (2.7)	0.8 (0.9)	3.83 (3.07)	4.08 (2.90)
NC	Men	19	69.2 (5.1)	15.2 (2.9)	–	–	–
	Women	22	66.6 (8.2)	15.0 (2.7)	–	–	–

Note. By-participant means and standard deviations (in parentheses) shown for each variable. Blessed Dementia Scale refers to the Information, Memory and Concentration subtest of this scale; see main text. Right- and left-side hypokinesia were based on the four hand and foot movements tests of the Unified Parkinson's Disease Rating Scale, with a minimum possible score of 0 and a maximum possible score of 16; see main text. PD: Parkinson's disease patients; NC: Normal control participants.

Stimuli comprised 20 irregular and 20 regular English verbs, as well as 80 filler verbs (Ullman et al., 1997, 2005). None of the 20 irregular verbs takes more than one past-tense form; that is, "doublets" such as *dive-dove/dived* were excluded. None of the 20 regular verbs were "rhyming regulars"; that is, none rhymed with a stem of an irregular verb (e.g., *swig-swigged*, cf. *dig-dug*). Rhyming regulars, like irregulars, show a strong tendency for storage (Ullman, 2001), and are thus not expected to show clear deficits in PD, including in males (indeed, all three studies finding associations between regular inflection and right-side hypokinesia examined non-rhyming regulars; Johari et al., 2019b; Longworth et al., 2005; Ullman et al., 1997). The filler items included doublet verbs, rhyming regulars, rhyming novel verbs (whose stems rhyme with the stems of irregulars), and non-rhyming novel verbs (whose stems do not rhyme with the stems of irregulars). These were not the focus of the present study, and are not discussed further.

Following Ullman et al. (1997, 2005), four irregular verbs were excluded from the main analyses: one because its past tense is also a distinct word (*grind-ground*) and three because their respective stem and past-tense forms are identical (*hit, slit, split*), so bare stems and past-tense responses cannot be distinguished. The 16 remaining irregulars had significantly higher past-tense frequencies ($M = 6.2084$; $SD = 2.6147$) than the 20 regulars ($M = 4.3376$; $SD = 2.0942$; $t(35) = -2.42$, $p = .021$). To reduce the problem of past-tense frequency differences between the regular and irregulars verbs (see Ullman et al., 1997), and to avoid regular verbs of particularly low frequency (which may be unlikely to be stored, even by females; Alegre and Gordon, 1999; Prado and Ullman, 2009), we excluded the regular verb with the lowest past-tense frequency (*scowl*) as well as the irregular verb with the highest past-tense frequency (*come*), producing a final set of 15 irregulars (*bend*, *bite*, *cling*, *dig*, *drive*, *feed*, *give*, *keep*, *make*, *send*, *stand*, *swim*, *swing*, *think*, *wring*) and 19 regulars (*chop*, *cook*, *cram*, *cross*, *drop*, *flap*, *flush*, *look*, *mar*, *rob*, *rush*, *scour*, *shrug*, *slam*, *soar*, *stalk*, *stir*, *tug*, *walk*) that did not differ significantly in past-tense frequency (irregulars, $M = 5.984$, $SD = 2.5426$; regulars, $M = 4.6152$, $SD = 2.0044$; $t(32) = -1.757$, $p = .088$). All main analyses, which are reported in sections 3.1 and 3.2, are performed on this set of 19 regulars and 15 irregulars. Sensitivity analyses on a smaller set of 16 regulars and 15 irregulars that was *better* matched on past-tense frequency showed the same pattern of results as the main analyses (section 3.3). Conversely, sensitivity analyses including *all* 20 regulars as well as *all* 20 irregulars again yielded the same pattern of results (section 3.3). Note that past-tense frequency as well as other variables (e.g., stem frequency, past-tense length, number of consonants in the coda of the past-tense form) were considered as covariates in all analyses, and included if warranted (see section 2.3 just below). All word frequencies are calculated from the sum of the counts from the Francis and Kucera corpus (Francis and Kucera, 1982) and the Associated Press corpus (Church, 1988; Ullman, 1999). This sum was then augmented by 1 (to avoid log of zero) and natural-log transformed (Ullman, 1999; Ullman et al., 1997, 2005).

2.3. Analysis

All analyses were performed using generalized linear mixed-effects logistic regression with crossed random effects for participants and items (Baayen et al., 2008), using the lme4 package (Bates et al., 2015). Following Barr et al. (2013), we started with a maximal random-effects structure and simplified the model in cases of convergence failure. In all cases models only converged without the inclusion of random slopes. The dependent variable in all analyses was the binary measure of past-tense production accuracy at the participant and item level (0 incorrect, 1 correct, for each item for each participant). Fixed factors, not all of which were included in all models (see below), were group (2 levels: PD, control), sex (2 levels: male, female), verb type (2 levels: regular, irregular), right-side hypokinesia (continuous), and left-side hypokinesia (continuous). Hypokinesia was natural log-transformed (after adding 1 to avoid log of zero) to avoid the excessive influence of high-hypokinesia outliers. Continuous predictors (right-side and left-side hypokinesia) were mean-centered; categorical predictors (group, sex, and verb type) were assigned sum-coded contrasts (e.g., −0.5 and 0.5) (Barr et al., 2013). All follow-ups to interactions with categorical predictors were performed by relevelling these predictors and refitting the model.

As described in section 1.3 (The present study), we performed two sets of analyses on regular/irregular past-tense production. For each of these, a different series of mixed-effects models were fit to the data. In each case, all main effects as well as interactions of the factors of interest (fixed predictors) were included in the model. The two sets of analyses were as follows. (1) Analyses comparing performance of the PD patients and control participants on regular/irregular past-tense production. These analyses contained the factors group, sex, and verb type. (2) Analyses examining the association between right-side (and/or left-side) hypokinesia and regular/irregular past-tense production accuracy in the PD patients. These analyses contained the factors right-side (and/or left-side) hypokinesia, sex, and verb type.

Ten covariates were considered for inclusion in all sets of models: three participant-level variables (chronological age in years, years of education, Blessed Dementia Scale score); one trial-level variable (trial number); and six item-level variables (past-tense frequency, stem frequency, past-tense form length as number of phonemes, the number of consonants in the onset of the past-tense form, the number of consonants in the coda of the past-tense form, and the voicing consistency of the rhyme of the past-tense form). Note that even when variables do not show significant group (or item) differences, including them as covariates can reduce the error term, and thus lead to more accurate results. A bottom-up process was employed to select the covariates for the analyses. See Supplementary Material section 1 (Covariates) for more details. Covariate effects included in the final models are presented in all results tables; in the interest of conciseness, we do not discuss these effects in the text.

Table 2
Mean accuracy on the past-tense production task, by group, sex, and verb type.

Verb Type	PD patients		NC participants	
	Males	Females	Males	Females
Regular	94.5% (11.6%)	98.7% (2.9%)	99.7% (1.2%)	99.5% (1.5%)
Irregular	91.2% (10.8%)	92.0% (7.7%)	87.4% (8.0%)	92.4% (5.9%)
All Verbs	92.8% (11.2%)	95.3% (6.7%)	93.5% (8.4%)	96.0% (5.6%)

Note. Means and standard deviations (shown in parentheses) computed over participants. PD: Parkinson's disease; NC: normal control.

3. Results

3.1. Group comparison

In this set of analyses, we compared the PD and control groups in order to examine effects of group (PD vs. control), sex (male vs. female), verb type (regular vs. irregular), and all of their interactions. See Table 2 for the raw (untransformed) past-tense production accuracy rates for male and female PD and control participants. See Table S1 in Supplementary Material for (untransformed) error rates.

The highest-level model (Fig. 1; Table 3) yielded a significant main effect of group (due to worse performance by the PD patients than the control participants across both sexes and both verb types) and a significant main effect of verb type (due to worse performance at irregulars than regulars across both groups and both sexes). However, a significant interaction between group and verb type indicated that even though both groups were significantly less accurate at irregulars than regulars, this effect was greater for the control participants than for the PD patients. Lastly, we found a marginally significant interaction between group, sex, and verb type.

Follow-up analyses on these interactions (through relevelling; see Methods) revealed different patterns in the two groups; see Table 4. The PD patients showed a significant main effect of verb type, as a result of worse performance at irregular than regular verbs (across males and females), as well as a marginally significant effect of sex, due to better performance by female than male patients (across regulars and irregulars). However, these effects were qualified by a significant interaction between sex and verb type. The interaction was due to the finding that whereas female PD patients showed worse performance at irregular than regular verbs ($b = -1.6757$, $SE = 0.5811$, $z = -2.88$, $p = .004$), male PD patients showed no such difference ($b = -0.3428$, $SE = 0.4204$, $z = -0.82$, $p = .415$).

The group of control participants, on the other hand, showed only a main effect of verb type, again due to worse performance at irregular than regular verbs; Table 4. Unlike the PD patients, there was no interaction between sex and verb type, consistent with females and males showing a similar degree of better performance at regulars than irregulars (females: $b = -2.6150$, $SE = 0.7870$, $z = -3.32$, $p = .001$; males: $b = -3.8558$, $SE = 1.0612$, $z = -3.63$, $p < .001$). There were no other significant main effects or interactions for either group.

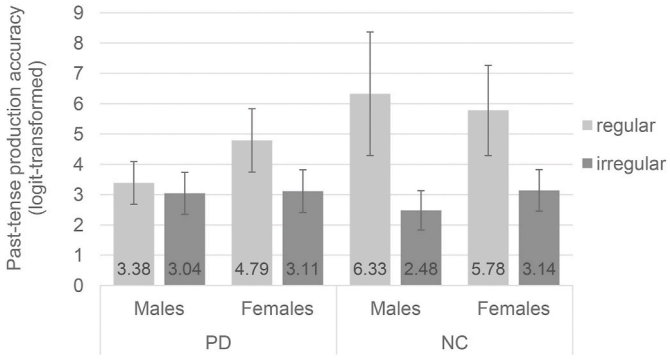

Fig. 1. Logit-transformed adjusted means and standard errors from the logistic regression performed for the group comparison. The means can be back-transformed into probabilities of correct responses with the equation $y = 1/(1+e^{-x})$, where x is the logit-transformed adjusted mean; standard errors cannot be back-transformed. PD: Parkinson's disease; NC: normal control.

Table 3
Results from the mixed-effects regression model on past-tense production accuracy across both groups and sexes.

Random effects:		Variance		*SD*	
Participant	Intercept	0.4940		0.7029	
Stimulus	Intercept	0.5547		0.7448	
Fixed effects:		*b*	*SE*	*z*	*p*
Intercept		4.0067	0.2565	15.62	<.001
Group		0.8490	0.3870	2.19	.028
Sex		−0.3976	0.3865	−1.03	.304
Verb type		−2.1274	0.4477	−4.75	<.001
Group x Sex		0.6844	0.7730	0.89	.376
Group x Verb type		−2.2361	0.6994	−3.20	.001
Sex x Verb type		0.0612	0.6996	0.09	.930
Group x Sex x Verb Type		−2.5426	1.3990	−1.82	.069
Covariate effects:					
Trial number		0.0154	0.0042	3.63	<.001

Note. Formula in R: DV ~ 1 + group*sex*verb type + trial number + (1 | participant) + (1 | stimulus). Group is coded as −0.5 for Parkinson's disease patients and 0.5 for normal control participants. Sex is coded as −0.5 for females and 0.5 for males. Verb type is coded as −0.5 for regulars and 0.5 for irregulars.

We also found different patterns for males and females when following up on the interactions by sex rather than by group; see Table 5. The males showed a significant main effect of group, due to worse performance by the PD than NC groups (across both sexes and verb types) as well as a main effect of verb type, as a result of worse performance on irregulars than regulars (across both groups and sexes). However, both of these effects were qualified by a significant group by verb type interaction. This was due to worse performance by the male PD patients than the male controls on regulars ($b = 2.9453$, $SE = 1.0579$, $z = 2.78$, $p = .005$) but not on irregulars ($b = -0.5623$, $SE = 0.3714$, $z = -1.51$, $p = .130$).

The females, by contrast, showed only a main effect of verb type, again as a result of worse performance at irregular than regular verbs (across both groups and sexes); Table 5. Unlike the males, the females showed no group by verb type interaction, consistent with the absence of a PD/NC group difference for either verb type in females (regulars: $b = 0.9902$, $SE = 0.8765$, $z = 1.13$, $p = .259$; irregulars: $b = 0.0186$, $SE = 0.3886$, $z = 0.05$, $p = .962$).

3.2. The relation between hypokinesia and regular/irregular morphology in PD

The second set of analyses examined associations between hypokinesia and regular/irregular inflection in male/female PD patients. The highest-level model (see Table 6), with sex, verb type, right-side hypokinesia and their interactions as fixed predictors (see below for left-side hypokinesia), yielded a significant main effect of verb type, a marginally significant effect of right-side hypokinesia, and significant interactions between sex and right-side hypokinesia and between verb type and right-side hypokinesia. However, all of these effects were qualified by a significant three-way interaction among sex, verb type, and right-side hypokinesia.

Follow-up analyses on the three-way interaction (through relevelling) revealed different patterns for males and females; see Table 7 and Fig. 2. For males, the analysis yielded significant main effects of verb type (worse performance at irregulars than regulars across right-side hypokinesia levels) and of right-side hypokinesia (worse performance at higher levels of right-side hypokinesia across both verb types). However, both of these effects were qualified by an interaction between

Table 4
Results from the mixed-effects regression model on past-tense production accuracy, relevelled for the PD and NC groups, respectively.

		PD patients				NC participants			
Random effects:		Variance		*SD*		Variance		*SD*	
Participant	Intercept	0.4938		0.7027		0.4940		0.7029	
Stimulus	Intercept	0.5551		0.7451		0.5547		0.7448	
Fixed effects:		*b*	*SE*	*z*	*P*	*b*	*SE*	*z*	*p*
Intercept		3.5821	0.2569	13.94	<.001	4.4349	0.3766	11.78	<.001
Sex		−0.7405	0.3809	−1.94	.052	−0.0300	0.6765	−0.04	.965
Verb type		−1.0107	0.4092	−2.47	.014	−3.2533	0.6954	−4.68	<.001
Sex x Verb type		1.3331	0.5996	2.22	.026	−1.2495	1.2724	−0.98	.326
Covariate effects:									
Trial number		0.0154	0.0042	3.63	<.001	0.0154	0.0042	3.63	<.001

Note. Sex is coded as −0.5 for females and 0.5 for males. Verb type is coded as −0.5 for regulars and 0.5 for irregulars. PD: Parkinson's disease; NC: normal control.

Table 5
Results from the mixed-effects regression model on past-tense production accuracy, relevelled for male and females, respectively.

		Males				Females			
Random effects:		Variance		*SD*		Variance		*SD*	
Participant	Intercept	0.4942		0.7030		0.4940		0.7029	
Stimulus	Intercept	0.5544		0.7446		0.5547		0.7448	
Fixed effects:		*b*	*SE*	*z*	*p*	*b*	*SE*	*z*	*p*
Intercept		3.8220	0.3420	11.18	<.001	4.2045	0.3049	13.79	<.001
Group		1.2176	0.5978	2.04	.042	0.5057	0.5054	1.00	.317
Verb type		−2.1309	0.6148	−3.47	.001	−2.1557	0.5312	−4.06	<.001
Group x Verb type		−3.5622	1.0977	−3.25	.001	−0.9619	0.8998	−1.07	.285
Covariate effects:									
Trial number		0.0154	0.0042	3.63	<.001	0.0154	0.0042	3.63	<.001

Note. Group is coded as −0.5 for Parkinson's disease patients and 0.5 for normal control participants. Verb type is coded as −0.5 for regulars and 0.5 for irregulars.

Table 6
Results from the mixed-effects regression model testing associations between right-side hypokinesia and past-tense production accuracy in the PD group.

Random effects:		Variance		*SD*	
Participant	Intercept	0.6732		0.8205	
Stimulus	Intercept	0.3109		0.5576	
Fixed effects:		*b*	*SE*	*z*	*p*
Intercept		4.0943	0.3288	12.45	<.001
Sex		−0.5802	0.4818	−1.20	.228
Verb type		−2.4747	0.5238	−4.72	<.001
Right-side hypokinesia		−0.5395	0.3243	−1.66	.096
Sex x Verb type		0.8718	0.7920	1.10	.271
Sex x Right-side hypokinesia		−2.3849	0.6587	−3.62	<.001
Verb type x Right-side hypokinesia		1.2774	0.5083	2.51	.012
Sex x Verb type x Right-side hypokinesia		2.6552	1.0258	2.59	.010
Covariate effects:					
Age		0.0535	0.0287	1.87	.062
Stem frequency		0.3261	0.0924	3.53	<.001
Trial number		0.0152	0.0053	2.88	.004
Age x Verb type		−0.1260	0.0465	−2.71	.007

Notes. Formula in R for the model across sex: DV ~ 1 + sex*verb type*right-side hypokinesia + verb type*age + stem frequency + (1 | participant) + (1 | stimulus). Sex is coded as −0.5 for females and 0.5 for males. Verb type is coded as −0.5 for regulars and 0.5 for irregulars.

Table 7
Results from the mixed-effects regression model testing associations between right-side hypokinesia and past-tense production accuracy, relevelled for male and female PD patients, respectively.

		Males				Females			
Random effects:		Variance		*SD*		Variance		*SD*	
Participant	Intercept	0.6731		0.8204		0.6733		0.8206	
Stimulus	Intercept	0.3109		0.5575		0.3114		0.5580	
Fixed effects:		*b*	*SE*	*z*	*p*	*b*	*SE*	*z*	*p*
Intercept		3.8042	0.3840	9.91	<.001	4.3856	0.4302	10.19	<.001
Verb type		−2.0391	0.6055	−3.37	.001	−2.9133	0.7047	−4.13	<.001
Right-side hypokinesia		−1.7320	0.4672	−3.71	<.001	0.6564	0.4574	1.44	.151
Verb type x Right-side hypokinesia		2.6053	0.7443	3.50	<.001	−0.0639	0.6990	−0.09	.927
Covariate effects:									
Age		0.0534	0.0287	1.86	.062	0.0534	0.0287	1.86	.062
Stem Frequency		0.3261	0.0924	3.53	<.001	0.3262	0.0925	3.53	<.001
Trial number		0.0152	0.0053	2.88	.004	0.0152	0.0053	2.88	.004
Age x Verb type		−0.1259	0.0465	−2.71	.007	−0.1259	0.0465	−2.71	.007

Notes. Verb type is coded as −0.5 for regulars and 0.5 for irregulars.

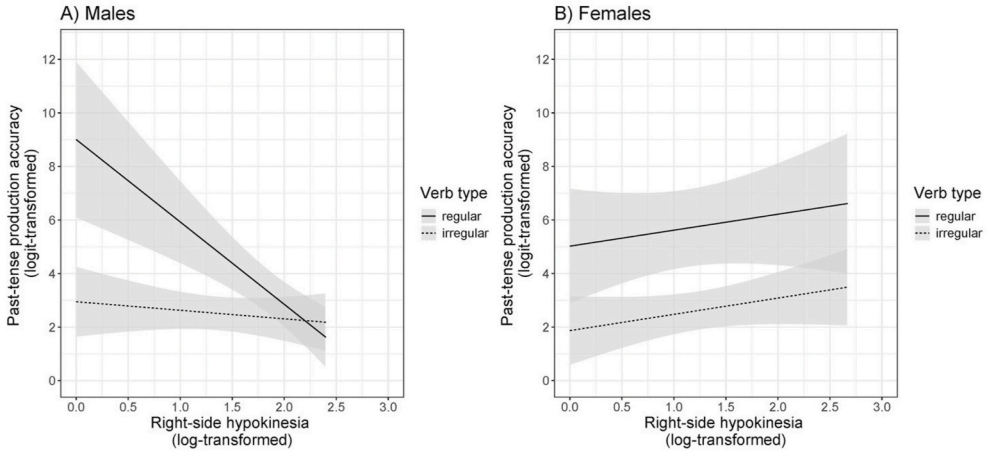

Fig. 2. Logit-transformed adjusted accuracy at the production of regular (solid lines) and irregular (dashed lines) past-tense forms, as a function of log-transformed right-side hypokinesia, separately for males (A) and females (B). Regression lines are shown for the range of right-side hypokinesia in each sex. Shaded bands represent standard errors (95% confidence intervals are approximately twice the width of standard error bands). See Figure S1 in Supplementary Material for scatterplots showing the untransformed by-subject data.

verb type and right-side hypokinesia. Follow-up analyses on this interaction showed that while there was a significant effect of right-side hypokinesia on regulars, such that more severe right-side hypokinesia was associated with worse performance at the production of regular past-tense forms ($b = -3.0342$, $SE = 0.7382$, $z = -4.11$, $p < .001$), this was not the case for irregulars ($b = -0.4293$, $SE = 0.4103$, $z = -1.05$, $p = .295$).

Females showed a different pattern. Although they showed a significant main effect of verb type (again, worse performance at irregulars than regulars), there was no main effect of right-side hypokinesia. There also was no verb type by right-side hypokinesia interaction. Rather, right-side hypokinesia was not significantly associated with accuracy for either regulars ($b = 0.6832$, $SE = 0.6630$, $z = 1.03$, $p = .303$) or irregulars ($b = 0.6258$, $SE = 0.4719$, $z = 1.33$, $p = .185$).

Finally, the same pattern of significance ($ps < .05$) was obtained in the right-side hypokinesia analyses for all effects of interest (sex, verb type, right-side hypokinesia, and their interactions) when left-side hypokinesia was covaried out. On the other hand, in the equivalent analysis focusing on left-side hypokinesia (i.e., with left-side hypokinesia rather than-right side hypokinesia as the predictor of interest, and right-side hypokinesia covaried out), the critical three-way interaction among sex, verb type, and left-side hypokinesia in the highest-level analysis was not significant ($p = .110$). This also held when right-side hypokinesia was not covaried out ($p = .109$).

3.3. Sensitivity analyses

The results above were robust, in that the same pattern of findings was obtained for all effects of interest (group, sex, verb type, right-side hypokinesia, and their interactions) across both the group and hypokinesia analyses in a range of sensitivity (i.e., alternate) analyses.[1] Each

[1] The same pattern of significance ($ps < .050$) was obtained in all sensitivity analyses as in the main analyses for all effects of interest (group, sex, verb type, hypokinesia, and their interactions) across both the group and hypokinesia analyses in the highest-level models. All follow-up analyses for the hypokinesia analyses also showed the same pattern of significance in the sensitivity and main analyses. For the group analyses, three of the effects shown in Tables 4 and 5 for the follow-up analyses changed between marginal significance and significance or vice versa, for the main analyses as compared to the sensitivity analyses (otherwise, these effects again show the same pattern of significance in the sensitivity and main analysis). First, in the sensitivity analysis in which the PD patient whose performance on the past-tense production task was an outlier was in fact included in analyses, the follow-up analysis for the PD patients yielded a marginal sex by verb type interaction ($p = .088$) rather than a significant interaction ($p = .026$; see Table 4). Second, in the sensitivity analysis on the 15 irregulars and 16 regulars that were even better matched on past-tense frequency than in the main analyses, the follow-up analysis for the PD patients yielded a significant effect of sex ($p = .038$) rather than a marginal effect ($p = .052$; see Table 4). Finally, in the sensitivity analysis on all 20 irregulars and all 20 regulars, the follow-up analysis for the males yielded a marginally significant group effect ($p = .056$) rather than a significant effect ($p = .042$; see Table 5).

sensitivity analysis involved one type of change to the main analyses presented above (e.g., the addition of a covariate, the inclusion of an outlier, or a more stringently-matched set of regular and irregular verbs).

We performed three sensitivity analyses with participant-level changes from the main analyses. First, the inclusion of participant testing site (MGH, GUMC) as a covariate yielded the same pattern of significance as the main analyses, with testing site also having a significant effect ($b = 0.6728$, $SE = 0.3120$, $z = 2.16$, $p = .031$). Second, the same pattern of significance was also obtained when excluding the four ambidextrous control participants, so that all participants were right-handed. Third, as stated in section 2.1, one PD patient whose performance on the past-tense production task was an outlier was excluded from the main analyses. A sensitivity analysis including this patient again showed the same pattern of results as the main analyses.

We also performed two item-level sensitivity analyses. First, it might be argued that the past-tense frequency-matching of the 15 irregulars and 19 regulars included in the main analyses was not stringent enough. In response to a reviewer comment, we therefore excluded the three regulars with the lowest past-tense frequencies (*flush, cram, tug*), yielding a set of 15 irregulars and 16 regulars (regular past-tense frequency, $M = 5.1077$, $SD = 1.7844$; irregular vs. regular past-tense frequency, $t(29) = -1.1187$, $p = .272$). This set of stimuli yielded the same pattern of results as the main analyses. Conversely, it might be suggested that frequency-matching was not necessary at all, since past-tense frequency was included in our bottom-up covariate selection process (section 2.3), even though this process did not result in the inclusion of this variable in any analysis. On this view, the most frequent irregular and least frequent regular verb need not have been excluded in the main analyses. We therefore performed a sensitivity analysis without excluding *any* verbs, that is, including all 20 irregulars and 20 regulars presented to the participants. This thoroughly tests for the robustness of the effects reported above both by minimizing past-tense frequency matching (irregulars, $M = 5.9359$, $SD = 2.5818$; regulars, $M = 4.4652$, $SD = 2.0636$; $t(38) = -1.99$, $p = .054$) and by including potentially problematic irregular items (*grind, hit, split, slit*). The sensitivity analysis on these verbs again yielded the same pattern of results as the main analyses.

3.4. Exploratory analyses

Here we report additional analyses that were not initially planned. These analyses are therefore exploratory; we suggest that further evaluation of these findings may be carried out in carefully designed replication efforts. To directly test the possibility that female PD patients retrieve chunked regular past-tense forms as well as irregular past-tense forms, while male patients retrieve only irregular forms (see Introduction), in each sex we examined past-tense form frequency effects, which indicate the retrieval of stored past-tense forms (Alegre and Gordon, 1999; Prado and Ullman, 2009), likely from declarative memory (Fell et al., 2006; Fernández et al., 2002; M. D. Lieberman, Chang, Chiao, Bookheimer and Knowlton, 2004; Morgan-Short and Ullman, 2020). For these analyses we performed linear mixed-effects regressions, with verb type, past-tense form frequency, and their interaction as fixed effects, as well as trial number as a covariate, and crossed random effects for participants and items. To maximize the frequency ranges for both verb types (in order to minimize false negative outcomes), we performed the analyses on the full set of 20 regulars and 20 irregulars.

For female patients, the analysis yielded a main effect of past-tense frequency (across regulars and irregulars; $b = -3.2449$, $SE = 1.1732$, $z = -2.77$, $p = .006$), but no interaction between verb type and frequency ($b = -0.3675$, $SE = 0.4306$, $z = -0.85$, $p = .393$). In contrast, for male patients the equivalent analysis yielded no main effect of frequency ($b = -0.1063$, $SE = 0.1597$, $z = -0.67$, $p = .505$), but a marginally significant interaction between frequency and verb type ($b = 0.2884$, $SE = 0.1665$, $z = 1.73$, $p = .083$). We followed up on this marginal interaction to test the hypothesis that males retrieve irregulars but not regulars from memory. Indeed, the interaction was due to a significant frequency effect for irregulars ($b = 0.3130$, $SE = 0.0946$, $z = 3.31$, $p = .001$) but not regulars ($b = 0.0228$, $SE = 0.1374$, $z = 0.17$, $p = .868$). Perhaps surprisingly, despite the smaller frequency range, the same pattern of significance ($ps < .05$) was obtained in analogous analyses performed on the main stimulus set of 19 regulars and 15 irregulars. Overall, the results are consistent with the retrieval from declarative memory of only irregular past-tense forms by males, but of regular and irregular past-tense forms by females.

4. Discussion

This study examined inflectional morphology in Parkinson's disease (PD), and tested whether impairments at regular versus irregular inflection are modulated by sex differences as well as by right-side hypokinesia, a measure that reflects left basal ganglia degeneration. Non-demented male and female PD patients with a wide range of (right-side and left-side) hypokinesia, as well as age- and education-matched normal control participants, were asked to produce the past-tense forms of English regular and irregular verbs. Analyses were performed with linear mixed-effects regression, with accuracy as the dependent measure. We considered, and included where warranted, a number of participant-level (age, education, Blessed Dementia Scale score), trial-level (trial number), and item-level covariates (past-tense form frequency, stem frequency, past-tense form phonological length, number of consonants in the onset and in the coda of the past-tense form, and voicing consistency of the rhyme of the past-tense form). Additionally, the male and female PD patients did not differ in right-side or left-side hypokinesia or in the number of patients taking PD medications. Thus, the observed patterns were unlikely to be explained by these various factors. Finally, a range of participant- and item-level sensitivity analyses yielded the same pattern of results as the main analyses, demonstrating that the findings were robust.

4.1. Interpretation of results

In the first set of analyses we compared the PD and control groups in order to examine effects of group, sex, verb type, and their interactions. The analyses revealed that both the male and female controls as well as the female PD patients were worse at producing past-tense forms of irregular than regular verbs, whereas the male PD patients showed no difference between the verb types. Moreover, the only PD impairment that was observed (i.e., worse performance by PD patients than controls) was on regulars in male PD patients; no PD impairments were found for either sex on irregulars, or for females on regulars. Overall, the pattern indicates that only regulars were impaired, and only in males. Note that regular inflection never actually showed worse performance than irregular inflection, even in male PD patients; this was not unexpected, given the baseline advantage of regular over irregular inflection.

The observed regular deficit in male patients, as compared to controls, was in fact somewhat surprising, given that the patients showed a wide range of hypokinesia levels, rather than only high levels. The present study may have been able to detect the regular impairment for several reasons, including the inclusion of a fair number of patients with higher levels of hypokinesia, a relatively large sample size, the use of sensitive analytical methods, and the examination of sex differences.

In the second set of analyses we examined the relation between right-side/left-side hypokinesia and regular/irregular inflection in male/female PD patients. The analyses revealed that right-side hypokinesia predicted only regular inflection, only in males. Left-side hypokinesia did not show this pattern. Interestingly, as can be seen in Fig. 2 (panel A), the males still showed better performance at regulars than irregulars at lower and even medium levels of right-side hypokinesia, with regular performance converging with and perhaps crossing irregular performance only at the highest levels of hypokinesia.

The pattern of findings has a number of implications for inflectional morphology in PD. Perhaps most importantly, the results suggest that PD is indeed associated with particular impairments of regular inflection, but indicate that these are modulated both by the degree of left (but not right) basal ganglia degeneration and by sex. Specifically, regulars appear to be reliably impaired only at higher levels of left basal ganglia degeneration in males. Note however that high levels of right-side hypokinesia may not be *sufficient* to obtain impairments of regular inflection in PD, even in males. For example, rhyming regulars should be minimally affected by hypokinesia in both male and female PD patients, since these forms seem to rely heavily on lexicalization in declarative memory (Ullman, 2001). To put it differently, though females are more likely than males to memorize regular inflected forms (and thus hypokinesia is less likely to modulate regulars in female than male PD patients), males can also memorize regulars. Thus, even male PD patients may not show clear deficits for all regulars.

In contrast to regular inflection, the study suggests that irregular inflection remains relatively spared in PD, across both sexes, and does not appear to be reliably modulated by left basal ganglia degeneration. We are *not* suggesting that irregular inflection or even lexical abilities more generally are completely spared in PD. As discussed in the Introduction, these may be affected by dementia in the disorder, and even basal ganglia degeneration is likely to impact aspects of lexical processing, such as uncued recall (section 1.1.2) or the representations of lexical items that involve motor-related knowledge (Johari et al., 2019). Additionally, in some circumstances irregulars may be affected by the same types of grammatical deficits that lead to problems with regulars, since irregular forms in some languages are affixed (Macoir et al., 2013; Penke and Wimmer, 2012; Stavrakaki et al., 2010; Terzi et al., 2005). If these affixed irregulars are composed by frontal/basal ganglia circuits (though whether such forms are composed or stored remains unclear; see Bowden et al., 2010; Clahsen, 1999), their processing should also be modulated by measures of left basal ganglia degeneration. Thus, it appears that multiple interacting factors affect the performance of regular (and irregular) morphology in PD.

Though the findings implicate left basal ganglia circuits in regular inflection, the mechanisms underlying the observed deficits cannot be fully elucidated in the present study. For example, it is possible that basal ganglia degeneration does not *directly* cause the regular impairments, but rather leads to the inhibition of frontal circuitry that underlies grammatical processing (a type of diaschisis). Indeed, this would be consistent with evidence that at least portions of the basal ganglia (anterior portions of the caudate nucleus and putamen) are primarily involved in learning new procedures, which seem to rely more on frontal regions after they have been automatized (Ashby et al., 2010; Doyon et al., 2009; Ullman et al., 2020). It might also be argued that functions other than procedural memory that are affected in PD and rely on the basal ganglia and/or frontal regions, such as executive functions (Draganski et al., 2008; Johari et al., 2019), could explain the observed pattern—for example, if regulars are indeed composed particularly by males, and this composition depends particularly on such functions. On this view, the findings obtained here would still indicate that regular composition is impaired in male PD patients, while female patients compensate with lexical/declarative memory (as suggested by the frequency effects), but the cause of this impairment would be an executive function deficit rather than or in addition to a procedural memory deficit. Although in principle such an account seems plausible, we are not aware of any evidence for a greater dependence of regulars than irregulars on executive functions. In fact, the past-tense production of irregulars might depend more than that of regulars on inhibitory aspects of executive function, given evidence suggesting that lexical competitors are inhibited during lexical retrieval (Grainger, O'Regan, Jacobs and Segui, 1989; Robert and Mathey, 2007). Nevertheless, such accounts may warrant further investigation.

Although the absence of an association between right-side hypokinesia and regular inflection in the female patients suggests that they did not rely strongly on left basal ganglia circuits for producing regulars, it does not provide evidence that they retrieve chunked regulars from declarative memory. The exploratory analyses (section 3.4) tested this more directly. The results of these frequency effect analyses suggest that the female patients indeed retrieved stored regular and irregular forms, likely from declarative memory, whereas the male patients retrieved only irregulars. The same pattern of frequency effects was found for regular Farsi past-tense forms in male and female Farsi-speaking PD patients (Johari et al., 2019b), strengthening the validity of the finding.

Overall, the results thus suggest that even higher levels of left basal ganglia degeneration in female PD patients may not yield impairments of regular past-tense inflection because these patients are relying on chunks stored in declarative memory. However, the findings do not reveal *when* these chunks were memorized. As discussed in the Introduction, the female PD patients may have stored regular past-tense forms either prior to onset of the disease ('pre-compensation') and/or afterwards (compensation). Given that independent evidence (including from frequency effect analyses) suggests that even healthy girls and women, but not boys or men, tend to store non-rhyming regular English past-tense forms (Dye et al., 2013; Prado and Ullman, 2009), pre-compensation seems extremely likely. Nevertheless, given that the female advantage at declarative memory is found in PD patients as well as in healthy adults (see Introduction), compensation post-onset also seems quite plausible. Indeed, evidence from other domains suggests such declarative memory compensation in PD (independent of sex) for tasks and functions that rely on procedural memory in healthy controls (e.g., category and sequence learning; see Introduction), underscoring the likelihood of post-onset declarative memory compensation in PD for language as well. Thus, both pre-compensatory and compensatory storage of regularly inflected forms in declarative memory seem likely. Interestingly, the finding that regulars in females constituted the least impaired condition among the patients (i.e., across both sexes and verb types) suggests that the compensatory memorization of regulars was quite successful, whether it involved pre-compensation and/or post-onset compensation. Johari et al. (2019b) also found the least impairment among female regulars, underscoring the robustness of this pattern.

One difference between the present study and the findings obtained by Johari et al. (2019b) is that in the latter study the PD patients over-regularized (e.g., *digged*, though of course in Farsi) more than the controls, with the female PD patients demonstrating a particularly high rate of over-regularization, as evidenced by a group by sex interaction. Moreover, phonological neighborhood analyses indicated that this pattern could be at least partly explained by female patients showing a particularly high rate of storage of similar sounding regular past-tense forms as chunks (e.g., *rigged, pigged*), which were likely over-generalized in associative memory to over-regularizations of irregulars with similar-sounding stems (e.g., *dig-digged*). In contrast, in the present study both male and female patients showed low rates of over-regularization, as did controls, with no group or sex differences (Table S1). The reasons for the different patterns in the two studies is unclear. However, one possibility is that such memory-based associative generalization of regular forms increases with greater (right-side) basal ganglia degeneration, due to a general increased reliance on underlying regular chunks as a result of compensation. In other words, as basal ganglia degeneration increases, compensatory reliance on stored regular forms should correspondingly increase, resulting in more such associative generalization to over-regular forms. Indeed, (right-side) hypokinesia levels were much higher in Johari et al., 2019b than in the present study: the mean levels were more than twice as high in both the male and female PD patients in Johari et al. (2019b; see Table 1) than in the present study (Table 1). Note that this view suggests a somewhat rosy outcome to language impairments in PD. That is, it suggests that increasing basal ganglia degeneration leads not only to greater difficulties composing regulars in procedural memory but also to increasing compensation with declarative memory—with the success of such

compensation also crucially depending on the capacity of this system to learn new information, consistent with the greater success of female than male compensation observed here. These issues may warrant further examination.

Finally, how should we think about sex? Although sex was a critical factor in the present study, it may not be the most explanatory variable regarding the observed effects. We focused on sex because it is both a general factor of interest, and a convenient variable that allows us to test whether two populations with broadly different declarative memory abilities both post- *and* pre-onset are associated with different patterns of regular inflection. More generally however, any populations or individuals with better declarative memory may tend to pattern with females regarding the effects observed here. For example, genotypes associated with better/worse declarative memory abilities, such as polymorphisms of *BDNF* (Pezawas et al., 2004), may yield dissociations in PD that are similar to those observed here for male and female patients (also see Ullman and Pullman, 2015).

4.2. Limitations, broader implications, and future directions

The study has limitations and suggests paths for further research. First, the research presented here relied in part on patients reported in a previous study (Ullman et al., 1997). Even though that study did not examine sex differences, which were the focus here, we emphasize the importance of a full replication study (ideally preregistered), with a new set of participants as well as a larger set of items. Examining response times in addition to accuracy could be informative (using a paradigm that allows for the collection of meaningful response times; see section 2.2). Crucially, future studies should address the various factors that appear to influence regular (and irregular) inflection in PD, both at the level of participants (e.g., regarding dementia, hypokinesia, and sex) and items (e.g., regarding frequency ranges and non-rhyming vs. rhyming regulars). Studies probing the predicted sex differences in grammatical constructions other than regular inflection would further elucidate the nature of the phenomenon. Additionally, future studies should include independent tasks probing learning (and retention) in declarative and procedural memory, which could further clarify the relation between language and the memory systems in PD.

The study has implications beyond inflectional morphology in PD. Theoretically, the results support a number of key claims of the DP model. Specifically, they provide further support for the hypothesis that regular but not irregular inflection, and perhaps grammatical combination more generally, relies importantly on left frontal/basal ganglia circuits. The findings also strengthen the DP model's hypothesis that regular inflected forms can also be stored as chunks in declarative memory alongside irregulars and other lexicalized forms, and that such grammatical chunking is found particularly in women, who show a declarative memory sex advantage.

To our knowledge, no other (neuro)cognitive theory of inflectional morphology makes the same predictions for regular/irregular forms in males and females, including regarding a reliance on the left (but not right) basal ganglia for regulars, especially in males (Bird et al., 2003; Clahsen, 1999; Joanisse and Seidenberg, 1999; McClelland and Patterson, 2002) – though this does not preclude the possibility that such theories might be able to explain the pattern, particularly with modifications. Note that it may be suggested that the findings reported here might be expected if regulars were more difficult to process than irregulars, and females showed language advantages as compared to males. On this view, any deficit in PD that affects language (including from non-linguistic functions such as executive function) might lead to a particular impairment in male regulars, as was observed. It has in fact been suggested that females show broad advantages at verbal abilities (Kimura, 1999; though this advantage may be specific to lexical/declarative memory; Ullman et al., 2008). However, regulars generally show better rather than worse performance at irregulars (Clahsen and Reifegerste, 2017; Prado and Ullman, 2009; Ullman, 2004; see Introduction). Indeed, among the healthy controls the males' regulars showed the best performance across both verb types and both sexes (Table 2, Fig. 1). Thus, this perspective does not appear to account for the findings.

More generally, beyond particular neurocognitive models, the results underscore the view that rule-governed aspects of grammar can be supported by distinct neurocognitive systems that play at least partially redundant roles, and that the relative dependence of grammar on the different systems is a function of multiple item-, task-, input-, and subject-related factors (Ullman, 2004, 2016, 2020). As we have seen in this study as well as in previous research (see Introduction), sex appears to be one such factor. In particular, whereas males appear to rely heavily on rule-governed combination (e.g., *soar* + *-ed*) in the frontal/basal ganglia procedural system for regular inflection, females show a greater reliance on the retrieval of lexicalized whole forms from declarative memory (e.g., *soared*). Consistent with the general principle of redundancy, this can crucially provide protection against the dysfunction of either system – in PD, the frontal/basal-ganglia-based procedural system.

Flipping the issue around to look at it from the perspective of sex differences, it appears that a sex difference exists in *how* language and other functions are computed in the mind and brain. Whereas the vast majority of work on sex differences tests male/female differences in performance or in measures of a particular neural substrate (e.g., hippocampal volumes) (Kimura, 1999; Ullman et al., 2008), this study and related research reveals sex differences in *how* language is computed in the mind and brain. Indeed, evidence suggests that females can rely on declarative memory for grammatical functions not only by chunking complex forms, but also (as we have seen above) in other ways, such as associative generalization. Such sex differences in the underlying neurocognitive mechanisms need not even lead to performance differences (Prado and Ullman, 2009; Ullman et al., 2008). Thus, an absence of differences in performance between males and females (or analogously between other groups) does not preclude the possibility that these groups differ in their underlying neurocognitive mechanisms. We believe this is an important point to keep in mind when examining individual or group differences in cognitive (neuro)science.

The study also has translation implications. The sex difference findings underscore the hypothesis that the higher prevalence of PD in males than females (Elbaz et al., 2002; Gillies et al., 2014; Miller and Cronin-Golomb, 2010) may be at least *partly* due to better compensation by females in declarative memory: thanks to their declarative memory advantages, females may be more likely to compensate their way out of diagnosis (the 'compensation underdiagnosis hypothesis'; Ullman and Pullman, 2015). Relevant to this point, evidence suggests that declarative memory can indeed underlie some aspects of motor function (Keisler and Shadmehr, 2010; Song, 2009; Song and Cohen, 2014) and may compensate for motor-related tasks in PD (Carbon et al., 2010; Gobel et al., 2013; Ullman and Pullman, 2015) as well as in other motor disorders (Zwicker et al., 2010). This in turn may have further diagnostic implications, since it suggests that diagnosis could be improved by focusing on symptoms that can be less easily compensated for by declarative memory (Ullman and Pullman, 2015). The fact that even aspects of motor function may be compensated for by declarative memory underscores the potential importance of this view (Ullman and Pullman, 2015; Zwicker et al., 2010).

5. Conclusion

In sum, the present study suggests that regular inflection is indeed impaired in patients with Parkinson's disease (PD), but not under all circumstances. Regular but not irregular inflection seems to be impacted by left (but not right) basal ganglia degeneration, in particular in male patients. The findings, which are consistent with the predictions of the declarative/procedural model, elucidate the nature of inflectional morphology in PD, as well as the neurocognition of language more

generally, and have both basic research and translational implications.

Credit author statement

Jana Reifegerste: Formal analysis; Investigation; Data curation; Writing - original draft; Writing - review & editing; Visualization; Supervision; Project administration; Funding acquisition. Ivy V. Estabrooke: Formal analysis; Data curation; Writing - original draft. Lauren E. Russell: Investigation. João Veríssimo: Formal analysis; Visualization; Writing - review & editing. Karim Johari: Writing - review & editing. Barbara Wilmarth: Resources. Fernando L. Pagan: Resources. Charbel Moussa: Resources; Writing - review & editing. Michael T. Ullman: Conceptualization; Methodology; Investigation; Resources; Data curation; Writing - original draft; Writing - review & editing; Supervision; Project administration; Funding acquisition.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2020.107633.

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