Behavioral and neuroimaging studies on language processing in Dutch speakers with Parkinson's disease
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9.1 General discussion

The research reported in this thesis aimed at gaining a better understanding of Parkinson’s disease (PD) patients’ language comprehension and production deficits. Ultimately, a detailed description of PD patients’ language deficits can lead to the development of more effective communication advice for the patients and their caregivers. Moreover, PD permits us to see the effects of poorly functioning, yet still engaged basal ganglia (BG) (Dubois & Pillon, 1995; Marsden & Obeso, 1994) during language processing. Therefore, all experiments in this thesis were conducted with PD patients and their performance was compared to healthy control (HC) participants. The experiments examined production or comprehension of morphosyntactic structures and were either off-line behavioral experiments, on-line Reaction Time (RT) measures or functional Magnetic Resonance Imaging (fMRI) experiments. These methods provided us with the means to contribute to the discussion on the role of the BG in language processing.

As a result of the insights from reviewed cognitive research in PD, two major research questions were put forward (see Chapter 3, section 3.6).

Is syntactic sequencing during comprehension and production of sentences disturbed in patients with mild to moderate PD who are known to have difficulties in performing sequences of voluntary movements?

Does language sequencing interact with other cognitive processes, that is, executive functioning in PD patients with obvious motor disorders?

In this final Chapter 9, the major results of the behavioral (Chapters 4 and 5) and the event-related fMRI experiments (Chapters 7 and 8) are discussed in order to answer these two questions. Finally, directions for future research are suggested.

9.1.1 Parkinson’s disease patients demonstrate disturbed sequencing in language processing

Sequential processing is a relevant characteristic of both motor and language processing. Karl Lashley (1951) suggested that neural mechanisms that were initially adapted for motor control are the basis for syntax and other aspects of human cognition. Lieberman (2006, 2007) defined the BG as a “sequencing engine” that can reiterate motor pattern generators as well as cognitive pattern generators. Applied to syntax, the BG can thus generate an
infinite number of possible sentences by combining a finite set of words using a finite set of rules (Lieberman, 2006, 2007). Within syntactic processing, then, the BG switch from one linguistic subprocess to the next at the right moment in time.

In our fMRI experiment focussing on the intact network of activation during comprehension of sentences in which canonicity and grammaticality were manipulated (see Chapter 7), a main effect of canonicity was evident in the right pallidum, in which more activation was found for the active sentences compared to the passive sentences. It was suggested that the output nucleus supported facilitation of heuristic routines in the comprehension of canonical sentences (i.e., active voice). In contrast, PD patients (see Chapter 8) failed to exploit sequential syntactic information and, consequently, lose their capacity to use heuristic routines in the comprehension of the canonical active sentences. Thus, due to dysfunctional BG, automatic sentence processing is failing in PD.

In our sentence comprehension study, PD patients were found to make more errors when processing non-canonical passive sentences compared to actives, and our correlation analyses showed that set shifting and the digit span backward score correlated with PD patients’ impairments for the comprehension of passives (see Chapter 5). These results were in line with Hochstadt et al. (2006), who reported for English that Reading Span and mean Voice Onset Time separation [associated with articulatory rehearsal in working memory (WM)] were related to passive sentence comprehension across a range of sentences. However, against our expectations, no association between the complex sequencing task and the comprehension of passive sentences was found (Chapter 5). Furthermore, cognitive sequencing was also not associated with verb production in PD (Chapter 4). Cognitive sequencing was assessed with a protocol based on Lelekov et al. (2000) (see Colman et al., 2009 or Chapter 4 for a detailed description of the Dutch version of the task). One possible explanation for the lack of association between the complex sequencing task and the comprehension of passive sentences in PD lies in the fact that a large number of participants were unable to perform the complex sequencing task, leading to too low a variance to see the effects of sequencing ability. It was furthermore suggested that the complex abstract sequence processing task of Lelekov et al. (2000) was a measure of WM (allowing for temporary storage and simultaneous manipulation of the information) and sustained visual attention rather than of pure abstract structure processing. Future research is necessary to further unravel the contribution of cognitive sequencing processing to the transformation of syntactic structure to meaning in language comprehension.

9.1.2 Language processing and its cognitive interactions

From the literature it is clear that PD patients have both deficits in executive functions and language processing (see review Chapters 2 and 3). It has been proposed (Dagher et al., 2001; Owen et al., 1998) that the executive deficits may be caused by disruption of BG outflow resulting in dysfunction of the different loops connecting the prefrontal cortex, BG, and thalamus (Alexander et al., 1986). However, controversy still exists regarding the impact of abnormalities of executive function upon the language system in PD.

In Chapter 4 of this thesis, the relation between possible verb-in-sentence-context deficits and executive functions that are relevant for sentence processing were explored in a group
of mild to moderate PD patients. In short, our results showed that executive dysfunctions underlie the performance of the PD patients on the verb production task. Specifically, PD patients’ score on the verb production ability-scale correlated significantly with WM and set-switching. First, the PD patients included in our verb production study did not show a decreased WM capacity compared to HC subjects. Nevertheless, a correlation between WM and the verb production score was only evident for the PD patients. This finding suggested that PD patients who performed worse on the verb production task showed a lower WM capacity. However, it was also shown that the production of verbs in sentence context was a rather automatic language processing task in HC. This reliance on WM was interpreted as a compensatory mechanism acting toward maintenance of performance during the verb production task. The difference in WM demands of the different sentence types may be responsible for the found error pattern. Due to the length of the subordinate sentences, PD patients with a relatively small WM capacity showed a WM overload and produced errors on the verb production task. Secondly, the performance on verb production task of PD patients was also associated with set-switching, suggesting that PD patients who showed a set-switching deficit had more difficulties with verb production in sentence context. In our study the PD patients performed poorly in producing the verbs in the present tense, independent of the regularity of the verb (contrasting Ullman et al., 1997). Thus, PD patients showed perseverations in the past tense framework, while task demands caused for them to switch to the present tense framework. The test materials and associated instructions were found to be responsible for the tense errors, rather than an underlying linguistic deficit. The inappropriate production of a simple past in the absence of an adverb of time in the present tense sentences did not lead to an ungrammatical sentence and only violated the instruction to be memorized. Consequently, impaired monitoring of their output resulted in the absence of detection and correction of errors when the adverb of time was missing, as was the case with the present tense sentences. This finding is consistent with the predictions based on Levelt's perceptual loop theory of self-monitoring (Levelt, 1989) that PD disrupts both the monitoring process in speech and comprehension.

In Chapter 5 of this thesis, the results of our picture-verification task, which investigated the functional basis of sentence comprehension deficits in PD, were described. The sentence materials varied in syntactic complexity (canonical versus non-canonical) and length and matched or did not match with the picture. In general, the PD patients showed a significantly decreased overall sentence comprehension, compared to the HC subjects. As in previous studies, both PD patients and HC subjects showed more difficulties with the non-canonical syntactic structure, i.e., the passive. However, the length manipulations did not significantly affect sentence comprehension in either group. Apparently the memory demands associated purely with length were not particularly burdensome. The fact that none of the effects differed significantly between the two groups is in contrast with previous findings of a specific deficit for syntactically complex or long sentences in PD (e.g., Grossman, 1999; Hochstadt et al., 2006).

The evaluation of the associations between the performances of the PD on the sentence comprehension task and relevant executive functions showed that PD patients’ impaired sustained visual attention was associated with a decreased total sentence comprehension score. This association is consistent with studies suggesting that certain aspects of impaired attention might influence sentence comprehension in PD (Grossman, et al., 1992a; Grossman, et al. 1992b; Grossman et al., 2002a; Lee, et al., 2003). This correlation is not
relevant for comprehension per se, i.e., the computation of a sentence meaning, but points to the effects of task demands on PD patients’ performance during a picture-verification task. In the future it might be interesting to specifically investigate impairments of selective attention in PD, and its interference with executive functions such as set-switching and WM, which in turn might impair sentence comprehension (see Chapter 2).

The impaired processing of non-canonical sentences in PD is consistent with a deficit in the monitoring process during comprehension as described by Kuperberg (2007), Van Herten (2006), Van Herten, Chwilla and Kolk (2006) and Vissers (2008). Related to Levelt’s monitoring process in speech production, comprehending a sentence demands that a listener flexibly guides his/her attention to relevant linguistic information (e.g., word order). In non-canonical sentences, the thematic roles based on word order (heuristic strategy) conflict with those generated syntactically. In our fMRI study, PD patients lacked the monitoring of the violation, or, in other words, patients might not experience the violations in the first place (Hochstadt, 2009).

Cognitive inflexibility or set-switching impairments in human behavior implies that an inappropriate automatic response cannot be easily aborted (inhibited) and concomitant planning of a new, more appropriate sequence is disturbed due to lack of appropriate activation (Marsden & Obeso, 1994). Neuroimaging studies in HC subjects show fronto-striatal activity when receiving a signal that a switch is needed (Monchi et al., 2001). In PD, set-switching impairments (e.g., Cools et al., 2001) and a lack of activation in the fronto-striatal circuit during a set-switching paradigm have been reported (Monchi et al., 2004). Logically, impaired set-switching contributes to difficulties comprehending passive reversible sentences. As expected, the comprehension of passive sentences of the PD patients was associated with impaired set-switching, which is in line with previous correlational studies (Colman et al., 2006; Hochstadt et al., 2006). Furthermore, even though PD patients did not show impaired inhibition, the difficulties with comprehension of passive sentences showed a trend to an association with a decreased inhibition in PD patients. According to the hypothesis that participants have to inhibit the dominant canonical thematic role assignment and switch to a less dominant non-canonical syntactic sequence (Hochstadt et al., 2006; Lieberman, 2000, 2002, 2006, 2007), we suggest that a decreased inhibition impairs participants’ ability to suppress the dominant canonical thematic role assignment, which would logically result in comprehension difficulties.

PD patients can have reduced WM capacity and have impairments in especially the manipulative aspects of WM (Gabrieli, 1996; Gilbert et al., 2005; Lewis et al., 2003). The comprehension of passives in PD was also associated with manipulative aspects of WM, as assessed by the backward digit span. This result suggests that particularly the manipulative aspects of WM are involved in the comprehension of passive sentences. Consistent with the results of our verb production task, PD patients’ reliance on WM during the comprehension of passive sentences was interpreted as a compensatory mechanism (Colman et al., 2009, Koerts et al., 2009; Marié et al., 2007). Increased activation of other brain areas than the striatum might help patients with PD to maintain task performance (Grossman et al., 2003). The behavioral evidence described in Chapters 4 and 5, is consistent with our findings from the fMRI study of PD patients compared to elderly HC subjects (see Chapter 8). Higher sentence complexity (such as in passives and object-relatives) is positively associated with higher demands on verbal WM (King & Just, 1991). PD patients did show an increased
recruitment of the left medial/superior prefrontal cortex (PFC, BA 10) during the reading of passive sentences compared to active sentences. Furthermore, the PD patients involved in the fMRI experiment did not show a reading span deficit, which makes it more likely that WM allocated in the PFC effectively contributed to the comprehension of the passive sentences in PD patients and that, as such, PD patients could maintain performance. Alternatively, consistent with the findings of Traxler et al. (2005), subjects relied on their intact WM capacity to make use of semantic information to reduce the difficulty of the syntactically more complex passive sentences. According to the theory of Mink (1996) for motor control, the BG provide a gating mechanism in action selection, such that only the selected motor program is initiated, executed and terminated at the appropriate timing, whereas other competing programs are inhibited. In line with the involvement of the BG in action selection (Mink, 1996), it has been hypothesized that during sentence processing, the BG contribute to a selective gating (or filtering) of relevant information into WM by inhibiting or disinhibiting the PFC (Frank, Loughry, & O’Reilly, 2001; McNab & Klingberg, 2008). According to this hypothesis, PD patients, who have dysfunctional BG, have disturbed filtering of lexical-syntactic information into WM, which might in turn complicate their sentence comprehension for complex or long sentences. To determine whether PD patients have disturbed filtering of lexical-syntactic information during comprehension of syntactically complex sentences, we should have probed the correct sentences with relevant questions on the thematic roles. In future fMRI research we could build in a check for comprehension of the sentences to be able to evaluate the intactness of this filter process into WM.

In short, the found associations between PD patients’ linguistic performance and specific executive functions offer additional evidence to the assumption that executive functions interact with the language faculty while comprehending or producing a sentence. Generally, our studies confirm that there does not appear to be a language faculty independent from executive control.

### 9.2 Conclusions

PD is a progressive, degenerative neurological disease in elderly people that has a clear impact on language processing. The results of our experiments in mild to moderate PD patients confirm that the BG are significantly involved in language processing. The research conducted in this thesis ultimately leads to two interesting and related observations. The first observation is the found alteration in processing word order during sentence comprehension in a behavioral test, and is related to not finding an effect of canonicity in either their pallidum or middle temporal gyrus (MTG), whereas these areas were activated in healthy seniors. However, PD patients recruited additional PFC areas when processing passive sentences: the BA 10 for passives compared to actives and the BA 6 for processing verb-argument structure violation in the passives compared to the actives. The lack of activation in the right pallidum confirms that PD is a de-automatisation disorder. Our behavioral results of language production and comprehension are consistent with this reliance on the prefrontal cortex. PD patients’ reliance on WM during the comprehension of passive sentences and the production of verbs was interpreted as a compensatory mechanism (Chapters 4 and 5 of this thesis; Colman et al., 2009; Grossman et al., 2003; Koerts et al., 2009; Marié et al., 2007) supporting maintenance of task performance.
Second, during the verb production task, PD patients displayed reduced sensitivity to linguistic context, and subsequently did not monitor their output sufficiently well to detect or correct errors when the external cue of a temporal adverb was absent. Related to this is the lack of monitoring of the violation during sentence comprehension in our fMRI study, meaning that PD patients might not experience the violations/error in the first place (Hochstadt, 2009).

These subtle deficits in language comprehension and production may lead to communication problems that may result in increased social isolation of PD patients, which in turn reduces their quality of life (Miller, Noble, Jones, & Burn, 2006). In addition, professionals and caregivers may not be fully aware of the changes in language processing in PD patients, which, of course, becomes an unnecessary frustration in communication with the patient. Thus, screening for cognitive decline early in the disease and information on appropriate communication strategies for caregivers could keep the PD patients from getting socially isolated. PD patients themselves can also profit from knowledge of their language disorders, for example it can prompt them to use effective compensation strategies. Examples of communication advice for caregivers could be to simplify and avoid redundancy of information.

9.3 Future research

It is pertinent to consider the limitations of the experiments described in this thesis to improve future research.

Only non-demented patients with no depression were included. It is likely that language deficits are more severe in patients with greater cognitive decline. The participants were matched in terms of age, gender and education with healthy older adults, but we did not assess socio-economic status, although it may be correlated with cognitive ability.

In spite of the matching for age, gender and education, we tested a rather cognitively heterogeneous PD group. Therefore the extent of dysfunction varies across patients, which explains their different cognitive profiles and the fairly mild language deficits. Furthermore, we did not control strictly for the influence of clinical factors such as the duration of the disease.

Additionally, to control for the influence of dopaminergic medication on cognitive processing, we suggest conducting experiments in the practically defined off state, which is typically following an overnight fast from the patient’s anti-Parkinson medications. More positive results are expected in this ‘off state’, but we suspect more influence of other factors such as frustrations with task performance and tremors and rigidity making fMRI impossible. Ultimately, we would prefer to have conducted our experiments in drug naïve patients, but clinically these patients were not easily accessible to invite to participate in our research.
Future studies of the relationship of set-shifting and WM to sentence processing in PD or other groups would benefit from the use of better-controlled and better-understood methods than the clinical accepted neuropsychological tests which were used in the described research. For example, the computerized version of the Reading Span Task in Dutch (Van den Noort et al., 2005) that we used may not have been a pure measure of WM. Reading span tasks have been used as tests of WM because they require active manipulation of information and concurrent item retention (Just & Carpenter, 1992). However, reading span tasks have been found to rely on many of the same processes as reading comprehension tasks (Engle, Tuholski, Laughlin, & Conway, 1999), which makes it difficult to draw any strong conclusions in terms of the mediating value of WM for exactly that language process.

In the near future, the question of the connectivity between the IFG and BG will be answered more in depth. Therefore, a functional connectivity analysis would provide functional evidence for a BG-frontal cortical network during the comprehension of sentences in which the variables of canonicity and grammaticality are crossed. However, it is generally known that in fMRI, temporal resolution is far inferior to ERP, and that it cannot index neural activity that is specifically time-locked to the critical word itself. Temporal coarseness of the fMRI method probably blurred the linguistic processes. Simultaneous ERP/fMRI may allow improved localization of neural generators as well as enhanced temporal resolution of BOLD activation foci. Functional connectivity analysis can be used to examine the degree of collaboration between language-specific cortical areas and the BG, when processing violated compared to non-violated sentences. In on-line behavioral tasks, the impact of executive functions necessary for syntactic processes per se and the executive functions necessary for the task could potentially be disentangled. Therefore, a valuable technique for obtaining online data from sentence-picture matching is the eye-tracking method suggested by Hochstadt (2009).

Finally, there exists an extensive amount of literature on language processing in PD (see review in Chapter 3), but processing in other motor syndromes has received little attention. The existence of a similar verb naming deficit in other movement disorders, such as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Cotelli et al., 2006) has provided a major argument supporting the idea that semantic mechanisms concerning the verb are grounded in the motor system of the brain. It will be interesting to test verb production related to cognitive functions in the following movement disorders:

Multiple system atrophy (MSA) is an adult-onset, sporadic, progressive neurodegenerative disease characterized by varying severity of Parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal disorders (Gilman et al., 2008). MSA is also accompanied by cognitive impairments associated with dysfunctional cortico-striato-cortical circuits (Herting et al., 2007).

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by defects in the vertical ocular gaze, bulbar dysfunction, increased frequency of falling, and akinetic-rigid features. In addition, cognitive impairments, in particular executive dysfunctions associated with alterations within the frontostriatal circuitry, occur (Millar et al., 2006).
Corticobasal degeneration (CBD) is characterized by slowly progressing, unilateral Parkinsonism with dystonia or myoclonus, unresponsiveness to Levodopa, and limb apraxia. Patients with CBD often demonstrate impairments in visuospatial processing and visuoconstruction (Tang-Wai et al., 2003) in combination with acalculia, dysexecutive symptoms and aphasia (McMonagle, Blair, & Kertesz, 2006).

Thus far, only a few studies have investigated language processing in patients with atypical Parkinson syndromes, such as MSA (Apostolova et al., 2006), PSP and CBD (Josephs & Duffy, 2008; McMonagle, Blair, & Kertesz, 2006).

To conclude, the knowledge developed in this thesis answered important questions and opened a window to further investigations of language processing in PD. There remains the implementation of the evidenced based communication guidelines in order to guarantee a better quality of life for patients suffering from PD.