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Sex, Dopamine, and Hypokinesia: A Study of Inflectional Morphology in Parkinson's Disease

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Objective: Parkinson's disease (PD), which involves the degeneration of dopaminergic basal ganglia neurons, appears to affect language. We investigated which aspects of language are impaired in PD and what moderates these impairments. Our predictions were based on the declarative/procedural model of language, which links grammar, including in regular inflection, to procedural memory and left-lateralized basal ganglia dopaminergic circuits but links lexical memory, including irregulars, to declarative memory. Because females tend to show declarative memory advantages as compared to males, the model predicts that females rely more on this system for regulars, which can be stored as chunks. ***Method:*** We probed regular/irregular Farsi past-tense production in 40 Farsi-speaking patients with moderate-to-severe nondemented PD (half female) and 40 normal controls (half female). ***Results:*** Consistent with our predictions, we found that male, but not female, PD patients showed greater deficits at regular than irregular past-tense production. The females' impairment was mildest for regulars, likely from compensatory storage, as revealed by regular past-tense frequency effects only in females. Right-side hypokinesia (linked to left basal ganglia degeneration) correlated negatively with accuracy of regulars but not irregulars. Similarly, the levodopa equivalent dose of patients' last medication correlated only with regulars. ***Conclusions:*** The results suggest that language is impaired in PD, but the impairments are moderated by multiple factors, including the type of linguistic knowledge, the degree of left basal ganglia degeneration, dopamine, and sex. The findings underscore the impact of sex on the neurocognition of language and the roles of left basal ganglia dopaminergic circuits in aspects of rule-governed grammar.

General Scientific Summary
The study advances our understanding of language impairments in Parkinson's disease. It suggests that certain grammatical abilities are more impaired in male than female patients, who rely on compensatory mechanisms. Additionally, left basal ganglia degeneration and dopaminergic medication appear to moderate the impairments. The findings elucidate the nature of language deficits in Parkinson's disease and have therapeutic implications.

Keywords: Parkinson's disease, inflectional morphology, sex differences, hypokinesia, dopamine

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Although Parkinson's disease (PD), a progressive disease involving the degeneration of dopaminergic neurons in the basal ganglia, has traditionally been associated with motor deficits, research has increasingly revealed that language can also be affected (Bocanegra et al., 2015; Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Johari et al., 2013; Lieberman et al., 1992). Deficits have been found in various aspects of language, including in the well-studied paradigm of regular/irregular inflectional morphology (Grossman, 1999; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Macoir et al., 2013; Ullman, 2004; Ullman et al., 1997).

However, findings have been mixed across studies, and a clear picture of regular/irregular morphology in PD has yet to emerge (Colman et al., 2009; Longworth et al., 2005; Macoir et al., 2013; Terzi, Papapetropoulos, & Kouvelas, 2005; Ullman et al., 1997). (In this article, we focus on native language, and thus do not discuss studies of second language in PD.) This has confused not only the status of this critical aspect of language in PD but also its neurocognition more generally. Given that the regular/irregular distinction is often taken as a model organism for the more fundamental distinction between grammar and lexicon, elucidating the status of regular/irregular inflection in PD seems warranted.

We hypothesized that several potentially interacting factors contribute to the observed variability of inflectional morphology in PD: (a) sex, that is, whether the PD patients are male or female; (b) the extent of basal ganglia degeneration; and (c) dopaminergic processes. In the remainder of the introduction, we first provide theoretical background for this perspective, and then briefly discuss the existing literature on inflectional morphology in PD, before turning to an overview of the present study. Whereas almost all PD language studies have probed English, with only a few testing other (European) languages (Bocanegra et al., 2015; Colman et al., 2009; Macoir et al., 2013; Penke & Wimmer, 2012; Prieto, Radanovic, Schmitt, Barbosa, & Mansur, 2007; Terzi et al., 2005), we investigated Farsi, the primary language of Iran.

The Declarative/Procedural Model and Its Predictions for Parkinson's Disease

This article focuses on the declarative/procedural (DP) model of language and its predictions regarding PD, as this model is arguably the best developed neurocognitive theory of inflectional morphology, particularly regarding sex differences and the role of the basal ganglia and dopaminergic processes, and it forms the basis of our predictions.

The DP Model

The DP model posits that the learning, storage, and processing of language depends on two evolutionarily ancient learning and memory systems in the brain: declarative and procedural memory (Hamrick, Lum, & Ullman, 2018; Ullman, 2001, 2004, 2016; Ullman et al., 1997). According to the model, idiosyncratic aspects of language, including simple words and their meanings (e.g., *sushi* and what it means), as well as representations of irregular morphological forms (e.g., *sang*), rely critically on declarative memory. This learning and memory system, which underlies both explicit and implicit knowledge, is rooted in the hippocampus and other medial temporal lobe structures (Eichenbaum, 2011; Squire & Wixted, 2011). 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—hence its posited role in idiosyncratic aspects of language, including irregularly inflected forms. In contrast, rule-governed combination in grammar, including in syntax and morphology (e.g., for regularly inflected forms, such as *walk* + *-ed*), is posited to depend importantly on procedural memory. This implicit memory system, which is rooted in frontal/basal ganglia circuits and involves dopaminergic processes, underlies the learning, storage and processing of a wide range of motor and cognitive skills and habits, include those involving sequences and rules (Ashby, Turner, & Horvitz, 2010; Eichenbaum, 2011; Squire & Wixted, 2011).

However, according to the DP model, grammatical functions that tend to rely on procedural memory can also be subserved by declarative memory. For example, complex forms such as regularly inflected forms can be not only composed (e.g., *walk* + *-ed*) by procedural memory but also stored as whole words, that is, as chunks, in declarative memory (e.g., *walked*). The extent to which grammar depends on procedural or declarative memory is predicted to be moderated by multiple item, task, input, and subject-level factors (Ullman, 2004, 2016). For example, higher frequency regular past-tense forms should be more likely to be lexicalized and stored in declarative memory than lower frequency forms (Alegre & Gordon, 1999; Prado & Ullman, 2009).

Crucially for our purposes here, the relative dependence of grammar on the two memory systems should depend on which system is more available for learning or use (Ullman, 2004, 2016). In particular, individuals or populations with better declarative memory abilities should rely more on this system for grammatical functions, for example, by storing and retrieving complex forms as chunks (Ullman, 2004, 2016; Ullman & Pullman, 2015). Given evidence that girls and women generally have better declarative memory than boys and men, in particular—but not only—for verbal material (Herlitz & Rehnman, 2008; Maitland, Herlitz, Nyberg, Bäckman, & Nilsson, 2004; Reifegerste, Veríssimo, et al., 2018; Ullman, Miranda, & Travers, 2008), the DP model predicts that females should, on average, rely more on declarative memory for aspects of grammar than males (Ullman, 2004, 2016; Ullman et al., 2008). Indeed, converging evidence increasingly supports this view, in particular, for regular inflection. That is, converging evidence suggests that females (girls and women) rely more than males (boys and men) on regularly inflected forms stored as wholes (e.g., *walked*) in declarative memory, whereas males rely correspondingly more on rule-governed composition (e.g., *walk* + *-ed*) rooted in procedural memory (Babcock, Stowe, Maloof, Brovetto, & Ullman, 2012; Dye, Walenski, Prado, Mostofsky, & Ullman, 2013; Hartshorne & Ullman, 2006; Prado & Ullman, 2009; Ullman, 2004, 2016; Ullman et al., 2002, 2008; Walenski, Prado, Steinhauer, & Ullman, 2018).

Finally, if the procedural system is impaired, declarative memory is posited to be able to compensate for resulting grammatical problems, for example, leading to an increased reliance on the chunking of regular forms (Ullman, 2004, 2016; Ullman & Pierpont, 2005; Ullman & Pullman, 2015). This has direct implications for the model's predictions for PD, including sex differences in inflection in the disorder.

Predictions for Parkinson's Disease

The DP model predicts that the degeneration of dopaminergic neurons in the basal ganglia in PD should lead to impairments of rule-governed combinatorial aspects of grammar, including of composed regularly inflected forms (e.g., *walk* + *-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 & Pierpont, 2005; Wright, Stamatakis, & Tyler, 2012).

However, not all PD patients are expected to show equivalent grammatical impairments. The degree 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 passing through the posterior putamen are primarily affected in PD, in particular, at earlier stages of the disease (Cheng, Ulane, & Burke, 2010; Rodriguez-Oroz et al., 2009). However, increasing evidence suggests that grammar (as well as procedural memory) depends heavily on circuits that pass through the caudate nucleus, especially anterior portions, as well as the anterior putamen (Janacsek et al., 2018; Moro et al., 2001; Rodriguez-Oroz et al., 2009; Tagarelli, Shattuck, Turkeltaub, & Ullman, 2018; Ullman, 2016). Thus, earlier stages of PD may not be associated with substantial grammatical deficits. Rather, such impairments should emerge only as the disease progresses, in particular, to the point of also affecting the relevant circuits in the caudate and putamen.

Therefore, only PD patients at more advanced stages, in particular, with greater degeneration of the left basal ganglia, should be expected to show marked impairments of aspects of grammar that depend on procedural memory, including regular morphology. 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, Rothwell, Thompson, & Hallett, 2001; Mazzoni, Shabbott, & Cortés, 2012). Additionally, given the posited dependence of grammar on dopaminergic circuits in the basal ganglia, dopamine levels in patients with PD may moderate grammatical impairments in the disorder, including impairments of regular inflection (Ullman, 2016).

Additionally, because aspects of grammar can also be learned in declarative memory, this system could play an important compensatory role for grammar in PD (Ullman, 2004, 2016; Ullman & Pullman, 2015). Indeed, evidence suggests that PD patients compensate with declarative memory for procedural memory deficits in a variety of tasks, such as probabilistic classification and sequence learning (Beauchamp, Dagher, Panisset, & Doyon, 2008; Dagher, Owen, Boecker, & Brooks, 2001; Moody, Bookheimer, Vanek, & Knowlton, 2004; Shohamy et al., 2004; Ullman & Pullman, 2015). The degree of such compensation should depend on various factors, including declarative memory abilities. In particular, those individuals or populations with PD that have better declarative memory should compensate more effectively, and so should show fewer grammatical deficits.

Importantly, the female advantage at declarative memory discussed above appears to extend even into old age, though the size of the advantage in older adults has varied across studies (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; de Frias, Nilsson, & Herlitz, 2006; Gale, Baxter, Connor, Herring, & Comer, 2007; Herlitz, Nilsson, & Bäckman, 1997; Jack et al., 2015; Maitland et al., 2004; Pauls, Petermann, & Lepach, 2013; Reifegerste, Veríssimo, et al., 2018; Rodríguez-Aranda & Martinussen, 2006). Therefore, female PD patients should compensate more effectively with declarative memory than male PD patients, including for regular inflection (see Discussion). Thus, male PD patients should tend to have greater impairments at regular inflection than female PD patients (Reifegerste, Estabrooke, Maloof, Johari, & Ullman, 2018; Ullman et al., 2008; Ullman & Pullman, 2015). In particular, this sex difference should be found for (reasonably common) existing regularly inflected forms (e.g., walked), because they are likely to have been previously encountered, and therefore could have been memorized as chunks, but not for regularly inflected forms of novel verbs (e.g., *plag-plagged*), because these could not have been previously memorized.

Finally, the DP model predicts that lexical memory (unlike grammar), including irregular morphological forms, should remain relatively spared in PD, as lexical memory is not expected to depend heavily on the basal ganglia. This should hold especially for individuals who are not demented, because declarative memory is generally impaired mainly with dementia in PD (Piatt, Fields, Paolo, Koller, & Tröster, 1999). Thus, unlike regulars, performance on irregulars in (nondemented) PD patients should not correlate with measures of basal ganglia degeneration such as hypokinesia, nor with dopamine levels.

In summary, the DP model makes the following predictions for inflectional morphology in PD. In particular, at high levels of disease progression (especially at higher levels of left basal ganglia degeneration, e.g., as measured by right-side hypokinesia), impairments are expected for regular inflection but not, or less so, for irregular inflection. However, this pattern should be moderated by three factors. First, it should be affected by sex. Males should show greater impairments than females at existing regularly inflected forms, though the two sexes should be similarly impaired at novel regulars. Second, measures of left (but not right) basal ganglia degeneration, as reflected for example in right-side (but not left-side) hypokinesia, should correlate with deficits of existing regulars and novel regulars but not irregulars. Third, measures of dopamine, such as the levodopa equivalent dose (LED) of the last anti-PD medication taken (Tomlinson et al., 2010) and the time from when this medication was taken to testing (because dopamine levels diminish over time; Nutt & Holford, 1996; Zappia et al., 1999), should also correlate with deficits of regulars and novels but not irregulars. Finally, these factors may interact. For example, the correlations between existing regulars and both right-side hypokinesia and dopaminergic measures may be expected to interact with sex, such that the correlations hold more reliably for males than females.

Previous Research on Regular/Irregular Morphology in PD

We are aware of nine studies that have examined regular/irregular inflectional morphology in PD patients and healthy controls. Four of these tested the distinction in English (Almor et al., 2002; Longworth et al., 2005; Reifegerste, Estabrooke, et al., 2018; Ullman et al., 1997), whereas the others probed Dutch (Colman et al., 2009), German (Penke & Wimmer, 2012), French

(Macoir et al., 2013), and Greek (Stavrakaki, Katsarou, Bostantzopoulou, & Clahsen, 2010; Terzi et al., 2005). Note that a 10th study (Phillips et al., 2012) investigated the effects of deep brain stimulation on regular/irregular English past-tense production, but did not directly compare regulars and irregulars either within PD patients or between patients and controls. The study by Cameli, Phillips, Kousaie, and Panisset (2005), which examined regular/irregular English and French inflectional morphology in bilingual PD patients, is also not directly relevant, because analyses were not performed separately either on the two languages or in first and second language.

The first study to examine the regular/irregular distinction in PD, Ullman et al. (1997), tested 28 nondemented PD patients (22 male, six female) and 11 healthy controls (two male, nine female) on the elicited production of English past-tense regulars (e.g., *walked*), novel regulars (e.g., *plagged*), and irregulars (e.g., *sang*). Here, we describe this study in some detail, because the design and predictions of the present study are partly motivated by it. In the Discussion, we summarize the subsequent eight studies and discuss them in relation to the findings of Ullman et al. as well as those of the present study.

In Ullman et al. (1997), correlations were found within the PD patients between right-side hypokinesia (reflecting left basal ganglia degeneration) and both regular and novel regular (but not irregular) past-tense production, even when a measure of dementia and left-side hypokinesia were partialed out. In contrast, left-side hypokinesia did not correlate with the past-tense production of any of the three verb types, including when both dementia and right-side hypokinesia were partialed out. Additionally, the PD and control groups were compared in their performance at producing past-tense forms; however, because many of the PD patients had not reached an advanced disease stage, as measured by hypokinesia, the comparison was carried out on a subset of the patients with the highest levels of right-side hypokinesia (four male, one female). In these analyses, significant interactions were found between PD patients and controls and both regular/irregular and novel regular/irregular verb types: The PD patients showed worse performance at the production of both regulars and novel regulars than irregulars as compared to controls. Together, the results suggest greater impairments of regular and novel regular than irregular past-tense production in PD, particularly in nondemented patients at more advanced stages (with higher levels of right-side hypokinesia), as well as a dependence of regulars and novel regulars, but not irregulars, on the basal ganglia, in particular, on the left side. The study did not examine either effects of sex or dopaminergic processes on inflectional morphology, though the preponderance of males in the sample suggests that the observed effects could be driven by male PD patients.

The eight subsequent studies of regular/irregular inflection in PD yielded a mixed pattern, though we suggest that, overall, the findings from the combination of the nine studies are not inconsistent with the predictions of the DP model (see Discussion). In brief, the data thus far suggest the following, though with clear gaps and weaknesses. Only at more advanced stages of PD disease progression do deficits of regular inflection seem to be reliable (Almor et al., 2002; Colman et al., 2009; Longworth et al., 2005; Macoir et al., 2013; Penke & Wimmer, 2012; Reifegerste, Estabrooke, et al., 2018; Stavrakaki et al., 2010; Terzi et al., 2005; Ullman et al., 1997). Limited evidence suggests that sex may also moderate the regular deficit, with particular impairments in males at more advanced stages (Reifegerste, Estabrooke, et al., 2018; Ullman et al., 1997). The data also appear to be consistent with the prediction that left basal ganglia degeneration, as reflected in right-side hypokinesia, moderates regular but not irregular inflection (Longworth et al., 2005; Reifegerste, Estabrooke, et al., 2018; Ullman et al., 1997). We are not aware of any research investigating the relation between regular/irregular inflection and dopaminergic processes. Moreover, most work has focused on the inflection of existing regular and irregular forms, even though the DP model makes different predictions for existing and novel regular inflection, in particular, regarding the role of sex. Previous research has also focused on English and other European languages, leaving open the possibility that the predicted outcomes might not hold for other languages.

The Present Study

The present study was designed to address these gaps and weaknesses, in particular, regarding the predicted roles of sex, hypokinesia, and dopaminergic processes on inflectional morphology in PD. The study examined the processing of Farsi inflectional morphology in native Farsi-speaking patients with nondemented moderate to severe PD and matched normal control (NC) participants, with half males and half females in each group. All participants were tested on the elicited production of regular, irregular, and novel regular past-tense forms. We examined potential effects of (a) sex, (b) both right-side and left-side hypokinesia, (c) the LED (Tomlinson et al., 2010) of patients' last anti-PD medication, and (d) the time since this medication.

Our predictions were generated by the DP model. We predicted that (a) impairments of regular inflection should be more severe for males than females, whereas this sex difference should not be found for novel regulars or irregulars; (b) right-side but not left-side hypokinesia should modulate regular but not irregular morphology; and (c) dopaminergic measures should moderate regular but not irregular morphology. Interactions were also examined.

Method

Participants

We tested 40 PD patients and 40 NC participants. All participants were right-handed (Edinburgh Inventory Total Score >33; Edinburgh Handedness Inventory; Oldfield, 1971) monolingual native Farsi speakers. None were demented (Farsi Mini-Mental State Examination [MMSE] ≥ 25; Ansari, Naghdi, Hasson, Valizadeh, & Jalaie, 2010) or had any known neurological or psychiatric disorder (other than Parkinson's disease for the PD patients), and none had any known brain injury or surgery. All female participants had completed menopause. All patients were diagnosed with idiopathic PD and were at Stage 3 (moderate stage; bilateral disease) or Stage 4 (advanced stage; severely disabling disease) on the Hoehn and Yahr scale (Hoehn & Yahr, 1967). None had secondary Parkinsonism. Patients were taking levodopa and other anti-PD medication, with different individually tailored dosages, to maximally reduce motor symptoms. The LED (Tomlinson et al., 2010) of the last anti-PD medication taken by each patient prior to testing was computed from this information.

Both participant groups (PD and control) were composed of 20 males and 20 females. The four subgroups (PD and control, males and females) were matched (see Table 1) on age, years of education, handedness (Oldfield, 1971), and MMSE scores, that is, on global cognitive functioning (Ansari et al., 2010). Additionally, the male and female PD patients were matched (see Table 1) on disease stage (Hoehn & Yahr, 1967) and on both right and left upper-limb hypokinesia (Goetz et al., 2008; Johari et al., 2013; Ullman et al., 1997), as well as the LED of their last medication and the time from this medication to language testing. All study procedures, including recruitment, testing, and informed consent were approved by the ethical committee of Shahid Beheshti University of Medical Sciences in Tehran. All participants gave informed consent.

Diagnosis of idiopathic PD, based on the Hoehn and Yahr scale (Hoehn & Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008), was performed by a neurologist with a specialty in movement disorders (Ashrafi). Left and right upper-limb hypokinesia was assessed by the neurologist on the basis of the finger taps, hand movements, and rapid alternating movement of hands items in Part 3 of the UPDRS (Goetz et al., 2008; Johari et al., 2013; Ullman et al., 1997). The neurologist also recorded the time and dose of the last anti-PD medications prior to testing.

Procedure

All participants completed a past-tense production task, which took about 25 min to complete. Item order was counterbalanced across participants (Order 1 and Order 2, in which the items were presented in the reverse order to Order 1). Half of each of the four participant subgroups (PD males, PD females, control males, control females) were given each item order. In both orders, the items were pseudorandomized so that no more than three consecutive items were of the same type (regular, irregular, novel regular).

Following Ullman et al. (1997) and other studies examining regular/irregular morphology, participants produced the past tenses of regular, irregular, and novel regular verbs. Similar to English, in Farsi, the formation of regular past tenses involves the addition of the regular past-tense suffix *-id* (instantiated as the allomorphs */id/* and */ad/*) to the stem (e.g., *khar-kharid* [he bought], *ferst-ferstad* [he sent]), whereas irregulars undergo a stem change with no affixation (e.g., *bin-did* [he saw], *band-bast* [he tied], *pardaz-pardakht* [he paid]). Although a number of irregular past-tense forms share word-final phonology (e.g., */st/*, */sht/*, */kht/*), this is not considered affixal (Henderson, 1978). Third-person past-tense forms in Farsi do not contain an overt person agreement affix, avoiding any additional affixation (Henderson, 1978). The third-person singular present-tense form, which was presented to the participants, is formed from the stem, the present tense prefix *mi-*, and the third-person agreement suffix *-ad*, both of which may be stripped off upon the presentation of the form. The extent to which any such stripping involves compositional (or lexical) processes should be equivalent for regular and irregular verbs, leaving regular versus irregular past-tense formation as the sole likely difference in the past-tense production task.

Participants were asked to produce out-loud past tenses of common real (existing) regular and irregular verbs, as well as of novel regular verbs, given their visually presented present tense forms (e.g., "*Ou alan midavad. Diruz ou* ____." [Right now s/he runs/is running. Yesterday s/he____.]). All verbs were presented in the third-person singular (*mi-STEM-ad*), which does not take person agreement in the past-tense form (see just above). All sentences, which the participants read out loud, had the same structure and the exact same words other than the verb stem ("*Ou alan mi-STEM-ad. Diruz ou* ____.").

The task contained 23 real regular, 23 real irregular, and 23 novel (made-up) regular verbs, which do not exist in the language (see Table 2). The stems of both the regular verbs and the novel verbs did not rhyme with the stem of any irregular verb in the language. Thus, both the real and novel regulars are "consistent," reducing the likelihood of memorization of the real regular past tenses by all participants (cf. "inconsistent" or "rhyming" regulars) and increasing the likelihood that the novel regulars would undergo regular affixation rather than irregularization (Ullman, 1993,

Table 1
Participant Demographic and Other Information

Participant information	Males		Females		Comparison
	PD	NC	PD	NC	
Age (years)	63.8 ± 10.2	59.9 ± 5.8	59.3 ± 7.1	59.1 ± 5.4	$F(3, 76) = 1.78$, $p = .15$
Education (years)	10.8 ± 2.7	11.1 ± 3.6	10.5 ± 3.7	12.0 ± 3.0	$F(3, 76) = .79$, $p = .50$
Handedness	70.0 ± .1	69.0 ± .1	72.0 ± .1	70.0 ± .1	$F(3, 76) = .18$, $p = .90$
MMSE	27.6 ± 1.0	27.2 ± 1.1	27.7 ± 1.1	27.7 ± .8	$F(3, 76) = .56$, $p = .64$
Disease stage	3.4 ± .5	NA	3.2 ± .4	NA	$t(38) = .88$, $p = .45$
Right-side hypokinesia	8.9 ± 2.1	NA	7.9 ± 1.6	NA	$t(38) = 1.55$, $p = .13$
Left-side hypokinesia	6.5 ± 1.9	NA	7.12 ± 1.5	NA	$t(38) = -1.00$, $p = .32$
LED of last medication	262.5 ± 42.5	NA	260.0 ± 41.7	NA	$t(38) = .19$, $p = .85$
Hours since last medication	6.5 ± 2.2	NA	6.8 ± 2.3	NA	$t(38) = -.42$, $p = .67$

Note. Means are presented together with standard deviations. Education reflects years of schooling starting from first grade. Handedness reflects laterality quotients from the Edinburgh Handedness Inventory (Oldfield, 1971), in which 100 represents strongly right-handed and −100 represents strongly left-handed. Disease stage reflects values from the Hoehn and Yahr scale (Hoehn & Yahr, 1967). Right-side and left-side hypokinesia each represent the mean of the three upper-limb items from the motor section of the Unified Parkinson's Rating Scale (Goetz et al., 2008), respectively, for the right and left sides. Comparisons reflect results from one-way ANOVAs with four levels (PD males, PD females, control males, control females) or, when values exist only for PD participants, independent-samples *t*-tests. PD = patients with Parkinson's disease; NC = normal control; MMSE = Mini-Mental State Examination; LED = levodopa equivalent dose; NA = not applicable.

Table 2
Regular, Irregular, and Novel Regular Verbs in the Past-Tense Production Task

Regular verbs			Irregular verbs			Novel regular verbs	
Stem	Past tense	Verb translation	Stem	Past tense	Verb translation	Stem	Regularized past tense
Avar	Avard	Bring	Afraz	Afrasht	Elevate	Barkh	Barkhid
Bakhsh	Bakhshid	Forgive	Amuz	Amukht	Learn	Chor	Chorid
Bus	Busid	Kiss	Andaz	Andakht	Throw	Das	Dasid
Charkh	Charkhid	Spin	Aviz	Avikht	Hang	Desh	Deshid
Chesh	Cheshid	Taste	Band	Bast	Tie	Fakhsh	Fakhshid
Dav	David	Run	Baz	Bakht	Lose	Fars	Farsid
Fahm	Fahmid	Understand	Bin	Did	See	Fas	Fasid
Jav	Javid	Chew	Duz	Dukht	Sew	For	Forid
Kesh	Keshid	Pull	Frush	Frukht	Sell	Fush	Fushid
Khan	Khand	Read	Gard	Gasht	Wander	Gash	Gashid
Khar	Kharid	Buy	Gozar	Gozasht	Put	Jar	Jarid
Khor	Khord	Eat	Gu	Goft	Say	Jor	Jorid
Kub	Kubid	Hit	Kar	Kasht	Plant	Khus	Khusid
Kush	Kushid	Try	Navaz	Navakht	Play	Lush	Lushid
Nush	Nushid	Drink	Nevis	Nevesht	Write	Markh	Markhid
Par	Parid	Jump	Pardaz	Pardakht	Pay	Nash	Nashid
Pash	Pashid	Spray	Paz	Pokht	Cook	Paghs	Paghsid
Pors	Porsid	Ask	Pazir	Paziroft	Accept	Parkh	Parkhid
Push	Pushid	Wear	Riz	Rikht	Pour	Pesh	Peshid
Raghs	Raghsid	Dance	Saz	Sakht	Build	Sav	Savid
Res	Resid	Arrive	Shekan	Shekast	Break	Takhs	Takhshid
Resan	Resand	Deliver	Shenas	Shenakht	Know	Tas	Tasid
Tarash	Tarashid	Shave	Shoi	Shost	Wash	Zush	Zushid

2001; Walenski, Mostofsky, & Ullman, 2007; Walenski et al., 2018); these expectations were confirmed by the results of the present study. The three verb types were matched group-wise on the number of syllables (one-way ANOVA, $F[2, 66] = 1.57$, $p = .22$) and the number of Farsi letters (one-way ANOVA, $F[2, 66] = .12$, $p = .72$). Additionally the real regular and irregular verbs were matched on natural logarithm-transformed past-tense frequency (independent-measures t test, $t[44] = .66$, $p = .51$). Frequency counts (here and elsewhere) were obtained from the Persian Linguistic Database (Assi, 2004; http://pldb.ihcs.ac.ir/).

Data Analysis

Accuracy for each verb type for each participant was computed as the log-odds (logit) transformation, that is, the natural log (number correct + 0.5/number incorrect + 0.5), in which 0.5 is added to avoid a denominator of zero (Jaeger, 2008). These transformed accuracy values were submitted to mixed effects models in SAS 9.4 (proc glimmix), with group (PD, control), sex (male, female), verb type (regular, irregular, novel regular), and their interactions as fixed effects, and a random effect of participant on the intercept (note that including a random slope of verb type decreased model fit, based on the Bayesian information criterion). An analogous mixed effects model was run on log-odds transformed overregularization values, with group and sex and their interaction as fixed effects, and a random effect of participant on the intercept. Type III F tests are reported for main effects and interactions. Follow-up contrasts were performed with unequal variance t tests (Ruxton, 2006); effect sizes for critical contrasts are indicated with Hedges' g (Lakens, 2013). Degrees of freedom for both the mixed effects models and the unequal variance t tests were computed with the Satterthwaite approximation. Correlations and partial correlations were performed (in SPSS 23) to examine associations between relevant variables (e.g., right-side hypokinesia and past-tense accuracy, separately for each verb type), with significance assessed using a false discovery rate (FDR) correction (Benjamini & Hochberg, 1995) for multiple comparisons for the number of comparisons at each level of the analysis (e.g., three comparisons for correlations between right-side hypokinesia and each of the three verb types). The FDR threshold was set at .05, and significance is expressed as the FDR-corrected q value.

Results

Effects of Regularity and Sex

The 2 (group: PD, control) × 2 (sex: male, female) × 3 (verb type: regular, irregular, novel regular) mixed effects model produced significant main effects of group, $F(1, 76) = 67.70$, $p < .0001$, and verb type, $F(2, 152) = 17.58$, $p < .0001$, but not sex, $F(1, 76) = 2.42$, $p = .12$. These main effects were qualified by two-way interactions between sex and verb type, $F(2, 152) = 28.59$, $p < .0001$, and group and verb type, $F(2, 152) = 3.42$, $p = .04$; there was no interaction between group and sex, $F(1, 76) = .94$, $p = .33$. However, all of these effects were qualified by a three-way interaction between group, sex, and verb type, $F(2, 152) = 13.42$, $p < .0001$. Following up on this three-way interaction with 2 (group) × 2 (sex) models for each verb type, we found that the interaction between group and sex was significant for regulars, $F(1, 76) = 10.77$, $p = .002$, but not for irregulars, $F(1, 76) = 2.98$, $p = .09$, or novel verbs, $F(1, 76) = .51$, $p = .48$. Rather, for both of these verb types, there were main effects of group, with PD patients (over both sexes) performing worse than

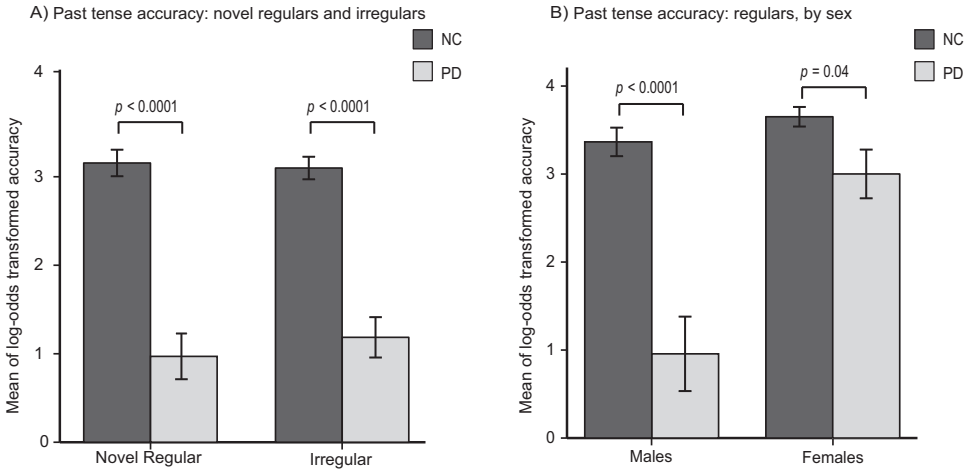
controls (irregulars: $F[1, 76] = 59.84$, $p < .0001$; novels: $F[1, 76] = 55.25$, $p < .0001$; see Figure 1A).

Follow-up unequal variance t tests on the Group × Sex interaction on regulars revealed that although the PD patients performed worse than the controls at regulars in both sexes, the impairment was much more pronounced for males, $t(23) = 5.41$, $p < .0001$, with Hedges' $g_s = 1.68$, a very large effect size, than females, $t(25) = 2.18$, $p = .04$, Hedges' $g_s = .68$ (see Figures 1B and 1C). Moreover, male PD patients performed worse than female patients at regulars, $t(33) = 4.04$, $p = .0003$, Hedges' $g_s = 1.25$, a very large effect size, whereas control participants did not show such a sex difference, $t(36) = 1.61$, $p = .12$, Hedges' $g_s = .50$.

Additionally, following up on the three-way interaction with 2 (group) × 2 (verb type) models separately for each sex, we found different patterns for males and females. Males showed significant interactions between group (PD/control) and regulars/irregulars, $F(1, 38) = 5.63$, $p = .02$, and between group and novel verbs/irregulars, $F(1, 38) = 4.40$, $p = .04$, consistent with the finding that the male PD patients performed worst at producing novel and regulars verbs (see Figure 1C). By contrast, the male patients showed no interaction between group and regulars/novel regulars, $F(1, 38) = 0.00$, $p = .96$, suggesting that they were similarly impaired at both of these verb types.

Females patients, however, were *least* impaired at regulars (Figure 1C), which helped drive the significant interaction between group and regular/novel verb inflection, $F(1, 38) = 23.49$, $p < .0001$. In addition, the female patients were most impaired at irregulars (see the Exploratory Analyses section), which also helped explain the interaction between group and regular/irregular inflection, $F(1, 38) = 20.63$, $p < .0001$, as well as the absence of an interaction between group and novel regular/irregular inflection, $F(1, 38) = 1.24$, $p = .27$.

Note that the control participants are close to ceiling on this task (see untransformed scores in Figure 1C), which could complicate interpretation of the interactions in the analyses above. That is, it is possible that with a more difficult task, the controls might show a similar pattern as the patients. We therefore performed an additional analysis to examine the pattern of inflection, focusing on the key distinction between regular and irregular inflection (we thank an anonymous reviewer for this suggestion). Specifically, we performed a 2 (group) × 2 (sex) chi-square test on the count of individuals who had a positive regular/irregular difference, excluding ties. This yielded a significant result, $\chi^2(1) = 4.7$, $p = .03$, indicating that this pattern of past-tense performance differed between the male and female PD patients as compared to the controls (number of participants better at regulars than irregulars: NC male = 6; NC female = 9; PD male = 2; PD female = 19). Specifically, this pattern is consistent with the male but not female PD patients being particularly impaired at regulars, and with females being relatively spared at regulars but not irregulars (Figure 1C). The females' particular impairment on irregulars was also reflected in the analogous 2 × 2 chi-square test on the novel regular/irregular difference, $\chi^2(1) = 5.8$, $p = .02$ (number of



C) Past tense accuracy, by verb type and sex

	Normal Controls			PD Patients		
Verb type	Males	Females	All controls	Males	Females	All patients
Regular	98% (3%)	99% (2%)	99% (3%)	71% (31%)	93% (16%)	82% (27%)
Novel Regular	95% (7%)	97% (6%)	96% (7%)	63% (33%)	77% (18%)	70% (27%)
Irregular	97% (3%)	95% (5%)	96% (4%)	81% (25%)	63% (24%)	72% (26%)
All verb types	97% (3%)	97% (4%)	97% (3%)	72% (27%)	78% (17%)	75% (23%)

Figure 1. NC (normal control) and PD (Parkinson's disease) performance at the Farsi past-tense production task. The bar graphs show the means and standard errors (error bars) of the log-odds transformed accuracy for each verb type. (A) Comparisons between NC and PD participants for novel regulars and irregulars. (B) NC/PD comparisons for regulars, separately for each sex, because regulars showed a group (PD/NC) by sex (male/female) interaction. (C) Full accuracy results, showing mean untransformed accuracy scores (and standard errors) for each group, broken down by sex, for each verb type.

participants better at novels than irregulars: NC male = 5; NC female = 6; PD male = 1; PD female = 15).

Overall, the data thus suggest that the male PD patients showed past-tense production deficits at regular and novel verbs, relative to irregulars, whereas the females did not show this pattern. Rather, their impairment was greatest on irregulars and was mildest for regulars.

Effects of Hypokinesia and Dopaminergic Measures

As discussed in the introduction, Ullman et al. (1997) examined correlations, across the PD patients, between hypokinesia and past-tense production, separately for right-side and left-side hypokinesia and each verb type (regular, novel regular, irregular), also while partialing out dementia scores and opposite side hypokinesia. To examine these associations in the PD patients here, we first ran linear regressions, with sex and hypokinesia (centered) and their interaction as independent variables and log-odds transformed accuracy as the dependent variable, separately for right-side and left-side hypokinesia and for each of the three verb types (regulars, novel regulars, irregulars). There were no significant Sex × Hypokinesia interactions for any of these six regressions (all ps $> .22$), indicating that the relationship between hypokinesia and past-tense production did not differ significantly between the sexes in any of these cases. Thus, we omitted the factor of sex and its interaction with hypokinesia (thereby also increasing power), and proceeded, following Ullman et al., with simple and partial correlations (adjusting for opposite-side hypokinesia and MMSE scores, as in Ullman et al., 1997) across all PD patients. As shown in Table 3, right-side hypokinesia correlated with past-tense accuracy for regular verbs (large effect sizes) and novel verbs (medium to large effect sizes), but not irregulars, even when partialing out MMSE scores and left-side hypokinesia. In contrast, left-side hypokinesia did not correlate reliably with past-tense accuracy for any of the three verb types (a correlation with irregulars did not survive partialing out MMSE and right-side hypokinesia).

To test the involvement of dopaminergic processes in morphology in PD, we examined associations between the past-tense production of each verb type and two variables reflecting dopamine levels: the LED of patients' last anti-Parkinson's medication prior to testing and the hours between taking this last medication and testing. As with the analyses presented just above with hypokinesia, we first ran linear regressions, with sex and LED (centered) and their interaction as independent variables, and log-odds transformed accuracy as the dependent variable, separately for each of the three verb types (regulars, novel regulars, irregulars). Likewise, we performed three analogous regressions with hours since last medication in lieu of LED. As with hypokinesia, there were no significant interactions between sex and either dopamine-related variable for any of these six regressions (all ps $> .11$). Thus, we omitted the factor of sex and its interactions, and proceeded, similar to the analyses above, with simple correlations and partial correlations (controlling for MMSE scores as well as right-side hypokinesia). As can be seen in Table 4, the LED of the patients' last medication as well as the hours since their last medication correlated with past-tense accuracy for regulars (large effect sizes) and novel regulars (medium to large effect sizes), but not for irregulars, even when partialing out MMSE and right-side hypokinesia.

Note that the contrasting patterns of correlations between the three verb types and both right-side hypokinesia and dopaminergic measures were not explained by greater variability in the past-tense accuracy of regulars and novel regulars than irregulars (Levene's test for equality of variances, $F = .69$, $p = .50$).

Exploratory Analyses

Here, we report additional analyses that were not initially planned. We emphasize that these analyses are therefore exploratory and suggest that further evaluation of these findings may be carried out in carefully designed replication efforts.

First, to directly test the possibility that females were relying on the retrieval of chunked regular past-tense forms, we examined past-tense form frequency effects, which indicate the storage of past-tense forms (Alegre & Gordon, 1999; Prado & Ullman, 2009; Ullman, 1999). These analyses (correlations between natural log-transformed past-tense form frequency and log-odds transformed accuracy at the item level) revealed past-tense frequency effects for regulars in female, $r(21) = .44$ $p = .03$ (a medium to large effect size), but not male, $r(21) = -.032$ $p = .88$, PD patients.

Second, if female PD patients are more likely than male patients to store regular past-tense forms, then these forms should be more likely in females than males to be generalized in associative memory to phonologically similar overregularizations of irregular verbs (Hartshorne & Ullman, 2006). For example, the storage of *snowed* and *flowed* may result in their generalization to (i.e., they should "attract") *blowed*, and this should be more likely in female than in male PD patients. Importantly, in other populations, such associative generalization has been found to lead not only to novel irregularizations (e.g., the storage of *sing-sang* and *spring-sprang* leads to the associative generalization of *spling-splang*; Prasada & Pinker, 1993; Ullman, 1993; Xu & Pinker, 1995) but also to the production of overregular-

Table 3
Correlations Across the PD Patients Between Hypokinesia and Log-Odds Transformed Accuracy in Past-Tense Production

Independent variables	Regulars	Novel regulars	Irregulars
Right-side hypokinesia	$r(38) = -.50$, $q = .001$	$r(38) = -.34$, $q = .04$	$r(38) = -.18$, $q = .25$
Right-side hypokinesia, partialing out MMSE and left-side hypokinesia	$r(36) = -.52$, $q = .003$	$r(36) = -.38$, $q = .01$	$r(36) = -.05$, $q = .25$
Left-side hypokinesia	$r(38) = -.15$, $q = .42$	$r(38) = -.12$, $q = .42$	$r(38) = -.37$, $q = .03$
Left-side hypokinesia, partialing out MMSE and right-side hypokinesia	$r(36) = .17$, $q = .43$	$r(36) = .12$, $q = .46$	$r(36) = -.27$, $q = .27$

Note. q values represent false discovery rate corrected p values (see Data Analysis section). PD = Parkinson's disease; MMSE = Mini-Mental State Examination.

Table 4
Correlations Across the PD Patients Between Levodopa Equivalent Dose, or Time Since Last Dose, With Log-Odds Transformed Accuracy in Past-Tense Production

Independent variables	Regulars	Novel regulars	Irregulars
LED of last anti-PD medication	$r(38) = .61$, $q = .0003$	$r(38) = .48$, $q = .001$	$r(38) = .06$, $q = .70$
LED, partialing out MMSE and right-side hypokinesia	$r(36) = .50$, $q = .003$	$r(36) = .39$, $q = .01$	$r(36) = -.02$, $q = .89$
Hours since last anti-PD medication	$r(38) = -.85$, $q = .0001$	$r(38) = -.62$, $q = .0001$	$r(38) = -.11$, $q = .47$
Hours since last anti-PD medication, partialing out MMSE and right-side hypokinesia	$r(36) = -.78$, $q = .003$	$r(36) = -.53$, $q = .001$	$r(36) = -.02$, $q = .87$

Note. q values represent false discovery rate corrected p values (see Data Analysis section). For p values less than .0001, q values were computed as $p = .0001$. PD = Parkinson's disease; MMSE = Mini-Mental State Examination; LED = levodopa equivalent dose.

izations (e.g., *blowed*). In particular, and consistent with evidence suggesting that girls, but not boys, memorize regulars (Dye et al., 2013), girls, but not boys, appear to depend on such associative generalization in the production of overregulars, as evidenced by the finding that only girls show "phonological neighborhood effects" (Hartshorne & Ullman, 2006, p. 26). That is, irregular verbs whose stems are phonologically similar to (rhyme with) a greater number of regular verbs yielded more overregularizations in girls (suggesting that their overregularizations were produced through associative generalization), whereas this pattern was not found in boys (Hartshorne & Ullman, 2006). In the present study, we likewise found phonological neighborhood effects for the female, but not male, PD patients, and for neither female nor male controls (female PD, $r[20] = .58$, $p = .004$, a large effect size; male PD, $r[20] = .31$, $p = .15$; female control, $r[20] = .11$, $p = .63$; male control, $r[20] = .10$, $p = .64$), in correlations between log-odds transformed overregularization rates for each group at the item level and the number of common regulars that rhyme with each irregular (Anvari & Ahmadi, 1995).

Third, a higher rate of memorizing regular past-tense forms might also lead to a *higher rate* of overregularization, as associative generalization to overregulars should be more likely in this case. Indeed, Hartshorne and Ullman (2006) found that girls overregularized more than boys (5.7% of irregulars in girls vs. 1.8% in boys). Likewise, in the present study, female PD patients overregularized almost *seven* times the rate of male PD patients (23.9% vs. 3.5%; unequal variance t test on log-odds transformed means, $t[38] = 4.25$, $p = .0001$, Hedges' $g_s = 1.32$, a very large effect size), a difference that was not significant in the controls (females = 4.1% vs. males = 1.7%; $t[37] = .78$, $p = .44$, Hedges' $g_s = .24$). Indeed, a 2 (group: PD, control) × 2 (sex: male, female) mixed effects analysis on log odds transformed overregularization rates yielded main effects not only of group, $F(1, 76) = 46.61$, $p < .0001$, and sex, $F(1, 76) = 16.64$, $p = .0001$, with higher overregularization rates in PD patients than controls and in females than males, but also a Group × Sex interaction, $F(1, 76) = 10.89$, $p = .002$. In fact, the PD sex difference in overregularization rates fully accounts for the PD sex difference in accuracy at irregulars (Figure 1C; males, 81% accuracy + 3.5% overregularization = 84.5%; females, 63% accuracy + 23.9% overregularization = 86.9%).

Discussion

This study examined regular/irregular inflectional morphology in moderate to severe nondemented male and female PD patients and healthy controls. All participants were native speakers of Farsi and were tested on Farsi inflection. Male PD patients showed relative deficits at producing regular and novel regular Farsi past-tense forms as compared to irregular past tenses, whereas females did not show this pattern for regulars, and indeed their impairment was mildest for regulars. Right-side hypokinesia in the PD patients correlated (over both sexes, with no interaction with sex) with the past-tense production of regulars and novel regulars but not irregulars; this pattern held even when partialing out MMSE scores (a measure of global cognitive functioning that can reflect dementia) and left-side hypokinesia. In contrast, left-side hypokinesia did not correlate reliably with any of the three verb types. The LED of the patients' last anti-PD medication prior to testing, as well as the time between taking this medication and testing, both correlated (over both sexes, with no interaction with sex) with the production of regulars and novel regulars, but not irregulars, even when partialing out MMSE scores and right-side hypokinesia. All critical effects yielded medium to large, large, or very large effect sizes.

The results do not appear to be explained by a number of potentially confounding subject- or item-level factors. The PD and control participants were matched, across the two sexes, on age, education, handedness, and global cognitive functioning (MMSE scores), and the male and female PD patients were additionally matched on disease stage (Hoehn and Yahr scores), degree of both right- and left-side hypokinesia, the LED of their last medication, and the time from this medication to testing. The items for the three verb types in the past-tense production task were matched on phonological and orthographic length, and the real regular and irregular items on past-tense form frequency. The observed pattern at past-tense production was also unlikely to be explained by a greater articulatory deficit at regular and novel than irregular past tenses, because, in addition to the verb types being matched on phonological length, the irregular past tenses had more complex final consonant clusters than the regular or novel past tenses (see Table 2); in addition, articulatory deficits could not easily explain the different pattern of male and female deficits at past-tense production. Finally, the contrasting patterns of correlations between the three verb types and both right-side hypokinesia and dopaminergic measures were not explained by greater variability in the past-tense accuracy of regulars and novel regulars than irregulars. Instead, the findings appear to suggest the following.

Interpretation

Effects of regularity and sex. The results suggest, first of all, that nondemented patients with moderate to severe PD are impaired at producing regular past tenses of existing verbs, but that this impairment is moderated by sex: Both sexes showed deficits at producing regular past tenses, but the males showed a greater

impairment. This is consistent with the view that the patients of both sexes had an underlying problem computing rule-governed inflected forms but that females showed a greater tendency to memorize existing regular past tenses as chunks in declarative memory, as predicted by the DP model. Furthermore, the presence of past-tense frequency effects for female, but not male, patients provides direct support for the view that the former, but not the latter, relied importantly on the storage and retrieval of chunked regular past-tense forms. The exact same past-tense frequency pattern was found for English regular past-tense forms in female versus male English-speaking PD patients (Reifegerste, Estabrooke, et al., 2018), strengthening the validity of the finding.

The results support the view that female PD patients show milder impairments of regular past-tense inflection than male patients as a result of a greater tendency for the females to store regular forms as chunks. However, the results do not reveal *when* these chunks were memorized. In particular, the female PD patients may have stored regular past-tense forms either prior to onset of the disease and/or afterward. If females rely less than males on basal-ganglia-based composition as children and adults, because of their increased reliance for grammar on declarative memory prior to disease onset (as independent evidence suggests; see introduction), 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 male patients. Indeed, evidence suggests that the female advantage in declarative memory also holds in PD, at least in nondemented patients and possibly in demented patients as well (Augustine et al., 2015; Fengler et al., 2016; Liu et al., 2015). Thus, the finding that regulars are less impacted in female than male PD patients could be caused by greater female memorization of regulars both before onset (which may be termed *precompensation*) and/or after onset (*compensation*).

Given that independent evidence (including from frequency effect analyses) suggests that healthy girls and women, but not, or less so, boys and men, tend to store consistent (nonrhyming) regular English past-tense forms as wholes (Dye et al., 2013; Prado & Ullman, 2009; Walenski et al., 2018), precompensation seems very likely. However, given that the female advantage at declarative memory may be found in PD patients as well as in healthy adults (see just above), compensation postonset also seems quite plausible. Indeed, evidence from other domains suggests postonset declarative memory compensation in PD (independent of sex) for nonlinguistic tasks and functions that rely on procedural memory in healthy controls (e.g., probabilistic classification and sequence learning; see introduction), underscoring the plausibility of postonset declarative memory compensation in PD for language as well. Thus, both precompensatory and compensatory storage of regularly inflected forms in declarative memory seems likely. Further research on this topic is warranted, particularly given the wide range of tasks and functions in language and other domains that can be affected in PD, and that may be compensated for by declarative memory, including apparently even motor functions (Ullman & Pullman, 2015).

Perhaps surprisingly, the female PD patients' performance at *irregular* verbs, in particular, at their production of overregularizations, lends further support to the view that these patients depended importantly on memorized regular past-tense forms. First of all, the presence of phonological neighborhood effects for female, but not male, PD patients suggests that only the female patients showed reliable associative generalization of overregularizations from stored regular past tenses. The absence of neighborhood effects in female controls may point toward a role for female PD compensation after onset (as opposed to precompensation), though lower variability in the controls (i.e., ceiling effects) is also likely to contribute to their lack of neighborhood effects. Moreover, the finding that the female PD patients overregularized almost seven times the rate of the male patients underscores the storage of regulars at a much higher rate by female than male patients. Thus, overall, the pattern of performance at irregulars, in particular, the pattern of overregularization, strengthens the view that the female PD patients compensated for their underlying grammatical deficit by relying on memorized regular past-tense forms. Paradoxically, whereas such compensation led to *better* performance for regulars, it yielded *worse* performance at irregulars, an example of how a strength can, in some circumstances, constitute a weakness (Hartshorne & Ullman, 2006).

The finding that female patients showed the *least* impairment at producing regular past tenses, across both sexes and all three verb types, suggests that the compensatory memorization of regulars was quite successful (whether it occurred prior to and/or following disease onset). Nevertheless, the female patients still showed a deficit at producing regulars, indicating that even the females did not fully compensate for the underlying impairment of rule-governed computation. This is in line with previous evidence showing that healthy adult females store many, but not all, English-consistent regular past-tense forms (Prado & Ullman, 2009). It may also help explain the lack of an interaction between sex and right-side (or left-side) hypokinesia, or between sex and dopaminergic measures, for real regulars.

Finally, further support for the existence of an underlying impairment in the computation of rule-governed inflected forms comes from the finding that, unlike for regulars, the two sexes were similarly impaired at *novel* regulars—as expected, because their past-tense forms cannot have been memorized as chunks and thus should be similarly susceptible to an impairment in rule-governed computation across the sexes.

The pattern of findings from the present study are both consistent with, and differ from, those of the previous nine studies of regular/irregular inflection in PD (see introduction). Our results are consistent with Ullman et al.'s (1997) findings that PD patients with high levels of right-side hypokinesia showed relative deficits at English regular and novel verbs, as compared to irregulars, and that right-side hypokinesia correlated with performance at real and novel verbs but not irregulars, whereas left-side hypokinesia showed no such correlations at all. The fact that most of the patients in Ullman et al. were male is also in line with the results obtained here.

Our findings are also consistent with those of a recent study that specifically examined the role of sex as well as of left- and right-side hypokinesia (Reifegerste, Estabrooke, et al., 2018). Seventeen male and 17 female nondemented English speaking PD patients with a range of hypokinesia levels (from very low to quite high) were tested on the past-tense production of existing regular and irregular verbs, together with healthy male and female controls. Over all patients, there was no indication of any particular

deficit at regulars, including in either sex. In contrast, a three-way interaction between regular/irregular, male/female, and right-side hypokinesia was obtained for the PD patients. Follow-up analyses revealed that higher right-side hypokinesia was associated with worse past-tense production, but only for regulars and only in males. No such pattern was found for left-side hypokinesia.

The results of the other seven studies that previously examined regular/irregular inflection in PD are in line with the patterns reported here as well as in Ullman et al. (1997) and Reifegerste, Estabrooke, et al. (2018). Across the latter three studies, regular deficits were found only at high levels of disease progression, in particular, at high levels of right-side hypokinesia, especially in males. However, in Reifegerste et al., no regular deficit was found (in either sex) across all patients, who showed a wide range of hypokinesia. Likewise, none of the seven other studies reported any clear PD deficit at regulars versus irregulars, compared to controls, and all seven of these studies tested patients at mild to moderate stages (Goetz et al., 2008; Hoehn & Yahr, 1967) of disease progression (Colman et al., 2009; Longworth et al., 2005; Macoir et al., 2013; Penke & Wimmer, 2012) or did not clearly specify the disease stage (Almor et al., 2002; Stavrakaki et al., 2010; Terzi et al., 2005). Moreover, some of these studies included a fair number of female patients (Colman et al., 2009; Longworth et al., 2005; Macoir et al., 2013; Penke & 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 attributable to the inclusion of female patients. Thus, overall, the pattern of results across studies suggests that, consistent with the predictions of the DP model, regular deficits in PD emerge at higher levels of disease progression, particularly with higher levels of right-side hypokinesia, and are found especially in males.

Effects of hypokinesia and dopaminergic measures. The correlations observed in the present study between right- but not left-side hypokinesia and the past-tense production of regular and novel regular, but not irregular, verbs link the PD deficit in regular inflection to the degeneration of left basal ganglia circuits. As stated above, the finding that right-side hypokinesia did not interact significantly with sex for regulars (or novel regulars) suggests a dependence of regulars (as well as novel regulars) on left basal ganglia circuits, even in females.

It is not clear why right-side hypokinesia showed similar associations with existing regular past-tense production across the sexes in the present study but differential associations with sex in Reifegerste, Estabrooke, et al. (2018). However, an important difference between the two studies is the higher levels of hypokinesia and disease progression in the present study, which thus might explain the different patterns. For example, it is possible that the relation between right-side hypokinesia and regular inflection in females is nonlinear, such that only at particularly high levels of hypokinesia are regulars negatively impacted in female patients. Indeed, there was a *positive* relation between right-side hypokinesia and regulars in females (but not males, in which it was negative) in Reifegerste et al., such that the best performance on regulars was found in female patients with *higher* levels of hypokinesia. Together with the negative relation between right-side hypokinesia and regulars in females in the present study, this suggests the possibility of a U-shaped curve. For example, perhaps as the disease progresses, females increasingly memorize regulars as chunks in declarative memory (because, over time, they encounter more forms, consistent with postonset compensation), but after a certain point, the underlying rule-governed deficit overwhelms any such benefits, and a negative correlation is observed. In this view, perhaps the best female performance on regulars can be found at moderate disease stages, after which performance begins to decline. These speculations may warrant further investigation, particularly since they may have consequences for declarative memory-based compensation more generally in PD, and thus therapeutic impacts (Ullman & Pullman, 2015; also see below).

In contrast, the lack of a correlation between right-side hypokinesia and irregular inflection further supports the hypothesis that irregular forms do not depend extensively on left basal ganglia circuits. Moreover, there appears to be no reliable reliance of either rule-governed or irregular forms on right-side basal ganglia circuits, as evidenced by the lack of reliable correlations between left-side hypokinesia and the past-tense production of any of the three verb types.

In sum, the hypokinesia correlation results, which replicate the findings of Ullman et al. (1997) in English (in which the vast majority of patients were male), suggest that the processing of rule-governed inflected forms in PD, but not the retrieval of lexicalized forms, is tied, across languages, to the degeneration of left basal ganglia circuits in the disorder. Nevertheless, some caution is warranted, since right-side hypokinesia does not solely reflect left basal ganglia degeneration (Berardelli et al., 2001; DeLong, 1990; Mazzoni et al., 2012). Future studies using other approaches to examine basal ganglia degeneration, such as functional MRI, are therefore warranted.

The correlations between both dopaminergic measures (LED and hours since this dose) and the past-tense production of both regular and novel regular, but not irregular, verbs directly implicate dopaminergic circuitry in regular inflection, but not in irregular inflection, in PD patients taking dopaminergic medication. The finding that this pattern held even when right-side hypokinesia and MMSE scores were partialed out suggests that dopamine levels may directly modulate rule-governed inflection in PD. The absence of interactions between sex and the dopaminergic measures for regulars (and other verb types) is consistent with the lack of such interactions between sex and hypokinesia. The similarity of the two patterns suggests that the dopaminergic effects observed here are closely related to the effects of right-side hypokinesia, and thus links the observed dopaminergic effects to the left basal ganglia. Indeed, this is consistent with the fact that degeneration of dopaminergic neurons in PD occurs preferentially in the basal ganglia, specifically among neurons projecting from the substantia nigra pars compacta to the striatum (Alexander, 2004). Thus, the dopaminergic correlations further implicate the basal ganglia, and these neurons, in particular, in regular inflection. Together with the correlations with right-side hypokinesia, this underscores a critical role for left basal ganglia dopaminergic circuits in rule-governed grammar, in particular, regular morphology.

Although the findings suggest that the degeneration of dopaminergic neurons in the left basal ganglia leads to the impairment of rule-governed inflection in PD, they do not directly implicate any neurocognitive mechanism. It is possible that the dopaminergic neuronal degeneration in the basal ganglia does not directly cause the observed deficits but rather leads to the inhibition of the frontal

circuitry that underlies grammatical processing (a type of diaschisis). This would be consistent with evidence that portions of the basal ganglia (e.g., the anterior caudate and putamen) may be primarily involved in learning new procedures, which seem to rely more on frontal neocortical regions after they have been automatized (Ashby et al., 2010; Doyon et al., 2009; Janacsek et al., 2018; Tagarelli et al., 2018; Ullman, 2016). Nevertheless, it is possible that the basal ganglia (also) play a more direct role in deficits of rule-governed computation in PD. For example, basal ganglia dysfunction could impair the (re)learning of grammar (such continued learning may be important to avoid declines) and/or the processing of already-automatized procedures, that is, in computing regular forms, since some evidence implicates portions of the putamen in processing well-learned motor-related procedures (Doyon et al., 2009). Further studies should elucidate this issue.

Implications and Conclusion

The study has a number of implications and suggests future directions of research. First, the findings clarify the status of inflectional morphology in PD. They suggest that regular inflection—and, more generally, perhaps other aspects of rule-governed grammatical computation—is indeed impaired in PD but that this impairment is moderated by sex, right-side (but not left-side) hypokinesia, and dopaminergic processes. In particular, the results suggest that regular inflection is impaired in moderate-to-severe nondemented PD patients, particularly in males, and is moderated by left (but not right) basal ganglia degeneration and by dopamine levels, which, moreover, appear to be related to left basal ganglia degeneration. The sex difference in the impairment of regulars appears to be largely explained by the memorization of previously encountered regular inflected forms as chunks by females, likely in declarative memory. The findings also suggest that, in contrast to regulars, irregulars seem to remain relatively unaffected by left basal ganglia degeneration. This is consistent with recent findings indicating the relative sparing of lexical processing, even in moderate to severe PD (Johari et al., 2018). Finally, the results reveal that, paradoxically, the memorization of regular forms by females leads to *worse* performance at irregulars, because of an ensuing higher rate of overregularization caused by associative generalization from the memorized forms.

The findings also elucidate the neurocognition of language more generally. They strengthen links between aspects of rule-governed grammatical computation and left frontal/basal ganglia circuits, and extend the links to dopaminergic processes that are likely instantiated in these circuits. They confirm the neurocognitive dissociation between grammatical and lexical aspects of language and provide further evidence for sex differences that moderate this dissociation. Specifically, they provide further support for the view that females rely (more than males) on chunking in declarative memory for at least some rule-governed complex forms and show that this can lead to significant downstream effects, including compensatory advantages (and, as we have seen for irregulars, disadvantages as well). The findings were largely predicted by the DP model and thus strengthen the model, as well as further specifying it, in particular, by providing evidence for basal ganglia-based dopaminergic processes in rule-governed grammar. Note that although other neurocognitive models of language have not, to our knowledge, predicted the patterns observed there, they may nonetheless be compatible with the findings. We leave this open to further investigation.

The sex differences should be interpreted with caution. First of all, the observed sex differences themselves may be further moderated by factors such as age (e.g., before vs. after menopause) and potentially the level of hypokinesia or disease progression as well (see above). Moreover, we emphasize that although sex was a critical factor in the present study, it may not be the most explanatory variable regarding the observed sex differences. 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 pre- and postonset are associated with different patterns of regular inflection. The direct examination of declarative memory (e.g., in episodic memory tasks) in PD, and whether it predicts performance at processing regular past-tenses, perhaps especially in females, could further elucidate the nature of grammatical compensation in the disorder and more closely tie it to declarative memory.

The study also has translational implications. In particular, the findings suggest that both dopaminergic medication and lexical/declarative compensation are possible paths for the amelioration of language deficits in PD. Thus, both are promising avenues for translational research and for the developmental of new therapeutic approaches for language impairments in PD, or the use of existing therapies (e.g., levodopa) that are currently primarily employed to target other deficits. Indeed, both behavioral and pharmacological interventions may be expected to facilitate lexical/declarative compensation (Ullman & Pullman, 2015), underscoring the potential utility of this approach.

In conclusion, the present study, which comprehensively examines inflectional morphology in PD, elucidates important aspects of the nature and mechanisms of language in PD, as well as of the neurocognition of language more broadly, and suggests future paths of research.

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