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Contribution of language studies to the understanding of cognitive impairment and its progression over time in Parkinson's disease

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Highlights

- Characterizing cognitive impairment is a priority of Parkinson's disease research.

- Cognitive impairment is heterogeneous in this disease.

- Language tasks could contribute to characterize and predict cognitive impairment.

- Sentence and lexical-semantic processing seem particularly promising.

Abstract

Parkinson's disease is a frequent neurodegenerative disease that is mostly known for its motor symptoms. However, cognitive impairment is now recognized as an important part of the disease. Studies of cognitive impairment in Parkinson's disease reveal considerable

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heterogeneity in terms of which cognitive domains are impaired, and of how cognitive impairment progresses over time. In parallel, a growing body of research reports language difficulties in Parkinson's disease, more specifically in the domains of sentence processing and lexical-semantic processing. In this review, the performance of Parkinson's disease patients in these domains of language will be reviewed with a focus on the links that they have with the rest of cognition and on how they could contribute to the earlier and more precise characterization and prediction of cognitive impairment in Parkinson's disease. More specifically, the potential for modulation of complexity and sensitivity of language task to mild deficits and difficulties that are predictive of further decline will be emphasized. Other motivations for studying language difficulties in this disease will also be discussed.

Keywords

Parkinson's disease; cognitive impairment; Mild Cognitive Impairment (MCI); language; syntax; sentence processing; semantic cognition; semantics; verbal fluency

1.Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease after Alzheimer's disease (Post et al., 2007). While the hallmarks of PD are motor symptoms, more specifically tremor, bradykinesia, rigidity and gait disorder, non-motor symptoms are now recognised as an important part of PD. Non-motor symptoms include sleep disorders, gastro-intestinal disorders, neuropsychiatric disorders, and cognitive impairment (Eichenseer and Goetz, 2013; Sauerbier et al., 2016). Importantly, cognitive impairment is an increasingly recognised

complication of PD, with the risk of developing dementia in PD being estimated as six times higher than in the general population (Aarsland et al., 1996; Emre, 2003). Cognitive impairment has a negative impact on quality of life (Leroi et al., 2012; Schrag et al., 2000). It is associated with excess disability, risk for psychosis, increased mortality, caregiver burden and nursing-home placement (Aarsland et al., 1999, 2000; Aarsland and Kurz, 2010; Buter et al., 2008; de Lau and Breteler, 2006). The identification and management of cognitive impairment is increasingly acknowledged as a priority of research on PD.

The neuropathology of PD is characterised by the loss of dopaminergic cells in the substantia nigra (Bernheimer et al., 1973) which outputs to the striatum, part of the basal ganglia (BG). Alexander et al. (1986) proposed the existence of parallel cortical basal ganglia loops, each comprising a specific location in the cortex, basal ganglia, and thalamus.

Multiple such circuits or loops are associated with several different aspects of behaviour and activities, depending on the cortical region they originate from. (Alexander et al., 1986; Cummings and Benson, 1984, 1988; Tekin and Cummings, 2002).

The understanding of PD pathology has progressed tremendously over the past 10 to 15 years (Jellinger, 2012). However, many aspects of non-motor symptoms, and especially of cognitive impairment remain to be understood. Overall, studies of cognitive impairment in PD reveal considerable heterogeneity in terms of which cognitive domains are impaired, and of how impairment progresses over time (Barker and Williams-Gray, 2014; Barone et al., 2011; Jellinger, 2012; Kehagia et al., 2010; Monchi et al., 2016; Tröster, 2011). Cognitive deficits in

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PD would initially be characterised by executive impairments related with the dysfunction of the dorso-lateral prefrontal-striatal loop (Middleton and Strick, 2000; Tekin and Cummings, 2002; Zgaljardic et al., 2006). As disease progresses, other regions of the brain would be impaired and the neocortex would be affected (Braak et al., 2004). The progression of Lewy bodies inclusion would explain the presence of wide-spread pathology in the brain and the impairment of several neurotransmitter systems and aspects of behaviour (Carlesimo et al., 2012; Caviness, 2014; Harding et al., 2002). Importantly, cortical atrophy would be linked with the progression of cognitive impairment (Braak et al., 2005; Christopher and Strafella, 2013; Hanganu et al., 2014; Meyer et al., 2007).

The heterogeneity of cognitive impairment in PD could be related to the presence of different underlying brain pathology in subgroups of patients. For instance, recent post-mortem studies show that between 30 and 40% of PD patients with dementia also have AD neuropathology (Aβ amyloid plaques and tau-containing neurofibrillary tangles) in addition to synucleinopathy (Lewy body depositions) (Kurosinski et al., 2002; Sabbagh et al., 2009). Patients with a combination of PD and AD pathology could have different patterns of cognitive progression, but this remains to be studied. Recently, a Movement Disorder Task Force has been commissioned with the task of establishing consensual diagnosis criteria for Mild Cognitive Impairment (MCI) in the context of PD (Litvan et al., 2012). MCI is an entity that was initially described as a stage falling on the continuum between normal aging and Alzheimer's disease (AD) (Petersen et al., 1999, 2009; Winblad et al., 2004). It was subsequently expanded to describe a stage characterized by cognitive deficits that are not severe enough to interfere significantly with activities of daily living in the context of other neurodegenerative diseases, including PD (Aarsland et al., 2009; Litvan et al., 2012). Estimates show that 26.7% of patients

(between 18.9% and 38.2% depending on studies) would fit the criteria for PD-MCI (Litvan et al., 2012). Even before the adoption of consensual criteria, the distinction of PD patients with normal cognition from those with mild cognitive deficits has proven useful to characterize the progression of the disease (Janvin et al., 2006; Williams-Gray et al., 2007).

The studies of cognitive impairment in PD-MCI and PD with dementia (PDD) report impairments in the domains of executive function (especially set-shifting: Flowers and Robertson, 1985; Monchi et al., 2004), attention, visuo-spatial processing and memory (Aarsland et al., 2003, 2009, 2010; Muslimovic et al., 2007; Walker et al., 2015).

Language is usually not mentioned as one of the affected cognitive domains, yet a large number of studies have reported significant difficulties in language tasks including sentence comprehension, verbal fluency and naming. Language alterations have also been reported in patients with lesions of the basal ganglia following stroke (Caplan et al., 1990; Damasio et al., 1982; Naeser et al., 1982; Pickett et al., 1998) and in Huntington's disease (HD) (*lexical-semantic processing*: Ho et al., 2002; Kargieman et al., 2014; Randolph et al., 1993; Rosser and Hodges, 1994; Testa et al., 1998; Tröster et al., 1998; Suhr and Jones, 1998; *connected speech, syntax, and morphology*: García et al., 2017a; Illes, 1989; Murray, 2000; Murray and Lenz, 2001; Saldert et al., 2010; Sambin et al., 2012; Teichmann et al., 2005, 2006, 2008a, 2008b), another neurodegenerative disease characterised by neuronal loss in the basal ganglia (Vonsattel and DiFiglia, 1998; Raymond et al., 2011).

The language difficulties that will be the focus of the present review concern the cognitive aspects of language production and comprehension. In PD, these difficulties are less-well known than motor speech disorders.

The most frequent type of motor speech disorder observed in PD is hypokinetic dysarthria, and it is estimated that up to 90% of PD patient will develop hypokinetic dysarthria in the course of the disease (Brabenec et al., 2017; Tjaden, 2008). The first symptoms are usually voice disorders, followed by articulation and fluency anomalies (Tjaden, 2008). Hypokinetic dysarthria is described as a disorder of motor speech execution, caused by an impairment in tone, range of motion, and coordination of speech effectors (e.g., tongue, lips) (Ogar et al., 2005). It is often contrasted with apraxia of speech (AOS), which is a disorder of motor speech planning and programming (Duffy, 2006; Spencer and Rogers, 2005), associated with lesions of the central nervous system. However, it is not excluded that the speech of PD patients could present some features of AOS (Spencer and Rogers, 2005; see Ogar et al., 2005 for a distinction between the phonological errors typical of conduction aphasia, the consistent/predictable speech alterations typical of dysarthria, and the inconsistent/unpredictable articulation alterations typical of AOS).

Each of the subsystems involved in speech production (respiration, phonation, articulation, resonance, and prosody) can be affected in hypokinetic dysarthria (Schulz and Grant, 2010; Brabenec et al., 2017). The impairment of prosody (variations of duration, pitch, and/or loudness to convey the emotional, social, or supra-linguistic aspects of a message) (Pell and Leonard, 2003) touches onto the pragmatic level of language, which concerns the use of language in context (McNamara and Durso, 2003). Several studies have shown that PD patients have difficulties modulating their intonation to convey emotions, interrogation, and lexical emphasis (Cheang and Pell, 2007; Schulz and Grant, 2000). Interestingly, PD patients also have

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difficulties interpreting cues provided by prosody to identify speakers' emotions and intentions (Dara et al., 2008; Monetta et al., 2008; Paulmann and Pell, 2010; Pell, 1996; Pell and Leonard, 2003), showing that limitations in terms of motor speech production may not be the only factor responsible for their prosody impairment. As will be shown in this review, impairments that are first identified in language production often turn out to be accompanied by similar impairments of language comprehension, which demonstrate their place among, and relation with other cognitive deficits in PD.

In summary, language can be conceptualised as a very complex behaviour that involves the contribution of several cognitive processes. Consequently, language tasks provide rich information on the cognitive status of patients with neurodegenerative disorders, whether the clinical portrait is centered on language impairment or not. Different language domains and language tasks could provide valuable information for the diagnosis and prognosis of cognitive impairment in PD at different stages of the disease. As will be shown in this review, language tasks could reveal impairments of the fronto-striatal loop early in the disease process, and show how performance can be modulated by dopaminergic medication and compensation mechanisms. This could lead to increased knowledge of the plasticity of cognitive processing in early PD, and at terms, in better treatment options for patients.

Another important goal of PD research is to predict the progression of the cognitive profile over time. This task is particularly hard given the complexity of the pathological processes involved, the overlap with other pathologies, and the heterogeneity of PD. Specific features of language processing in PD are starting to emerge.

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In this manuscript we will argue that in combination with longitudinal study designs and other markers, language measures could help identify the patients that are most likely to evolve to dementia and potentially contribute to identify those that present concomitant AD pathology. We will provide a review of studies focusing on two sub-domains of language: sentence processing and lexical-semantic processing focusing on their implications for the understanding of cognitive impairment and its progression over time in PD.

2.

Sentence Processing

One remarkable characteristic of language is productivity: speakers can produce countless number of sentences with a predictable meaning, based on a finite number of words. Productivity would rely on syntax, which can be (briefly) defined as the ensemble of grammatical principles of a given language that govern word order in sentences (Frazier, 2013). While the capacity to access the form and meaning of isolated words plays a role in sentence processing, it is the capacity to understand relationships between words that is the most important when processing sentences. These relationships are conveyed by word order and morphology (e.g., inflectional morphemes) and are supported by world knowledge (e.g., logical succession of events) and contextual information (e.g., earlier mention of an element). Producing and understanding sentences is therefore a very complex act of language that likely requires the timely intervention and coordination of several cognitive processes.

Several studies have focused on the production and comprehension of sentences in PD. While severe language impairment such as those found in aphasia are not found in the first stages

of PD, sentence processing difficulties are present early in the course of the disease, and even in the absence of other cognitive deficits. This makes PD relatively unique compared to other neurodegenerative diseases, such as AD, in which difficulties are observed at the mild dementia stage, but are not observed in MCI (Hodges et al., 2006; Lambon Ralph et al., 2003). Studies of sentence processing have the potential to inform us on cognitive processing in early PD and on the interaction of language with cognition, particularly with executive functions.

2.1

Sentence Production

The first studies of sentence processing in PD patients focused on the oral production of sentences (Illes et al., 1988; Illes, 1989). The authors found that PD patients tended to produce short chunks of connected speech in a list-wise fashion. Overall, patients produced sentences that were longer but less complex, without being incomplete or grammatically incorrect. The authors interpreted reductions in sentence complexity as a way to convey relevant information in less speaking time. In other words, PD patients would focus on the production of content words instead of dedicating resources to the production of morphemes, prepositions and conjunctions, which are necessary to build more complex sentences, but do not convey essential information. According to Illes et al. (1988; Illes, 1989), changes in spontaneous sentence production constituted an adaptation to motor speech deficit in PD. However, this conclusion was ruled-out by Lieberman, Friedman and Feldman in 1990 and was challenged by several other studies.

The evidence on sentence production deficits in PD is mixed. Studies found that PD patients produced fewer complete sentences (Murray, 2000; Troche and Altmann, 2012), less

informative sentences (fewer correct information units) (Murray, 2000) and fewer grammatically correct sentences (Batens et al., 2014; Troche and Altmann, 2012). However, other studies found no difference between PD patients and control participants in terms of sentence length, complexity and accuracy (Murray and Lenz, 2001; Vanhoutte et al., 2012), and even increases in the use of subordinating conjunctions and dependent clauses (García et al., 2016). Overall, the hypothesis that changes in sentence production in PD constitute an adaptation to motor-speech difficulties in terms of "economy of speech" is not supported. The fact that PD patients use more optional subordinating conjunctions and dependent clauses (García et al., 2016) and that they produce less informative speech (Murray, 2000) does not support an optimisation of speech to convey as much essential information in as little speaking time as possible. However, it is possible that these changes reflect adaptations to avoid disruptions in the flow of conversation (Illes et al., 1988; Illes, 1989; García et al., 2016), although PD patients' difficulties at the pragmatic level (Holtgraves and McNamara, 2010; McNamara and Durso, 2003) and the fact that they are relatively unaware of these difficulties (McNamara and Durso, 2003) make it unlikely.

Overall, the literature shows that motor-speech disorders cannot be the sole cause of sentence production deficits in PD. Murray (2000) found that difficulties were not related to dysarthria severity. Walsh and Smith (2011) found that increased length and sentence complexity negatively affected the performance of both PD patients and controls, for both behavioural and motor-speech kinematic measures. However, although length and complexity did not lead to a disproportionate increase in difficulty for PD patients compared to controls in sentence production, PD patients were impaired in complex sentence comprehension and their

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performance correlated with production accuracy and some motor-speech measures (reduced loudness, reduced accuracy precision).

2.2

Sentence Comprehension

A major element that challenges the motor-speech hypothesis of sentence production deficits is the presence of sentence *comprehension* deficits in PD. Since motor demand is minimal in sentence comprehension tasks, other factors are likely involved in PD patients' difficulties.

Nevertheless, it should be mentioned that studies of PD patients identified links between motor-speech performance and sentence comprehension (Hochstadt et al., 2006; Lieberman et al., 1992), but the relationship is not systematic (Hochstadt et al., 2006) and other studies found no relationship (Geyer and Grossman, 1994). The interaction between language production and language comprehension remains an intriguing topic (MacDonald, 2013; Pickering and Garrod, 2007). Motor-speech disorders and sentence processing impairments are found together in different clinical entities, like agrammatism in Broca's aphasia (Thompson and Bastiaanse, 2012) and the non-fluent/agrammatic variant of Primary Progressive Aphasia (Gorno-Tempini et al., 2011). Studies of language development provide support for a very close relationship between the maturation of the motor speech system and the emergence of more abstract/conceptual aspects of language processing capacities (Malas et al., 2015; Nip et al., 2011). Also, as further explained in the second part of this review, language and motor processing interact, not only in the context of speech production, but also at the semantic level.

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In the case of PD, the effect of dopamine replacement therapy over the performance should be closely monitored to clarify the impact of motor impairment over sentence production and comprehension deficits since dopamine replacement therapy has been shown to have an impact on different aspects of motor speech (prosody, voice quality, articulation, etc.) in this disease (De Letter et al., 2007; Poluha et al., 1998; Schulz and Grant, 2010). In future studies, patients' medication state should be carefully monitored and ideally, closely matched between speech and language testing in order to draw conclusions over their relationship.

The first studies of complex sentence comprehension in PD assessed a variety of sentence structures and concluded that difficulties were caused by a grammatical/syntactic impairment (Geyer and Grossman, 1994; Grossman et al., 1992a; Lieberman et al., 1990, 1992). However, many of these early studies noted that performance was also influenced by cognitive processes such as attention and executive functions (Geyer and Grossman, 1994; Grossman et al., 1992a; Lieberman et al., 1990, 1992).

As more studies were published, the cognitive hypothesis became more prominent and authors began to interpret sentence comprehension difficulties as one of the many consequences of the fontal-executive cognitive impairment which is characteristic of early cognitive deficits in PD.

The types of sentences that were assessed was narrowed-down to target sentences that were longer and/or more grammatically complex. Overall, studies show that length cannot in itself account for the pattern of performance seen in PD (Colman et al., 2011; Geyer and

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Grossman, 1994), and that grammatical complexity is an important factor in the performance. Several factors of grammatical complexity have been explored, including the correspondence to the canonical structure.

2.2.1

Canonical vs. Non-Canonical Sentences

Canonical sentences are those in which the order of constituents respects the most common ordering of thematic roles: the subject (who performs the action) is presented first, followed by the verb (the action itself), and the object (who undergoes the action). Canonical or subject-verb-object (SVO) sentences are considered to act as a template of sentence processing. Consequently, all the sentences that cannot be correctly processed by applying canonical sentence heuristics would be more complex and more cognitively demanding (Kemmerer, 1999). Considering the presence of cognitive impairment, PD patients are expected to have difficulties understanding sentences that violate expectations regarding canonical order of presentation, i.e., sentences in which the component performing the action is presented *after* the component that undergoes the action. Passive sentences (e.g, "*The cat is chased by the dog*") are a type of non-canonical sentence. A strong version of the hypothesis according to which PD patients are impaired in non-canonical sentence comprehensionwould consist in expecting patients to systematically apply the canonical sentence heuristic and to commit systematic errors for non-canonical sentences. Kemmerer (1999) tested canonical vs. non-canonical versions of complex raising-to-subject sentences (e.g., canonical: "*It's easy for Bill to catch Susan*"; non-canonical: "*Susan is easy for Bill to catch*"). For sentences of equal grammatical complexity, he found that PD patients only had difficulties with non-canonical versions (Kemmerer, 1999). However,

patients did not commit systematic errors and their performance was at chance level, showing that they did not systematically apply the canonical heuristic. Overall, studies that tested passive sentences in PD reported inconsistent results. Some studies found that PD patients had significant difficulties with passive sentences (Colman et al., 2006; Hochstadt et al., 2006; Terzi et al., 2005). According to Hochstadt et al. (2006), PD patients would be impaired because they are unable to "switch away" from the canonical sentence template while processing passive sentences. However, other researchers did not find significant difficulties for passive sentences when PD patients were compared to healthy controls (Colman et al., 2011; Geyer and Grossman, 1994; Grossman et al., 1992a). Similarly to Kemmerer (1999), Grossman et al. (1992a) noted that the patients were not treating the first noun of passive sentences as the agent, or in other words, that they were not applying the canonical sentence heuristic. In fact, the non-canonical ordering of sentence constituents cannot fully account for the difficulties of PD patients. A closer look at studies shows that difficulties with passive sentences were revealed when processing demands were increased because of other factors such as length, absence of semantic cues, or increased grammatical complexity (Colman et al., 2006, 2011; Hochstadt et al., 2006; Hochstadt, 2009). As will be shown in the following section, several factors can mitigate the difficulty of non-canonical sentences and support sentence comprehension.

2.2.2

Factors that Support Sentence Comprehension

2.2.2.1.World-Knowledge

Word order is only one of the many cues that guide sentence comprehension. In fact, context and world-knowledge also plays an important role in supporting sentence processing (Hagoort et al., 2004; Lieberman, 1963). One aspect of world-knowledge can be assessed by comparing reversible and non-reversible sentences. A reversible sentence is a sentence in which the action is equally likely to be performed by both characters involved (e.g., a cat can chase a dog and vice-versa; an eagle can eat a worm but the opposite is very unlikely). Studies found that non-reversible sentences were easier to process than their reversible counterparts in PD (Grossman et al., 1992a; Hochstadt et al., 2006). This suggests that PD patients use world-knowledge to support the attribution of thematic roles ("*who does what to whom*"), even when sentences are more grammatically complex.

However, this effect could be confounded with the animacy of sentence constituents. Animate entities (e.g., humans, animals) are more likely to perform actions and inanimate entities (e.g., static objects) are more likely to undergo actions (Szewczyk and Schriefers, 2011). This could potentially create a confound in studies that manipulated reversibility by using an animate and an inanimate element in sentences (e.g., the nouns "cook" and "box", Hochstadt et al., 2006), since the attribution of thematic roles could be facilitated not only by the lack of reversibility, but also by expectations related to animacy. It should also be mentionned that some of the facilitation that is attributed to the lack of reversibility could be driven by probabilistic inferences about language, which are based on the frequency and plausibility of specific word sequences and co-occurrences (Chater and Manning, 2006). Probabilistic inferences are based on both distributional *and* semantic factors, which suggest that reversibility's exclusive focus on semantics constitutes an over-simplification.

Lastly, PD patients would also be influenced by expectations based on the chronological order of events. Patients have better performances when sentences present events in the order in which they actually occurred than when the order is inverted, as in sentences of the type "Before B, A". (Natsopoulos et al., 1991; Ye et al., 2012).

2.2.2.2. Morphology

The study of Ullman et al. (1997) reported that PD patients had more important difficulties for the production of the regular English past tense, formed by adding –ed to the verb stem (e.g., walk: walked) than the irregular past tense (e.g., tell: told). According to Ullman et al. (1997), linguistic rule application, including regular past tense inflection, would depend on procedural memory, which would rely on the basal ganglia and their connections to the frontal lobe. The retrieval of linguistic elements that cannot be produced by rule application, such as irregular verbs in the past tense, would depend on declarative memory, supported by the temporal lobes. This proposal was formalised as the Declarative/Procedural model of language (Ullman et al., 1997; Ullman, 2001).

In the following years, several studies attempted to reproduce the results of Ullman et al. (1997) with PD patients but obtained mixed results. Longworth et al. (2005) found no evidence for a more severe impairment of regular past-tense inflection compared to irregular past tense inflection in PD, HD, and patients with lesions of the basal ganglia following stroke. Terzi et al. (2005) found significant difficulties for *both* the inflection of regular and irregular verbs when comparing PD patients to normal controls. Colman et al. (2009) created a verb production ability scale based on their participants' performance in verb production. PD patients obtained lower scores than control participant on the ability scale, but their performance was not influenced by verb regularity. Interestingly, the scores on the verb production ability scale correlated with set-

switching and working memory in the PD group. Penke et al. (2005) and Macoir et al. (2013) found no differences between PD patients and controls for both regular and irregular verbs. These studies do not support the claim that basal ganglia play a central role in linguistic rule application. In fact, several aspects of performance indicate an influence of executive functions, more specifically inhibition and set-switching, over performance in the production of inflected verbs (Longworth et al., 2005; Colman et al., 2009). However, the automatic processing of morphological markers would be preserved, as shown by normal priming effects (Longworth et al., 2005).

Morphology can play an important role in sentence processing by providing cues that support the comprehension of a sentence. For example, passive sentences are characterised by past-tense inflection on the main verb and the preposition "by". However, studies have shown that patients with PD have difficulty paying attention to those cues, which could limit their contribution to comprehension (Grossman et al., 1992b, 1993, 2002a; Lee et al., 2003). On the contrary, other studies have underlined the contribution of morphological cues to good performance (Geyer and Grossman, 1994; Kemmerer, 1999).

To clarify the contribution of morphological markers to sentence processing, modulation by dopamine replacement therapy should be carefully monitored. Studies have shown that dopaminergic treatment is tuned specifically to improve motor symptoms and that it might be detrimental to cognition (Cools et al., 2001; Cools, 2006). A study using a selection task has shown that different aspects of cognition could be differentially impacted by dopamine, depending on which part of the basal ganglia they rely on (MacDonald et al., 2011). The striatum can be divided in a dorsal part and a ventral part. As MacDonald et al. (2011) put it, "[d]orsal

striatum prevents attention being directed to a single salient feature and promotes integrating more varied influences to reduce bias in selection". Ventral striatum, on the other hand, would be in charge of learning and would signal the need or the possibility for learning, which is consistent with its link with reward behaviour. In PD, the dorsal striatum is more affected by dopamine deprivation than the ventral striatum. Consequently, functions that are dependent on the dorsal striatum are more likely to be improved by dopamine. Functions that depend on the ventral striatum could be negatively affected because dopamine replacement therapy would place it in a situation of "overdose" (Cools, 2006). Considering that sentence comprehension requires the integration and consideration of a varieties of cues, it could be improved by dopaminergic medication (MacDonald et al., 2011). More specifically, dopaminergic medication would promote shifting attention to less salient (e.g., morphological markers) or previously ignored cues (e.g., non-reversibility of roles in a complex sentence vs. a simple declarative sentence), which would lead to improved performance in sentences in which they can guide thematic role mapping. Considering that the ventral striatum is mostly involved in learning and that sentence comprehension is an overlearned behaviour in adult speakers, it is unlikely that it would be made worse by dopaminergic medication. Results of studies comparing the performance of PD patients ON and OFF medication show improvements (Grossman et al., 2001; McNamara et al., 1996) or no change (Skeel et al., 2001) in the ON vs. the OFF state, which is consistent with the idea that dopaminergic medication could improve performance under certain circumstances (Grossman et al., 2001; McNamara et al., 1996) but is unlikely to impair it (Skeel et al., 2001).

Overall, considering the fact that sentence processing is guided by a variety of factors, an explanation in terms of non-canonicity or violation of the expected order of sentence constituents

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seems overly simplistic and cannot fully account for sentence comprehension difficulties in PD patients. Other sources of sentence complexity have been explored.

2.2.3

Sentences with Subordinate Clauses

Several studies tested the comprehension of sentences with subordinate clauses, especially center-embedded subordinate clauses (CESC) (Angwin et al., 2005, 2006, 2007; Bocanegra et al., 2015; DeVita et al., 2001; García et al., 2017b; Gross et al., 2012; Grossman et al., 1991, 1992a, 2000, 2001, 2002a, 2002b, 2003; Hochstadt et al., 2006; Hochstadt, 2009; Lee et al., 2003; Seidl et al., 1996; Walsh and Smith, 2011). Many of these studies contrasted two types of CESC sentences: subject-relative clauses and object-relative clauses. As their names indicate, subject-relative (SR) clauses refer to the subject of the sentence (e.g., *The boy [that kissed the girl] was tall*") while object-relative (OR) clauses refer to the object of the sentence (e.g., *The boy [that the girl kissed] was tall*"). SR and OR sentences have received a lot of attention in the field of psycholinguistics due to the finding that OR sentences are more difficult to process than SR sentences, as shown by longer reading latencies for OR sentences in normal, competent speakers (Heider et al., 2014; Roland et al., 2012; Van Gompel, 2013).

Results are globally consistent with the idea that CESC sentences are more difficult to process in PD (Grossman et al., 1991, 1992a; Hochstadt et al. 2006; Hochstadt, 2009), and many studies show a more pronounced impairment for OR sentences compared to SR sentences (Angwin et al., 2005, 2006, 2007; Grossman et al., 2000, 2002a, 2002b; Lee et al., 2003; Seidl et

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al., 1996; but see Gross et al., 2012; Walsh and Smith, 2011). However, not all PD patients would be equally affected in sentence comprehension, and studies addressed this heterogeneity.

2.2.3.1

Variability of performance in Sentence Comprehension

Some studies of sentence comprehension subdivided their group of PD patients with normal cognition in subgroups of good and poor sentence comprehenders (Angwin et al., 2005, 2007; Grossman et al., 2000, 2002a, 2002b). Poor comprehension of complex sentences was associated with different factors, including limitations in general cognitive resources (Grossman et al., 2000), impaired planning and inhibitory control (Grossman et al., 2002a) and delayed lexical activation (Angwin et al., 2005, 2007; Grossman et al., 2002b). On the other hand, there is evidence that good performance could be supported by the recruitment of additional brain regions during sentence comprehension.

Early in the disease, PD patients can recruit brain regions that are not usually recruited by normal controls during the performance of executive and sequence-learning tasks, and this additional recruitment is linked with better performances (Carbon et al., 2010; Dagher et al., 2001; Nagano-Saito et al., 2014). For example, Nagano-Saito et al. (2014) found that better verbal episodic memory scores on the RAVLT was correlated with increased hippocampus activation during the execution of a set-shifting task. This is coherent with the results of Carbon et al. (2010) who found that PD patients with good performance recruited the hippocampus during a sequence-learning task while normal controls and PD patients with poor performance

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did not. These findings suggest that PD patients could recruit the hippocampus in tasks in which it is not normally required to achieve normal levels of performance. Neuroimaging studies of sentence comprehension in PD are consistent with the idea of activation of additional brain region as a means of compensation (DeVita et al., 2001; Grossman et al., 2003). Using fMRI, DeVita et al. (2001) found no caudate activation and less activation of the right posterolateral temporal cortex in PD patients compared to controls for sentences that put high demands on working memory. To achieve a level of comprehension equivalent to that of control subjects, PD patients recruited other brain regions that are associated with verbal short-term memory and that are not recruited by controls (left parietal cortex, right premotor-dorsal inferior frontal cortex, and right parietal cortex). Similarly, Grossman et al. (2003) found less activation in PD patients compared to controls in the striatum, specifically for sentences that put high demands on working memory. PD patients also showed less anteromedial prefrontal and right posterolateral temporal cortex activation in all sentence conditions. To achieve normal levels of performance, patients recruited several brain regions that are not activated in controls and that are associated with working memory (left posterolateral temporal-parietal cortex, right inferior frontal cortex and right parietal cortex). Patients that are still able to benefit from compensation mechanisms might not show sentence comprehension impairments in the early stages of the disease.

However, considering that the concept of MCI is relatively new, especially in the context of PD (Litvan et al., 2012), some studies might have included people that would fit the current criteria for MCI in groups of patients without cognitive impairment.

Recent studies that carefully controlled for normal cognition at inclusion did not find

impairment in PD patients but found impairment in PDD and in Lewy Body dementia patients (Gross et al. 2012; Grossman et al., 2012). It is possible that some of the effects observed in older studies were driven by PD-MCI subjects but it is unlikely that the inclusion of PD-MCI patients accounts for all the differences with normal controls. Grossman et al. (2002b) estimate that between 45 and 65% of PD patients without dementia have sentence comprehension difficulties, which exceeds the prevalence of MCI in PD (26.7%, between 18.9 and 38.2% depending on studies; Litvan et al., 2012). Also, studies show that performance in sentence comprehension can be modulated by increasing cognitive demands. Studies that tested sentence comprehension while patients also needed to perform a concurrent task showed that increasing the cognitive load had a negative impact on performance, sometimes causing performance that was initially equivalent to that of the control group to fall below the normal range (Grossman et al., 2000; Seidl et al., 1996). Studies or experimental conditions that reveal difficulties in PD patients with normal cognition could indicate the level of cognitive demand required to exceed compensation capacities and identify difficulties in PD patients at the very onset of mild cognitive deficits. The cognitive factors that are linked with sentence comprehension difficulties could indicate which manipulations are necessary to influence performance.

2.2.3.2

Explaining the Complexity of OR Sentences

Studies that compare OR and SR sentences have identified different factors to explain why OR sentences are more difficult to understand. Even though OR sentences do not follow the canonical order of sentence component presentation, this factor was not put forward by

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psycholinguistic studies to explain why they are harder to process. Instead, the most prevalent explanations can be summarized in three theories (reviewed in Van Gompel, 2013; see also Just and Carpenter, 1992, for a similar proposition focused on storage and computation costs). According to the first theory (Gibson, 1998), OR sentences would be more complicated to process because they are associated with increased storage and integration costs. In OR sentences, many words separate the object and its dependent verb, which increases memory demands and delays the integration of the object and the verb. An alternative account (Lewis and Vasishth, 2005) proposes that processing difficulties occur because of interference in working memory. In OR sentences, the integration of the object is still pending when the subject is presented, which could cause interference in integration and role attribution. Lastly, expectation-based syntactic comprehension (Levy, 2008) suggests that difficulties occur when the presented structure does not match expectations. In such cases, allocation of attentional resources has to be re-ranked in order to adapt processing to the sentence at hand. Because OR sentences are less frequent than SR sentences, in a sentence that starts with "*The boy*", the continuation "*that the girl kissed* […]" would be less expected and more resource demanding than the continuation "*that kissed the girl* […]". Overall, it is likely that all suggested factors (storage and integration, interference, and re-ranking of attentional resources) contribute to performance (Van Gompel, 2013).

These theories are coherent with cognitive factors that have been related to sentence comprehension difficulties in PD. The storage and integration account and the interference theory are consistent with studies that linked syntactic difficulties with impaired short-term and working memory (Grossman et al., 2003), attention and frontal-executive deficits (Grossman et

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al., 1991, 1992a, 1992b, 2001, 2002a; Lee et al., 2003), and general limitation in cognitive resources (Grossman et al., 2000; Seidl et al., 1996). Since it is crucial that the integration happens in a timely manner as sentence constituents are encountered, the interference theory is also coherent with studies that relate impaired sentence comprehension with delayed lexical-semantic activation (Angwin et al., 2005, 2006, 2007; Grossman et al., 2002b; Lee et al., 2003). Interesting parallels can also be drawn with the study of Friederici et al. (2003), which used other types of sentences. Using ERP, this study showed that PD patients presented normal processing of semantic violations, and normal early automatic syntactic processes. However, later-occuring syntactic and semantic integration processes were altered in these patients. Lastly, expectation-based syntactic comprehension and the necessity to re-consider the original allocation of attentional resources is consistent with studies that identified deficits of executive functions, and especially of set-shifting, as the cause of sentence comprehension difficulties (Hochstadt et al., 2006; Hochstadt, 2009). In fact, the claims of expectation-based syntactic comprehension are very similar to the explanation proposed by Hochstadt (2009). Set-shifting would be critical in sentence comprehension to adapt processing when a less expected continuation to a sentence is presented. This is consistent with the idea that lesions of the basal ganglia have little impact on behaviours that are already well-learned and consolidated, but that they alter performance in situations that require flexible adaptation to changing conditions and formation of new habits (Marsden and Obeso, 1994; Graybiel, 2008). The idea that set-shifting could be involved in language processing is also consistent with findings on phonemic and semantic categorisation that show that set-shifting with lexical and semantic rules depends on the same brain regions that are activated in set-shifting with non-verbal material (Simard et al., 2010, 2013).

Expectations in sentence processing would emerge as the consequence of differences in the distributional frequencies of different sentence types. However, expectations would also emerge "online" as a consequence of the broader discourse context. In fact, a criticism that can be made about sentence comprehension studies is that they may not reflect functional capacities of PD patients in real-life communication contexts. Some features of studies' design could have a considerable influence over performance.

2.2.3.3

The Influence of Study Design Over Performance

For reasons ranging from feasibility to consistence and control of confounding variables, target sentences are presented in isolation in language studies. However, this could create a confound in studies that compare OR and SR sentences. Nouns that are included in OR clauses (like "*girl*" in "*The boy that the girl kissed was tall*") are usually already part of the broader discourse context whereas nouns in SR clauses are usually new elements (Roland, et al., 2012). This could create a potential confound between OR sentences for which an antecedent is expected but is not provided, and SR sentences for which an antecedent is not necessarily expected. In fact, studies show that normal subjects have longer reading times for sentences that violate the antecedent expectation, but that difficulty is eliminated by providing appropriate antecedents (Mak et al., 2008; Roland et al., 2012). Testing sentences with and without providing a context, and varying the extent to which the following sentence fits the reader's expectations could further clarify the causes of sentence comprehension deficit in PD.

The necessity to flexibly adapt oneself when expectations are violated is a recurrent theme in sentence comprehension studies. This relates to set-shifting, which was linked with sentence processing difficulties in PD (Colman et al., 2011; Hochstadt et al., 2006; Hochstadt, 2009). However, to the best of our knowledge, no study has directly questioned the extent to which the impact of set-shifting on performance would be due to a task effect. Studies that test sentence comprehension in PD typically contrast several types of sentences and present them in a pseudo-random order. It is possible to ask if the successive alternation of different sentence structures that include similar elements or characters but that are not coherently related to one another is in part responsible for the effect seen in sentence comprehension studies in PD. Furthermore, studies include a higher proportion of complex sentences, which could place unusual processing demands on the participants. Not only are these sentences less frequent than sentences with a simpler structure (Roland et al., 2007), but their presentation in immediate succession does not reflect the usual conditions of reading a text or having a conversation. In fact, speakers tend to reuse the same sentence structures in order to reduce difficulties (MacDonald, 2013). Also, sentence structure priming has been demonstrated in sentence production (Bock, 1986) and comprehension (Arai et al., 2007; see Frazier, 2013, for a review). It is therefore plausible that sentences influence other sentences that are presented later in the list, causing either facilitation or perturbation of performance.

A recent study of picture naming in bilingual PD subjects is in line with this idea (Cattaneo et al., 2015). In this study, patients were asked to name pictures in Catalan or in Spanish. The target language was indicated by a cue on each trial, and the authors compared consecutive trials in which the target language was the same vs. consecutive trials in which it was different. They found that PD patients were more affected by having to switch from one

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language to another than normal controls. The results also support the involvement of the basal ganglia in language control. In studies of sentence comprehension, the extent of task-design-related set-shifting effect could be assessed by comparing the performance between trials that require and do not require a set-shift, either in terms of processing the same or different sentence structures, or in terms of processing a sentence that corresponds or not to expectations. This might also provide results that are more relatable to functional communication capacities of PD patients.

2.3

Summary

In summary, even though the precise linguistic factors that make some sentences more complex to understand than others are still debated, both studies of normal subjects and studies of PD patients emphasize the necessity to be able to flexibly switch between cues or modes of processing, and to reorganize processing strategies when the sentence at hand is not conform to expectations. Sentence comprehension is guided by a variety of cues. While some of these cues might be more or less important depending on the context, none of them should be ignored, nor given a disproportionate importance compared to the others. Discourse context and experience with language shape expectations, and processing is complicated when these expectations are not met. Impairment of sentence comprehension can be conceived as a multi-faceted set-shifting disorder in PD, consistent with the conclusions of other authors (Colman et al., 2011; Hochstadt et al., 2006; Hochstadt, 2009). Studies of sentence comprehension can bring a significant contribution to reveal early deficit and track their progression over time.

3. Lexical-semantic Processing

The capacity to access the meaning conveyed by words and to select the appropriate words to express a certain meaning is central to language processing. While word-finding difficulties and single-word comprehension deficits are not typically mentioned among the characteristic features of PD, several studies report different forms of lexical-semantic difficulties in PD patients. As will be shown in the following sections, these difficulties have long been thought to be the consequence of frontal-executive deficits. However, recent studies reveal the presence of difficulties that appear to be essentially semantic in nature.

3.1

Early Studies of Executive Deficits and Language Production

Verbal fluency tasks are often used to assess language and cognition in neurodegenerative diseases, including PD (Henry and Crawford, 2004; Taler and Phillips, 2008). Typically, this type of task requires participant to generate a maximum number of words that conform to a criterion (e.g., words that start with a certain letter or words from a specific semantic category) within a given period of time. Both letter and category (semantic) fluency put heavy demands on executive functions and rely on the frontal lobe (Henry and Crawford, 2004; Williams-Gray et al., 2007). As such, impairment of verbal fluency has been associated with frontal-executive impairment (Henry and Crawford, 2004; Koerts et al., 2013). However, because these tasks involve word generation, they are both influenced by lexical-semantic processes (Clark et al., 2014), although to different degrees. While semantic knowledge may support letter fluency to

some extent, the preservation of semantic associations between members of a category and their subordinate term is crucial to the performance of category fluency (Henry and Crawford, 2004; Taler and Phillips, 2008).

Performance of PD patients on verbal fluency tasks have been reported in several studies, with varying results. The overall pattern of performance shows that semantic fluency is more frequently impaired than letter fluency in PD (Auriacombe et al., 1993; Koerts et al., 2013; Zec et al., 1999; see Henry and Crawford, 2004 for a review and meta-analysis) although patterns of impairments in both variants (Obeso et al., 2012; Suhr and Jones, 1998) and preserved semantic fluency with impaired letter fluency (Bayles et al., 1993; Epker et al., 1999) have also been reported. Ellfolk et al. (2014) found that only letter fluency, and not category and alternating fluency, was associated with caudate gray matter volumes at the early stages of the disease. The complex and inconsistent pattern of results drawn by these studies could be explained by several factors.

3.1.1

Heterogeneity and Modulation of Performance

Earlier studies conducted before the creation of the entity of MCI might have included patients at different stages of the disease. PD is characterized by early frontal-executive deficits that can remain mild and stable in some patients, but goes on to progress to more severe and more generalized cognitive impairment in others (Aarsland et al., 2010; Muslimovic et al., 2007; Sauerbier et al., 2016). Depending on factors like recruitment procedure and selection bias, some studies might have included people with MCI in different proportions, which could explain some of the discrepancies between studies. In addition, patients that do not have MCI might have

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benefited from the recruitment of other brain regions as a means of compensation for the decrease in activation of the fronto-striatal loop, as shown in studies of cognition (Carbon et al., 2010; Dagher et al., 2001; Nagano-Saito et al., 2014) and sentence comprehension (DeVita et al., 2001; Grossman et al., 2003). Overall, the inclusion of MCI patients in normal PD groups and the presence of compensation in PD non-MCI could explain why some studies found verbal fluency difficulties in PD (Auriacombe et al., 1993; Bayles et al., 1993; Donovan et al., 1999; Epker et al., 1999; Randolph et al., 1993; Zec et al., 1999) while others only reported difficulties in PD with dementia (Piatt et al., 1999a; Testa et al., 1998; Tröster et al., 1998).

Even in studies of PD, results vary. As already mentioned, PD is characterized by an impairment of the dorsolateral prefrontal-striatal loop (Middleton and Strick, 2000; Monchi et al., 2001, 2004, 2007; Tekin and Cummings, 2002; Zgaljardic et al., 2006). Considering the possibility of patients to compensate deficits by recruiting other brain regions (Carbon et al., 2010; DeVita et al., 2001; Grossman et al., 2003; Nagano-Saito et al., 2014), regular conditions of the verbal fluency task might not be demanding enough to reveal difficulties in patients that still benefit from compensation. However, variants of the fluency task can modulate executive demands and assess their impact on performance.

Alternating fluency requires patients to alternate between two different letters or two different categories, or between a letter and a semantic category. By enhancing shifting requirement, it is assumed that alternating fluency puts heavier demands on executive functions than regular verbal fluency (Downes et al., 1993; Zec et al., 1999). The impact of increasing the executive burden varies from study to study. Downes et al. (1993) found no difference between PD patients and normal controls in regular letter and category fluency and in intra-domain (letter-letter, category-category) alternating fluency. However, PD patients were impaired in the

letter-category alternating fluency condition. Zec et al. (1999) found no impairment in letter and American States fluency but patients were impaired at generating animal names and boys' names. In contrast to Downes et al., (1993), the patients were also impaired on tree trials of intra-domain alternating fluency, including two category-category trials, and their deficit was more severe for alternating that standard fluency (Zec et al., 1999). Taken together, these results show that increasing the executive demands of the fluency task can reveal difficulties in patients that do not have difficulties in the standard conditions of the task. Increasing demands might be sufficient to reveal difficulties in patients with very mild cognitive difficulties and preserved aspects of cognition.

On the other hand, executive demands can be lowered by providing cues during the execution of the task. Randolph and al. (1993) compared PD, AD and HD patients' performance on standard and a cued category fluency tasks (animals and items of the supermarket). The two categories were counterbalanced across tasks so that half of the participants performed the cued version for animals and the other half for items of the supermarket. All groups were impaired compared to normal controls on the standard, un-cued version of the task. However, the addition of cues (e.g., for animals: animals that people keep in their homes as pets) significantly improved the performance of PD and HD patients, PD patients even reaching the level of normal controls. However, the cues did not improve performance in AD. The authors concluded that impaired access to semantic representations would be responsible for impaired category fluency in PD and HD, while AD patients would have an impairment of semantic stores. They also suggested that semantic access would depend on the integrity of the prefrontal cortex, which is coherent with studies in vascular aphasia (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). Interestingly, other authors have suggested that the basal ganglia hold a central role in regulating

semantic access (Copland, 2003; Longworth et al., 2005). The possibility to compensate impairments through experimental manipulations and interventions reported by Randolph et al. (1993) is compatible with the hypothesis of impaired semantic access. Impaired semantic access is susceptible to be momentarily facilitated or even restored, while impaired semantic stores cause more stable and permanent deficits.

The different nature of semantic impairment seen in PD compared to AD patients denotes another factor that could account for discrepancies. Recent studies have shown that between 30 and 40% of PD patients with dementia have concomitant AD neuropathology (Kurosinski et al., 2002; Sabbagh et al., 2009). These patients could have a different cognitive progression compared to those that are only affected by synucleinopathy. Considering that AD is associated with semantic deficits in the middle to late stages of the disease (Taler and Phillips, 2008), the concomitant presence of AD could explain the presence of more generalized, and not easily compensated semantic deficits. In fact, impaired category fluency has been identified as a marker of progression to dementia in PD (Williams-Gray et al., 2007, 2009).

There is considerable heterogeneity in the performance of PD patients reported in different studies. The stage of the disease, the progression of cognitive deficits and apparition of MCI, and the presence of concomitant AD pathology could all account for this heterogeneity. As will be shown in the following sections, one feature of PD's cognitive portrait could help clarify the progression of cognitive impairment over time: the disproportionate impairment for action words with a rich semantic motor content compared to other types of words.

3.2

Specific Deficit for Action Words: A Unique Feature of PD

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Words that designate actions are typically verbs while words that designate objects, both natural and man-made, are typically nouns. Over the years, several studies have emphasized the dissociation of performance between nouns and verbs in PD. The first study to address this dissociation used a variant of the verbal fluency task, action fluency (Piatt et al., 1999a). Action fluency requires participants to name as many "things that people do" as possible in a given period of time. Morphological variants (e.g., play, playing) and phrases built with the same verb (e.g., play hockey, play football, etc.) do not count towards the total number of words produced (Piatt et al., 1999a, 1999b, 2004; Woods et al., 2005). Based on studies that showed dissociable networks involved in the retrieval of nouns and verbs (Cappa and Perani, 2003; Damasio and Tranel, 1993; Daniele et al., 1994), Piatt et al. (1999a, 1999b) predicted that action fluency would be sensitive to fronto-striatal pathophysiology. Previous studies had shown that nouns would be represented in temporal regions whereas verb retrieval would be supported by frontal neural circuits (Cappa and Perani, 2003; Damasio and Tranel, 1993; Daniele et al., 1994).

Piatt et al. (1999a) studied letter, category and action fluency in 77 PD patients, including 20 patients with impaired cognition. The authors found no difference between normal controls and PD patients with normal cognition on any of the three fluency measures. PD patients with impaired cognition, however, showed deficits on the three fluency tasks compared to normal controls. Interestingly, their impairment on action fluency was significantly more severe than their impairment on letter and category fluency. The authors concluded that action fluency was useful to reveal fronto-striatal impairment, which would constitute a marker of progression to dementia. However, another study (Signorini and Volpato, 2006) showed impaired action fluency in non-demented PD patients. In this study, patients had a normal performance on letter and category fluency. Furthermore, the global pattern of performance remained stable over a

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two-year period. The authors concluded that impaired action fluency was indeed sensitive to fronto-striatal impairment but that it could not be considered as a marker of conversion to dementia in PD. Herrera et al. (2012a) studied dopamine medication modulation over letter, category and action fluency in 20 PD patients without cognitive impairment and 20 normal controls. PD patients were tested twice (ON dopamine medication and OFF dopamine medication) on each task, counterbalancing the order of ON vs. OFF performance between patients. PD patients were not impaired on any of the tasks when ON medication. However, compared with controls, they were impaired on letter and action fluency (but not on category fluency) while OFF medication. Also, their performance for letter and action fluency was significantly lower OFF medication compared with ON medication. Interestingly, an analysis of word frequency showed that the action verbs produced by PD patients OFF medication were of significantly higher frequency than those produced by normal controls. The authors concluded that patients OFF medication show specific deficits in tasks that depend more on the frontal lobe functions: letter fluency because of it is more essentially executive in nature, and action fluency because of verb retrieval's reliance on the frontal lobes. Authors concluded that dopamine treatment would restore frontal processing in PD patients with normal cognition.

Several other studies have shown a disadvantage or abnormal processing for verbs compared to nouns in a variety of tasks such as word generation (generating a word starting from a picture or another inducing noun or verb) (Crescentini et al., 2008; Herrera and Cuetos, 2013; Péran et al., 2003, 2009, 2013) naming (Bertella et al., 2002; Cotelli et al., 2007; Rodríguez-Ferreiro et al., 2009; Silveri et al., 2012) and priming (Boulenger et al., 2008).

Like the study of Herrera et al. (2012a) on action fluency, a number of studies have shown dopamine treatment effects over verb processing. Boulenger et al. (2008) found no

priming effects for identical verb pairs but normal priming for noun pairs when patients were OFF medication. The performance with verb pairs was restored to normal level by dopamine medication. Herrera and Cuetos (2013) found that patients OFF medication generated words that were less associated with their inducing word compared to when they were ON medication. Interestingly, this difference was only significant for words produced in response to verbs. Péran et al. (2013) showed that dopamine medication was associated with increased activation of the motor and premotor cortex during action generation and mental simulation of action. However, this increase in activation was not associated with an improvement of performance, which was lower for verb generation compared to object naming, whatever the dopamine treatment state of patients.

Overall, studies on the modulation of performance by dopamine replacement therapy show that performance can be modified by restoring the connectivity between the cortex and the basal ganglia. Some authors have concluded that the improvement in performance would be due to the restoration of frontal processing (Herrera et al., 2012a). However, the restoration of frontal processing by dopamine replacement therapy is controversial (Cools, 2006; MacDonald et al., 2011). In fact, dopamine replacement therapy would be optimized for the treatment of motor symptoms, to the potential detriment of cognition. As will be explained below, another possibility is that the facilitated access to verbs would be caused by the restoration of the motor loop.

3.2.1

Explaining the Specific Deficit for Action Words: From a Grammatical to a Semantic Distinction

The noun-verb dissociation generated a lot of research, not only in Parkinson's disease but also in aphasia and other acquired language disorders. Developments in brain imaging techniques allowed researchers to investigate the neural correlates of noun and verb retrieval directly, and to see if the retrieval of the two types of words was supported by two distinct neural circuits. Research report conflicting results, but the general conclusion is more compatible with the idea of a shared network that includes the left inferior frontal gyrus (not limited to Broca's area) as opposed to segregated processing for nouns in the temporal lobe and verbs in the frontal lobe (Crepaldi et al., 2011; Vigliocco et al., 2011). As made clear in reviews of the literature (Crepaldi et al., 2011; Vigliocco et al., 2011), words would not be organized according to grammatical categories in the brain, but would rather be represented differently according to their semantic content.

Most models of semantic cognition agree that regions involved in motor planning and execution (e.g., primary motor cortex and premotor cortex) and sensory perception (e.g., infero-posterior temporal lobe, temporo-parietal junction) are also involved in the formation and retrieval of related concepts (see Meteyard et al., 2012 for a review). In consequence, different categories of content would be represented in different regions of the brain depending on the sensory and motor processes that were involved in the acquisition of these contents (Barsalou, 2008; Binder and Desai, 2011; Coslett et al., 2002; Kiefer and Pulvermüller, 2012; Martin and Chao, 2001; Patterson et al., 2007; Pulvermüller et al., 2005, Pulvermüller, 2005). For example, typical verbs are words that designate actions. Therefore, their representation is rich in motor content. Importantly, this motor content is supported by regions that are directly involved in motor planning and execution, such as the primary motor cortex and premotor cortex (Barsalou, 2008; Binder and Desai, 2011; Coslett et al., 2002; Kiefer and Pulvermüller, 2012; Martin and

Chao, 2001; Patterson et al., 2007; Pulvermüller et al., 2005, Pulvermüller, 2005). In comparison, the semantic representation of nouns, which typically designate objects, is constituted mostly of perceptual/sensory content (e.g., shape, colour, etc.). This content is represented in the infero-posterior temporal lobe , for example (Patterson et al., 2007). This means that the production of action words would depend more heavily on the preservation of motor semantic features, and incidentally, on the preservation of motor brain areas, than the production of other contents. Importantly, this difference would be independent of grammatical category, such that the retrieval of nouns that have a high motor content (e.g., keyboard, shovel) would also involve motor brain areas (Oliveri et al., 2004).

Research shows that the primary motor cortex is not simply a static motor control structure and that it is involved in the acquisition of representation patterns that regulate skilled motor actions and learning (Sanes and Donoghue, 2000). Interestingly, some studies even suggest that these patterns are also involved in cognition. For example, changes in primary motor cortex neurons' discharge rates have been observed when monkeys that remained immobile had to wait for an instruction to initiate movement (Tanji and Evarts, 1976). According to Sanes and Donoghue (2000), these results and other consistent results that followed "indicated that [primary motor cortex] neurons could hold premotor information for short periods, which suggests that [these] neurons might exhibit the functional equivalent of elementary memory functions". It is possible to think that this premotor information and the representation pattern that underlies it would correspond to the motor features of semantic motor content. Consequently, the deterioration of motor control induced by the alteration of the motor cortico-striatal loop in PD could also result in impaired access to the semantic motor content of action words.

Instead of focusing on the dissociation between nouns and verbs as two different grammatical categories, recent studies have narrowed their focus on words' motor content. Herrera et al. (2012b) had raters judge the motion content of 100 verbs and this rating was used to select two subsets of 25 verbs that have a significantly different rate of motion content. Overall, PD patients had more difficulties to name verbs compared to normal elderly controls. The performance for verbs with a high motion content was lower than for low motion content in the PD group but not the control group, and performance was negatively affected by the level of motion content at the item level in the PD group. Fernandino et al. (2013a) compared the performance of non-demented PD patients and healthy controls for action and abstract verbs in a lexical decision with priming and a semantic similarity judgment task. In lexical decision, both groups showed near-perfect performances in terms of accuracy. However, healthy controls were faster to respond to action verbs than abstract verbs but this difference was not significant in PD patients. The effect of priming was significantly higher in the control group, and showed a trend towards higher priming for action compared to abstract verbs, while PD patients showed the opposite trend. In semantic similarity judgment, both groups were significantly slower to respond to action verbs than abstract verbs, and on average, PD patients made more errors for action compared to abstract verbs. The same group of authors (Fernandino et al., 2013b) showed that PD patients took more time to judge if a sentence made sense if it included an action verb than an abstract verb, even when the action verb was used in its figurative meaning.

Other studies investigated motor-language coupling through the use of the Action Compatibility Effect (ACE) (Cardona et al., 2014; Ibáñez et al., 2013). In the ACE paradigm (Glenberg et al., 2008a, 2008b; Glenberg and Kachak, 2002), participants are asked to push a button as soon as they understand the meaning of a sentence. The ACE is shown by faster

response time when the task's response mode (e.g., pushing on a button with an opened hand (OH) vs. a closed hand (CH)) matches the way the action in the sentence is performed (e.g., clapping (OH) vs. hammering (CH)). The ACE is coherent with models that claim that action semantics is represented in motor brain areas (primary motor cortex, premotor cortex, SMA). According to this view, the ACE would emerge as a form of priming of the action verb over the action that needs to be executed. Ibáñez et al. (2013) found a significantly reduced ACE in early PD patients with normal cognition compared to healthy controls. Subtraction analyses within groups showed that contrary to healthy controls, PD patients showed no advantage for compatible sentences compared to incompatible or neutral sentences, which included verbs like "to visit". Furthermore, PD patients were impaired compared to healthy controls on an action semantics test (*The Kissing and Dancing Test*, KDT, Bak and Hodges, 2003). When considering only KDT items that involve hand movement, the authors found a significant negative correlation between hand-item errors and ACE in the PD group only. Cardona et al. (2014) compared patients with central motor brain impairments (PD), patients with peripheral motor impairments (neuromyelitis optica (NMO) or acute transverse myelitis (ATM) and normal controls. They found that ACE was altered in PD patients only. Also, PD patients were impaired on the KDT while the two other patient groups were not. Overall, studies using the ACE paradigm suggest that the activation of motor areas is necessary for normal action word processing. They also provide a demonstration of the bi-directionality of interactions between motor processing and language: motor processing influences the representation of concepts and semantic processing influences the execution of actions.

3.2.2

Independence of the Semantic Action Word Impairment from the Executive Impairment:

Implications for the Clinical Profile

The presence of disproportionate difficulties for semantic motor contents compared to other categories of content challenges the conclusion that language difficulties in PD are completely due to executive deficits. Bocanegra et al. (2015) tested if different forms of language impairments were dissociable in PD, and whether they were related to executive functions. They investigated several aspects of lexical-semantic processing (action naming, action semantics, and object semantics) and syntax in PD patients with normal cognition, PD-MCI, and normal controls. Both patient groups were impaired compared to their relative control groups on executive functions, and the PD-MCI group showed more severe impairments than the PD non-MCI group. Verb naming and action semantics (assessed with the KDT) were impaired in both PD patient groups compared to their relative control groups. The two patient groups obtained similar performances in both tasks. The difference between PD and normal controls remained significant after controlling for executive functions and the impaired performance of both patient groups remained similar after adjusting for executive functions. This pattern of result contrasts with the one observed for object semantics. Object semantics (assessed with the *Pyramids and Palm Trees Test* (PPT) – Howard and Patterson, 1992) was impaired in both patient groups compared with their control group, but was more impaired in PD-MCI than in PD non-MCI. Furthermore, the difference between the patient groups disappeared after adjusting for executive functions. Interestingly, both patient groups were impaired in the comprehension of two types of complex sentences, but only the performance for center-embedded sentences was related to executive functions. Results suggest that action semantic impairments are present early in the course of PD (even in the absence of MCI) and that they are independent of executive deficits. Another study by the same group of authors (Bocanegra et al., 2017) compared the performance

of PD-MCI and non-MCI patients in picture naming of objects with a high vs. low motion content, and action verbs with a high vs. low motion content. Compared to control subjects, PD-MCI patients were impaired for both nouns and verbs, at both levels of motion content. However, PD non-MCI patients presented a selective impairment for the naming of verbs with a high motion content.

Considering that deficits for semantic motor content are present early in the course of the disease, that they are independent of executive deficit and that the presence of more generalized semantic deficit in the form of impaired category fluency is a marker of progression to dementia (Williams-Gray et al., 2007, 2009), the attenuation in the difference between semantic motor content and other categories of content could be a marker of progression to dementia in PD. For example, Rodríguez-Ferreiro et al. (2009) found that both PD and AD patients had difficulties naming objects and actions compared to normal controls. However, PD patients with normal cognition had more difficulties in action naming compared to object naming. AD patients had similar performances for the two categories of content. The comparison of performance for semantic motor contents and other categories of content could reveal subgroups of "AD-like" patients among PD patients. The presence of AD pathology in these patients could be tested to see if it is coherent with the behavioral performance.

3.3

Summary

In summary, PD patients initially present executive deficits that can negatively impact word generation. Performance is negatively affected when executive demands are increased (Downes et al., 1993; Zec et al., 1999) and can be improved by lifting executive burden

(Randolph et al., 1993). In addition, action semantic deficits appear early in the course of the disease and in the absence of MCI (Bocanegra et al., 2015, 2017). This deficit is reflected by lower performance for action words in a variety of tasks (see Cardona et al., 2013, and García and Ibáñez, 2014 for a review). Recent studies that have focused on the semantic properties of action words, namely their rich motor content, have shown that deficits would be related to the impairment of motor planning and execution that characterizes PD (Ibáñez et al., 2013; Cardona et al., 2014). The apparition of difficulties that affect a broader range of categories of content and that cannot be modulated by experimental manipulation or treatment would be related to the progression to dementia and, in combination with other markers, might even indicate the presence of concomitant AD pathology.

4.

Discussion and Conclusion

In summary, many of the difficulties that are observed in the language domain in PD can be related to executive deficits. However, there seems to be an early impairment of motor semantic processing in PD, which is independent of executive deficits and is found even in the absence of MCI (Bocanegra et al., 2015, 2017). Language can be conceptualized as a very complex behavior that offers great possibilities in terms of experimental manipulation and performance modulation. Including more detailed evaluations of language in PD studies would be beneficial both for our understanding of this disease and the neurobiology of language.

The subdivision of non-demented PD patients in MCI and non-MCI subgroups and longitudinal studies of these subgroups will clarify the timing and order of apparition of

cognitive impairments, which can be provide crucial information regarding their origins. Consensual criteria for the identification of MCI in PD have only been published recently (Litvan et al., 2012) and some aspects of the criteria's application remain uncertain (e.g., use of a full neuropsychological battery vs. a screening tool, threshold to determine the presence of a significant impairment of performance, etc.). Provided that clear diagnostic criteria are described and that results for each patient groups are clearly reported, studies recruiting patients with PD non-MCI, PD-MCI and PDD in a transversal design can bring a very important contribution to the understanding of the progression of cognitive deficits in PD. However, longitudinal studies have the potential to reveal patterns of progression that are masked in transversal designs. Most importantly for research on cognition in PD, and for the clinical implications that they can generate, longitudinal studies are crucial to clarify the relationship between PDD and Lewy Body dementia (LBD). The fact that PDD and LBD are two distinct entities is still debated (Goldman et al., 2014; Walker et al., 2015). Regarding cognitive performance, impairments in executive functions are similar in PDD and LBD, but show some differences in the domain of memory (Goldman et al., 2014). A few studies conducted with LBD patients report language features consistent with those presented by PD patients. Patients with LBD (and PDD) have sentence comprehension difficulties (Gross et al., 2012; Grossman et al., 2012), and compared with AD patients, patients with LBD have similar performances in category fluency for animals, but lower performances in action verbal fluency (Delbeuck et al., 2013). These results would need to be expanded and replicated, but these initial findings indicate that language performance in LBD is coherent with the portrait observed in PD and PDD. It is possible to think that future studies could reveal influences and qualitative differences in language performance linked with the visuoperceptual dysfunction that is characteristic of LBD (Lambon Ralph et al., 2001).

Just as it is well-acknowledge that the progression of cognitive deficits may follow different paths in PD, is now well-acknowledged that PD is a complex disorder and that research needs to address this complexity. For example, other non-motor symptoms of PD include neuropsychiatric disorders (Eichenseer and Goetz, 2013; Sauerbier et al., 2016). Studies on the impact of neuropsychiatric disorders on language in PD are scarce, but a study showed that of all the cognitive domains, language is the most susceptible to be negatively affected by depression in PD (Fernandez et al., 2009). Another study compared depressed and non-depressed PD patients with normal cognition and found impaired semantic fluency in PD patients with depression only (Tremblay et al., 2012). Considering these studies and the fact that depression is associated with enhanced cortical atrophy in the supplementary motor area and middle temporal gyrus in PD (Hanganu et al., 2017), the influence of neuropsychiatric disorders on language performance should also be studied.

For a majority of PD patients, genetic causes do not seem to have a primary role in the development of the disease (de Lau and Breteler, 2006). However, autosomal dominant forms of PD have been identified (de Lau and Breteler, 2006; Guerreiro and Singleton, 2010). Recently, a study has identified mild sentence comprehension difficulties in asymptomatic first degree relatives of parkin (PARK2) or dardarin (LRRK2) mutation carriers (García et al., 2017b). Genetic vulnerabilities could be manifested by subtle alterations of basal ganglia function, and be translated in mild language difficulties affecting very specific domains. In addition, the ApoE ε4 allele, as well as SNCA and MAPT mutations have been identified as genetic risk factors for the development of dementia in PD (Guerreiro and Singleton, 2010). Considering these results, it is interesting to draw parallels between PD and what can probably be considered as the best known gene mutation associated with language and speech impairment, FOXP2. FOXP2 is a gene that is

required for the normal development of speech and language abilities. Mutations of this gene are associated with anomalies of the basal ganglia and lateral frontal areas (Enard et al., 2009; Lieberman, 2009; Vargha-Khadem et al., 2005). FOXP2 was discovered following the identification of a mutation in members of the same family who presented with severe and persistent speech and language disorders. On examination, affected members of the KE family presented with orofacial dyspraxia, and semantic and grammatical deficits. Brain imaging studies showed morphological and functional anomalies in basal ganglia and the frontal lobe (Vargha-Kadem et al., 2005). The introduction of the human version of Foxp2 in mice has been associated with increased synaptic plasticity and connectivity between the basal ganglia and cortex (Enard et al., 2009). This supports the view that in humans, these changes and the enhanced efficiency of cortico-striatal circuits that they induce are key to the mastery of a range of behaviors, including fine motor control involved in speech production, word recognition and retrieval of the associated semantic content, and sentence comprehension (Lieberman, 2009). Overall, these results indicate that FOXP2 would be important in the development of fronto-striatal networks, and that these networks would play an essential role in speech and language. Several alterations of speech and language are to be expected in diseases that alter or disrupt these networks, such as PD.

Difficulties manifested in language tasks are important from a research and a clinical point of view, whether they are seen as the consequence of central language impairment or of other cognitive deficits. They provide valuable information on a patient's global profile, they can have a predictive value, and they can influence the treatments and interventions offered to patients. Pharmacological and surgical treatments offered to PD patients are geared towards the improvement of the major motor symptoms that characterise the disease (tremor, rigidity). While

these treatments are associated with striking improvements of motor function, they are not accompanied by matched improvements in voice and motor speech (Brabenec et al., 2017; Poluha et al., 1998), and cognition (Combs et al., 2015; Cools et al., 2001; Cools et al., 2006). The introduction of new treatments that address these symptoms would constitute a major improvement for the quality of life of PD patients. In the meantime, PD patients and their families should be informed about the possible impact of the disease on their communication and about the different strategies and attitudes that can be adopted to facilitate communication in everyday life (Saldert et al., 2014; Paulmann and Pell, 2010).

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