Chapter 9

General discussion and conclusions

PD is a heterogeneous disorder, characterized by motor and cognitive impairments, depression and other signs and symptoms. The motor and non-motor symptoms are to a large extent the consequence of a common underlying neurodegenerative disease and can therefore not be considered as separate entities, they are associated or overlap. The studies included in this thesis investigated cognition and depression in PD using neuroimaging and clinical methods.

9.1 Cognition

Behavior can be regulated in an automatic or in a (consciously) controlled manner. In general it is assumed that many activities involve a mix of automatic and controlled regulation. Automatic processes take advantage of previously established and learned relationships between external or internal contexts and behavioral patterns (see figure 4.1). Controlled processing, on the other hand, involves deliberate planning and regulation in situations where current schemata are not sufficient. It requires maintenance and stabilization of goal representations in working or prospective memory and the flexibility to update these goal representation when necessary (Cools, 2008). Also the inhibition of automated responses and retrieval from declarative memory are involved. In PD impairments in both automatic and controlled processing have been reported.

In the context of automatic processing, it has been reported that PD patients show deautomatisation. This is most visible within in the motor domain, e.g. a decreased stride length when walking for which patients compensate by thinking about each step (Wu & Hallett, 2005). Deautomatisation has, however, also been reported within the cognitive domain, i.e. PD patients relied more on executive functions when performing a verb production task (Colman et al., 2008). In addition to deautomatisation, PD patients also show difficulties achieving automaticities, or learning skills. Neuroimaging studies show that in healthy individuals, motor and cognitive task learning is reflected by cortico-cortical and cortico-striatal shifts of activation (Beauchamp et al., 2003; Debaere et al., 2004; Poldrack et al., 1999; Van der Graaf et al., 2004). Since PD is characterized by a dysfunctional striatum it can be hypothesized that impairments in achieving automaticities are (partly) associated with an inability to shift from cortical to striatal areas.

In the process of achieving automaticities or procedural or implicit learning, feedback plays an important role. Studies show that in PD the achievement of automaticities is especially difficult when implicit learning is based upon feedback (Shohamy et al., 2004), opposed to purely observational implicit learning. These learning impairments are in turn influenced by the use of levodopa: PD patients on levodopa show a better performance on a procedural

learning task when exposed to positive feedback, while PD patients off levodopa show a better performance on a procedural learning task in the context of negative feedback (Frank et al., 2004). According to our data, PD patients on levodopa showed a decreased striatal activation during positive feedback processing, relative to healthy elderly controls. In addition, they showed increased mPFC activation during positive feedback processing, which was not found in healthy elderly controls. Since the task that was used during neuroimaging was prelearned before scanning, it can be suggested that PD patients on levodopa did not show a shift from cortical to subcortical areas during learning. This is consistent with the hypothesis that implicit learning impairments of PD patients can be caused by an inability to shift from cortical to striatal areas. In addition to this explanation for implicit learning impairments, Frank (2005) specifically offered an explanation for the dissociation between positive and negative feedback processing. It is known that dopaminergic cells fire in response to positive feedback, while the amount of dopamine decreases when confronted with negative feedback (Schultz, 2001). According to Frank (2005) these bursts and dips of dopamine are critical for procedural learning, i.e. the bursts stimulate the responses to positive feedback, while the dips of dopamine inhibit the responses to negative feedback. Because of the dopaminergic dysfunction of the striatum this range in dopamine is restricted in PD. Furthermore, PD patients who are on levodopa can not show a decrease of dopamine in response to negative feedback, while they can show the burst of dopamine in response to positive feedback. Consequently these patients learn relatively better when confronted with positive feedback. PD patients off levodopa, on the other hand, show a constant dip in the amount of dopamine and can not show a burst of dopamine in response to positive feedback. These patients thus learn relatively better when confronted with negative feedback (Frank, 2005).

Combining this explanation of Frank (2005) with the above described hypothesis it can be suggested that implicit learning impairments in PD are caused by:

1. a restricted range in the neuronal dopamine due to which PD patients cannot show the optimal increases or decreases of dopamine in response to respectively positive and negative feedback;
2. an inability to shift from cortical to subcortical areas during implicit learning.

The inability to shift from the mPFC to the striatum might indicate that the mPFC cortex compensated for the striatal dysfunction in PD. This is in line with the previously described role of the mPFC, which is thought to be activated when performance adjustment is needed, e.g. when anticipated rewards need to be obtained (Ridderinkhof et al., 2004; Van der Graaf et al., 2006). The prefrontal cortex thus stays increasingly involved in positive feedback processing in PD and probably facilitated that PD patients on levodopa were able to

respond to positive feedbacks. It would be interesting to investigate whether PD patients on levodopa show the same activation when confronted with negative feedback. The same accounts for PD patients off levodopa. Do they show different activation patterns compared to PD patients on levodopa? In future research it should be investigated whether there is a difference.

Our data further suggested that when PD patients on levodopa were confronted with meaningless feedback they showed increased striatal activation, relative to the positive feedback conditions of our task. This part of our task may have induced an uncertainty about their performance in PD patients, i.e. PD patients most likely had some knowledge about the accuracy of their performance, while they did not receive information about the actual results. Our results are in line with findings that an internally modulated response associated with reward uncertainty also induces striatal dopamine release in PD (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2004). In addition, the mPFC did not show increased activation in PD patients during the meaningless feedback condition. The mPFC, which facilitated the compensation when confronted with positive feedback, apparently did not compensate when PD patients on levodopa were confronted with meaningless feedback. The mPFC is thought to be involved in performance monitoring and is specifically activated when performance adjustment is needed, for example when anticipated rewards need to be obtained (Ridderinkhof et al., 2004). Possibly the meaningless feedback was not salient enough to require performance adjustment.

In summary, PD patients show deautomatisation and implicit learning impairments. The latter can first of all be explained by a restricted range of neuronal dopamine due to which PD patients do not show the optimal increases or decreases of dopamine in response to respectively positive and negative feedback. And second, by the finding that PD patients do not show the expected shift from cortical to striatal areas during implicit learning. Instead the prefrontal cortex stays increasingly involved and enables PD patients to respond, at least when stimuli are salient enough.

The prefrontal cortex, which showed increased activation in PD, is strongly associated with cognitive control or executive functions. Specifically, the medial prefrontal cortex is thought to be associated with a monitoring function, i.e. this area signals when increased control is needed, for example when performance needs to be adjusted. The lateral prefrontal cortex, on the other hand, is engaged in regulatory processes and implements these performance adjustments (Ridderinkhof et al., 2004). Concerning dopamine and the prefrontal cortex, it has been hypothesised that prefrontal dopamine supports the active

maintenance of goal representations, which is critical for the suppression of irrelevant responses and the selection of relevant responses. Striatal dopamine on the other hand is thought to play an important role in cognitive flexibility (Cools, 2008).

In our study and also in other neuroimaging studies focused on cognition in PD a decreased striatal and increased prefrontal activation was reported (Bruck et al., 2005; Kunig et al., 2000; Monchi et al., 2004). Regarding the above described functions of the prefrontal cortex and the role of dopamine (Cools, 2008; Ridderinkhof et al., 2004) these findings suggest that PD patients show increased cognitive control. In addition, it suggests that PD patients can actively maintain goal representations, however cannot flexibly adjust when necessary. These suggestions are confirmed by our behavioral data. We showed that when PD patients were confronted with the goal to perform three tasks without being offered a structured method, they tended to plan sequential instead of simultaneous task performance. This planning was significantly predicted by a decreased psychomotor speed, which suggests that PD patients deliberately planned to perform the task sequentially by which they compensated for their bradyphrenia or bradykinesia. This adjusted planning was maintained over time, since PD patients indeed performed tasks sequentially instead of simultaneously. Apart from planning, however, the ability to work simultaneously was further limited by decreased cognitive flexibility.

PD patients thus adjusted their goals with regard to their bradyphrenia or bradykinesia. These goals were maintained over time, however, PD patients showed difficulties adjusting these goals during the actual performance of the tasks. This adjustment of activities by PD patients indicates that they take into account their limitations and impairments and try to give their best performance.

Concerning the behavioral trait novelty seeking (NS; which can be defined as a heritable tendency toward intense exhilaration or excitement in response to novel stimuli, cues for potential rewards or potential relief of punishment (Cloninger, 1987)) this was also the case, according to our data. PD patients presented themselves as performing on the same level as healthy controls and showed equal levels of NS, even though the activation patterns (partly) underlying this behavioral trait were different.

PD patients thus show increased cognitive control. In addition, they maintain goal representations over time, but they show difficulties in flexibly adjusting these goals.

Within the comprehensive mental schema framework (see figure 4.1; Brouwer & Schmidt (2002)) cognitive control has been described as having a number of constituent more elementary functions, such as monitoring, planning and cognitive flexibility, which have been reported to be impaired in PD (Cools et al., 2001; Green et al., 2002; Muslimovic et

al., 2005; Van Beilen et al., 2008; Weintraub et al., 2005a). In addition, this framework reflects the dynamic relations between the subprocesses of automatic and controlled processing. Considering this framework, the increased reliance on cognitive control in PD suggests that the regulation of behavior shifts from automatic to controlled processing. This is consistent with deautomatisation and implicit learning impairments in PD patients as described above. The shift from automatic to controlled processing however indicates that if there is something wrong with automatic information processing, this will also affect controlled processing, suggesting that impairments in the subprocesses of controlled processing may be secondary to impairments in automatic processing. In addition, impairments within the subprocesses of cognitive control may also influence each other (see figure 4.1). The strongest evidence for impairments in controlled processing in PD will therefore be studies that control for confounding influences of impaired automatic processing and other subprocesses of controlled processing (see figure 4.1). The problem with tests used to assess the cognitive functions in PD however, is that they not only assess the cognitive function they declare to measure but also many other cognitive functions, such as implicit learning, working memory and visuospatial functions. For example, the Odd Man Out test (Flowers & Robertson, 1985) requires both the implicit learning of rules and cognitive flexibility (Cools et al., 2001). According to our knowledge, only Cools et al. (2001) studied cognition in PD controlling for these confounding influences. They reported cognitive flexibility impairments in PD, which were specifically present when the load on selection mechanisms increased. PD patients thus show genuine cognitive flexibility impairments. Future research should be focused on unraveling which cognitive impairments are specific for PD by designing paradigms in which confounding influences are excluded or minimized.

Besides automatic processing impairments and impairments within other subprocesses of cognitive control, other non-motor symptoms of PD may influence cognition in PD, in particular depression. Previous studies reported larger impairments of memory, language, concept formation and cognitive flexibility in PD patients with depression, compared to PD patients without depression (Kuzis et al., 1997; Troster et al., 1995). The depressed PD patients included in our study showed a slightly higher frequency of cognitive impairments than non-depressed PD patients. However, no significant differences were found between depressed and non-depressed PD patients (most likely due to the relatively small group of depressed PD patients). Our data therefore do not (completely) confirm these previous studies. One interesting finding in our study was however, that depressed PD patients and their independent observers rated the problems associated with the dysexecutive syndrome

as significantly worse than non-depressed PD patients and their independent observers. Depressed PD patients thus come across and also experience themselves having significantly more dysexecutive problems in daily life than non-depressed PD patients. This is in line with reports of associations between a decreased quality of life and an increased severity of depression (Schrag et al., 2000) and indicates that it is important to treat depression in PD in order to alleviate their experienced dysexecutive problems in daily life.

A non-motor symptom that is closely related to depression is apathy. Apathy can be part of depression in PD, which was reflected by our finding that the dysexecutive problems experienced by depressed PD patients in daily life were to a large extent represented by apathy, i.e. the largest differences between depressed and non-depressed PD patients were found for negative affect (shallow affect and apathy) and intentionality (planning and maintenance of goal-directed behavior in daily life). Depression and apathy can however also be dissociated in PD (Kirsch-Darrow et al., 2006) and Levy & Dubois (2006) suggested that PD patients mainly show a cognitive inertia subtype of apathy, i.e. reductions in self-generated voluntary and purposeful behavior. This cognitive inertia subtype may specifically be reflected by impairments initiating behavior in PD, even in non-depressed PD patients. This expectation could however, not be confirmed by our data. PD patients initiated behavior as often as healthy controls and no associations were found between cognition and apathy in our group of PD patients. Future research is needed to determine what the effects are of apathy on cognition and the functioning in daily life of PD patients.

For now it can be concluded that depression and apathy may influence cognitive control or executive functions in PD at least in the experience of patients and their relatives, even though this is not always visible on neuropsychological tests.

In conclusion, within the cognitive domain PD patients show a heterogeneous set of impairments. They show deautomatisation and difficulties achieving automaticities, specifically when implicit learning is based upon feedback. The latter can be ascribed to (1) a restricted range of neuronal dopamine due to which PD patients do not show the optimal increases or decreases of dopamine in response to respectively positive and negative feedback and (2) an inability to shift from cortical to striatal areas during implicit learning. PD patients however, compensate by showing an increased involvement of the prefrontal cortex, which indicates that they show an increased reliance on cognitive control and a decreased reliance on automatic processing. The shift from automatic to controlled processing however, indicates that if there is something wrong with automatic information

processing this will also affect controlled processing, suggesting that impairments in the subprocesses of controlled processing are secondary to impairments in automatic processing. Also depression and apathy may have a negative influence on cognition in PD. Future research is needed to unravel which cognitive impairments are specific for PD.

9.2 Depression

Symptoms of depression accompanying PD can be discussed from two different points of view: they may be an expression of a common underlying neurodegenerative disease or they may be part of a co-morbid depression separate from PD. Since it has been shown that depression is more common in PD than in other chronic disabling disorders (Ehmann et al., 1990), and that in both primary depression and PD a dopaminergic dysfunction of the striatum has been reported (Martinot et al., 2001; Meyer et al., 2001), it is most likely that depression in PD can be considered an expression of a common underlying neurodegenerative disease. Comparing however, depressed and non-depressed PD patients, it has been reported that depressed PD patients show a decreased dopaminergic and noradrenergic transporter binding ([^{11}C]RTI-32 PET) in the locus coeruleus, anterior cingulate cortex, thalamus, amygdala and ventral striatum relative to non-depressed PD patients (Remy et al., 2005). Also, depression in PD has been associated with a decreased dopamine transporter availability in the left putamen (Weintraub et al., 2005b) and with cortical cholinergic denervation (Bohnen et al., 2007). It can therefore be suggested that even though depression in PD appears to be an expression of a common underlying neurodegenerative disease, depression in PD may be associated with a more severe or partly different neurodegenerative process than PD without depression. This is in line with our finding that depressed PD patients had a shorter disease duration and used more antiparkinsonian medication than non-depressed PD patients, while depressed and non-depressed PD patients were similar in the severity of motor symptoms and the level of activities in daily life. In addition, depression in PD has been associated with more severe cognitive impairments found on neuropsychological tests (Kuzis et al., 1997; Troster et al., 1995) or in the experience of these patients), a decreased quality of life (Schrag et al., 2000) and increased mortality (Hughes et al., 2004). Depressed PD patients thus appear to be more severely affected, both at a neurochemical and behavioral level, than non-depressed PD patients.

The finding that depressed PD patients are more severely affected indicates that especially these patients need to be adequately treated. Pharmacological treatments might alleviate symptoms of depression in PD, however, to prevent or slow down the disablement process

(Verbrugge & Jette, 1994) cognitive rehabilitation may also be helpful in these patients. These therapies should be focused on avoiding patients to be drawn into negative images about aging and disease and need to give them control over their own lives wherever possible (Coleman, 1999). According to our knowledge, the effectiveness of cognitive rehabilitation for depression in PD compared to pharmacological treatments has not been investigated and studies in this field are thus warranted.

The common neurodegenerative disease underlying both PD and depression causes that depression and PD show an overlap of symptoms. Examples of overlapping symptoms are sleep disorders, fatigue, loss of appetite, apathy and cognitive impairments. This overlap of symptoms causes that the diagnosis of depression in PD can be difficult to establish. Consequently, depression can be both underrated or overrated in PD. For clinical purposes it is therefore important to determine which items of often used depression rating scales are likely to assess PD symptoms. According to our data particular the Reduced sleep and Lassitude items of the MADRS are likely to be influenced by motor symptoms of PD. In addition, the items Concentration difficulties, Lassitude and Inability to feel were associated with the typical striatal dysfunction of PD, suggesting that these symptoms are likely to be part of PD. Symptoms that are more suitable to assess depression in PD are consequently the affective symptoms of depression, such as a depressed mood and pessimistic thoughts, which is consistent with previous research (Leentjens et al., 2003a).

Although only the MADRS was investigated, it is likely that also rating scales such as the Hamilton Depression Rating Scale and the Beck Depression Inventory are influenced by motor symptoms and assess symptoms actually belonging to PD. Indeed, it was reported that the somatic items Reduced appetite and Early morning awakening of the Hamilton Depression Rating Scale significantly contribute to the diagnosis of depression in PD (Leentjens et al., 2003a). Fortunately, for several of the most often used depression rating scales in PD adjusted cut-off scores have been determined (Leentjens et al., 2000; Visser et al., 2006) and it is strongly advised to use these adjusted cut-off scores. A valuable addition could be to qualitatively describe the answers of PD patients on the items of depression rating scales, since the quantitative scores are not always sufficient.

An important cause of depression in PD thus most likely is the underlying neurodegenerative pathology, which may be more severe or partly different in depressed PD patients compared to non-depressed PD patients. In addition, depressed PD patients may be more severely affected and show a faster disease progression than non-depressed PD patients. The treatment of depressed PD patients requires special attention. In addition to pharmacological treatments, also cognitive rehabilitation could be considered, but more research is necessary. Besides a neurochemical overlap, depression and PD also show

symptom overlap. The somatic and cognitive symptoms of depression can be primary symptoms of PD but they can also be secondary to motor symptoms. The diagnosis of depression in PD thus needs to be carefully considered.

9.3 Future directions

Since PD is a heterogeneous disorder affecting the motor, cognitive and emotional domains, either domain cannot be studied without considering the others. In other words, to gain a better understanding of the symptoms of PD one needs to focus on the associations between motor, cognitive and emotional impairments in PD. In addition, different impairments within a domain can also influence each other. It is thus important to determine which symptoms are primary and which are secondary both within and between domains. Within a domain, mainly within the cognitive domain, new paradigms need to be designed in which the confounding influences of other cognitive impairments are excluded or minimized. These paradigms can help us determine which cognitive impairments are specific for PD.

An example of research which investigates the association between domains are studies focused cognition, depression and freezing of gait (FOG) in PD. FOG is a debilitating phenomenon that is present in 30-50% of PD patients. It can be defined as intermittent episodes of inability to initiate or maintain locomotion or performing a turn and mainly occurs in challenging situations, such as a change of walking environment (an open road), busy traffic or when confronted with a revolving door. In these situations fixed movement programs are not sufficient and an individual will be required to use cognitive control or executive functions. FOG and cognition appear thus to be associated. Also, depression may play a role. Studies focused on the effectiveness of the different therapies showed that a higher degree of depression at baseline was associated with earlier development of FOG and a risk factor for the development of FOG during the course of the study (DATATOP, 1989; Rascol et al., 2005). FOG in PD may thus (partly) be the consequence of cognitive impairments and depression. Studying FOG is thus an interesting topic to learn more about the interactions between motor and non-motor symptoms in PD.

9.4 Conclusion

PD is a heterogeneous disease, many symptoms are associated or overlap. These associations occur both within domains of impairment as well as between domains of

impairments. Within the domain of cognition PD patients show deautomatisation and difficulties achieving automaticities, specifically when implicit learning is based upon feedback. The latter can be ascribed to (1) a restricted range of neuronal dopamine due to which PD patients do not show the optimal increase or decrease of dopamine in response to respectively positive and negative feedback and (2) an inability to shift from cortical to striatal areas during implicit learning. PD patients however, compensate by showing an increased involvement of the prefrontal cortex, which indicates that they show an increased reliance on cognitive control and a decreased reliance on automatic processing. The shift from automatic to controlled processing however, indicates that if there is something wrong with automatic information processing this will also affect controlled processing, suggesting that impairments in the subprocesses of controlled processing are secondary to impairments in automatic processing. In addition, impairments within the subprocesses of cognitive control have also been reported in PD. The strongest evidence for impairments in controlled processing in PD will therefore be studies that control for confounding influences of impaired automatic processing and other subprocesses of controlled processing.

Depression is another domain of impairment in PD. Depression may have a negative influence on cognition in PD. However, both cognitive impairments and motor symptoms can also influence the assessment of depression in PD, since these cognitive impairments and motor symptoms can be part of both PD and primary depression. The diagnosis of depression in PD thus needs to be carefully considered.

Future research is needed to further unravel which impairments are primary and which are secondary in PD. This needs to be performed within the domains of impairment in PD as well as between the domains of impairment.