Eight

General Discussion
The aim of this thesis was to get a better understanding of the neurobiological factors that contribute to the development of anxiety, depression and impulse control disorders (ICD) in Parkinson’s disease (PD) using multiple neuroimaging techniques. We used dopamine transporter (DaT) SPECT images to study the integrity of the striatal dopamine system in association with the symptoms of depression (Chapter 3) and ICD (Chapter 4). Structural and functional MRI were used to investigate the neural correlates of anxiety symptoms (Chapter 2) and response inhibition (Chapter 6), respectively. This chapter revisits these studies and discusses them in a broader context. This chapter also reviews the literature on PD-related alterations in neurotransmission and cortico-striato-thalamocortical (CSTC) signaling and their effect on the development of neuropsychiatric symptoms. Lastly, this chapter considers the clinical implications of our findings and directions for future studies on neuropsychiatric disorders in PD.

The role of dopamine

The general introduction already stated that neuropsychiatric disorders do not arise simply because PD patients have trouble adjusting to the disabilities that come with the disease, but that their development is associated with pathological alterations caused by PD itself. A hallmark pathological feature of PD is the degeneration of dopamine neurons in the midbrain (Dickson et al. 2009). Degeneration of dopamine projections towards the striatum can be visualized in vivo with DaT SPECT imaging (Booij et al. 1999). Our results of Chapter 3 showed that depressive symptoms are related to dopamine denervation of the caudate nucleus, while motor symptoms are related to denervation of the putamen. These findings corroborate those of previous studies on PD-related depression (Weintraub et al. 2005; Rektorova et al. 2008; Hesse et al. 2009) and motor symptom severity (Benamer et al. 2000; Pirker 2003; Ravina et al. 2012). The novelty of this study lies in the fact that we observed a double dissociation between depressive and motor symptoms on striatal DaT availability that concurs with our understanding of the CSTC circuits and their functions. The caudate nucleus is involved in associative and limbic functions, while the putamen is involved in sensorimotor control (Groenewegen and Uylings 2010). The projections of the CSTC circuits as well as further evidence for the association between dysfunction of the associative and limbic CSTC circuits and depression were extensively described in Chapter 5. In Chapter 5 we also stated that symptoms of depression might develop due to degeneration of dopamine projections towards the ventral striatum. This leads to reduced dopamine signaling and tips the balance between the activity in the direct and indirect pathway of the limbic CSTC circuit in favor of the indirect pathway (figure 5.2). The result is overactivation of the indirect pathway and inhibition of reward and motivation related brain areas, such as the orbitofrontal cortex, which may lead to a state of anhedonia.
In Chapter 4 we showed that like depressive symptoms, ICD symptoms are also related to reduced striatal DaT availability. Previous cross-sectional studies have interpreted this as a down-regulation of the DaT – possibly in response to dopaminergic medication – or premorbidly decreased DaT expression leading to reduced dopamine reuptake from the synapse and increased postsynaptic dopamine signaling in patients vulnerable to ICD development (Cilia et al. 2010; Lee et al. 2014b; Voon et al. 2014). Our own results of reduced baseline DaT availability in medication-naïve PD patients that later develop ICD symptoms exclude the possible effects of dopamine replacement therapy on DaT availability. Furthermore, we postulate that the reduced DaT availability reflects dopamine degeneration rather than down-regulation of the DaT. According to our pathophysiological model presented in Chapter 5, degeneration of ventral striatal dopamine projections can lead to supersensitivity of postsynaptic dopamine D3 receptors (Gerfen et al. 2002). Subsequent treatment with dopamine agonists, that have a high affinity for the D3 receptor, leads to exaggerated activation of the direct pathway of the limbic CSTC circuit and consequently increased activity in reward-related brain areas and disruption of reward-based learning (Figure 5.2) (Frank et al. 2004; Vriend et al. 2014c).

Our model is partly in disagreement with the prevailing ‘overdose theory’ for ICD development. This theory states that treatment with dopamine agonists, of which the dosage is titrated to supplement dopamine loss in the putamen to treat the motor symptoms, overdoses the relatively preserved ventral striatum with dopamine (Voon et al. 2011b). The theory is based on the observation that striatal dopamine denervates along a ‘caudo-rostral’ gradient with the posterior putamen being affected first and the caudate nucleus and ventral striatum only getting affected in the later stages of the disease (Kish et al. 1988; Damier et al. 1999; Hsiao et al. 2014a). This gradient in dopamine degeneration was also observed in our own data (figure 3.3). Due to the compensatory mechanisms of the brain, motor symptoms do not develop until approximately 30% of the dopamine neurons in the substantia nigra and 50-60% of the dopamine projections towards the putamen are lost (Fearnley and Lees 1991; Cheng et al. 2010). However, it is unknown what the threshold is for the development of ICD and other neuropsychiatric symptoms after loss of dopamine projections to the caudate nucleus and ventral striatum. It is very well possible that neuropsychiatric symptoms are more sensitive to dopamine depletion than the motor symptoms (figure 8.1). This might also explain why depression and anxiety often arise in the premotor stage in PD patients (Schuurman et al. 2002; Prediger et al. 2012).

One way to determine whether reduced striatal DaT availability in PD patients at risk for ICD development reflects DaT down-regulation or dopamine degeneration – or in essence determine whether the overdose theory or our theory holds more merit – is to scan PD patients using both a DaT selective tracer and a tracer selective for the presynaptic vesicular monoamine transporter 2 (VMAT2). VMAT2 is responsible for uptake and storage of monoamines, like
dopamine, in vesicles prior to release at the presynaptic terminal (Bohnen et al. 2006). Two often used VMAT2 radiotracers are 9-[(18)F] fluoropropyl-(-) dihydrodihydrotetabenazine ([(18)F]AV-133) and [11C]-(-)-dihydrotetabenazine ([11C] DTBZ). VMAT2 is an established selective biomarker for striatal dopamine degeneration and may be less influenced by compensatory changes that can occur after dopamine degeneration compared with DaT (Bohnen et al. 2006; Okamura et al. 2010; Hsiao et al. 2014b). If both DaT and VMAT2 availability are reduced in PD patients at risk for ICD development, compared to PD patients not at risk, this provides evidence for a more pronounced dopamine degeneration as a vulnerability factor for ICD. If DaT is reduced, but there are no changes in VMAT2 availability, then this provides evidence for a down-regulation of DaT availability. To the best of our knowledge, no prior study has investigated VMAT2 availability in relation to ICD in PD and therefore this warrants further investigation.

Although not specifically studied in this thesis, there is also some evidence that striatal dopamine dysfunction may play a role in the pathophysiology of anxiety. Only a few studies have investigated the pathophysiology of anxiety in PD. Severity of anxiety symptoms correlated negatively with striatal DaT availability in PD patients in some studies (Weintraub et al. 2005; Erro et al. 2012) but not all (Moriyama et al. 2011; Ceravolo et al. 2013). DaT SPECT studies in non-PD patients with anxiety disorders have also shown mixed results (Tiihonen et al. 1997; van der Wee et al. 2008; Schneier et al. 2009; Hoexter et al. 2012). In a rodent model, chemically-induced lesions of the substantia nigra lead to anxiety-like behavior that is alleviated by dopamine agonists (Carnicella et al. 2014; Drui et al. 2014). This contrasts, however, with observations in PD patients where dopamine replacement therapy is not equally successful in treating anxiety symptoms (Vazquez et al. 1993; Maricle et al. 1995; Richard et al. 1996; Lemke et al. 2005; Stacy et al. 2010). A meta-analysis was also unable to find a positive effect of dopamine replacement therapy on anxiety symptoms although the authors admit that this could have been due to the fact that only very few randomized controlled trials have been conducted on this subject (Troeung et al. 2013).

Anxiety symptoms are common in PD patients suffering from response fluctuations, i.e. recurrences of motor and non-motor symptoms when dopamine plasma levels start to wear off that dissipate after a scheduled dose (Witjas et al. 2002; Stacy et al. 2005). This type of anxiety symptoms is therefore referred to as 'wearing-off' anxiety and might be more sensitive to dopamine dysfunction than other anxiety subtypes, such as social anxiety and generalized anxiety disorder. The etiology and pathophysiology of response fluctuations and wearing-off anxiety are, however, still incompletely understood. Current evidence thus suggests only a limited role of dopamine in the pathophysiology of anxiety symptoms. Nevertheless, there is a relative paucity of studies on the pathophysiology of anxiety in PD. Furthermore, until very recently there was no rating scale available for anxiety symptoms in PD with acceptable clinimetric properties (Leentjens et al. 2014). This may have hampered accurate classification
of anxiety symptoms in PD and it is up to future studies to use this new scale, the Parkinson Anxiety Scale (PAS), in association with neurobiological measures.

In summary, depression, ICD and some types of anxiety (mainly wearing-off related anxiety symptoms) are all associated with dopamine dysfunction, most probably due to PD-related degeneration of dopamine projections. Dopamine depletion, however, does not provide the full story for the development of these neuropsychiatric symptoms and the involvement of other neurotransmitters cannot be overlooked.

Figure 8.1 – Severity of striatal dopamine degeneration and putative thresholds for the development of Parkinson related motor and neuropsychiatric symptoms.
The role of other neurotransmitters

Dopamine is not the only neurotransmitter system affected by the neuropathological changes associated with PD. Degeneration of the raphe nuclei and locus coeruleus in the brainstem leads to depletion of serotonin and noradrenaline, respectively (Braak et al. 2003).

Serotonin

According to the neuropathological staging by Braak et al. the raphe nuclei are affected in stage II, while the substantia nigra is not affected until stage III (Braak et al. 2003). This may suggest that serotonergic cell loss precedes dopaminergic cell loss (Huot and Fox 2013). In contrast, in vivo SPECT studies using a selective tracer for the serotonin transporter (SERT) in early-stage de novo PD patients have shown preservation of midbrain serotonin (Beucke et al. 2011) and (extra) striatal serotonin (Strecker et al. 2011), despite markedly reduced DaT availability. Other nuclear imaging studies in medicated PD patients in various stages of the disease have revealed decreased SERT levels in the midbrain, hippocampus,
amygdala, basal ganglia and cortical areas compared with healthy controls (Brucke et al. 1993; Kerenyi et al. 2003; Guttman et al. 2007; Politis et al. 2010a). Interestingly, one study showed that with progression of the disease striatal serotonin denervates in a rostrocaudal direction; from the caudate nucleus to the putamen (Politis et al. 2010a). This is opposed to the pattern observed for striatal dopamine loss (Figure 8.2)(Kish et al. 1988). At first glance the work by Braak et al and these nuclear imaging studies seem contradictory; Braak's staging suggest that serotonergic neuronal loss precedes dopaminergic neuronal loss whereas in vivo neuroimaging studies suggest the opposite. Nevertheless, it is possible that the Lewy body pathology does not significantly affect the functioning of the neurons in the raphe nuclei until later in the disease, whereas the neurons in the substantia nigra are more vulnerable to Lewy body pathology and degenerate faster. It has also been proposed that at least 15% of all PD patients do not adhere to the Braak staging sequence (Jellinger 2012), which may provide another explanation for the observed discrepancy.

Studies investigating the association between depression and the serotonin system in PD using nuclear imaging with [11C]DASB have shown increased extrastriatal SERT (Boileau et al. 2008; Politis et al. 2010b), correlating with the severity of depressive symptoms (Politis et al. 2010a) and decreased limbic 5-HT1A receptor availability (using [(18)F]MPPF) (Ballanger et al. 2012). The increased SERT availability in depressed PD patients is interpreted as an (inappropriate) upregulation of SERT resulting in increased clearance of serotonin from the synaptic cleft, and decreased serotonergic signaling (Politis and Niccolini 2015). Conversely, studies in patients with major depressive disorder without PD have generally shown reduced SERT availability (Newberg et al. 2005; Selvaraj et al. 2011; Ho et al. 2013), particularly in the midbrain (Gryglewski et al. 2014). It is as yet unclear how these findings relate to the results in depressed PD patients and warrant further investigation, ideally in a prospective longitudinal study.

Serotonin has also been studied in association with ICD. Most evidence for a role of serotonin in the ability to inhibit responses comes from studies in animal models. Inhibitory control is, however, not a unitary construct and consists of several cognitive processes (Bari and Robbins 2013b; van Velzen et al. 2014) that are differently affected by (induced) alterations in serotonin signaling (Winstanley et al. 2004; Pattij and Schoffelmeer 2014). Enhancement of serotonin signaling, e.g. with selective serotonin reuptake inhibitors (SSRIs), reduces impulsive action as measured by the number of premature responses in the five-choice serial reaction time task (Homberg et al. 2007; Baarendse and Vanderschuren 2012) but has no effect on impulsive choice in the delayed reward task (Baarendse and Vanderschuren 2012) and action cancellation in the Stop-signal task (Bari et al. 2009). Similarly, chemically lesioning serotonin neurons in the raphe nucleus decreases inhibitory control in the five-choice serial reaction time task (Winstanley et al. 2004) and Go/No-Go task (Harrison et al. 1999), but has no effect on performance on the delay discounting task, a measure of impulsive
choice (Winstanley et al. 2004) or action cancellation (Eagle et al. 2009). In healthy humans, the SSRI citalopram enhanced activity of inhibition-related brain areas during action restraint but had no effect on behavioral performance (Del-Ben et al. 2005; Macoveanu et al. 2012). Modulating serotonin signaling during action cancellation also does not affect inhibitory control in humans (Chamberlain et al. 2006b; Nandam et al. 2011), although the influence of serotonin on action cancellation seems to depend on individual differences in the (integrity of the) serotonin system (Macoveanu et al. 2012; Ye et al. 2014a). A more extensive account of the neurochemistry behind inhibitory control is provided in Chapter 7 and (Dalley and Roiser 2012; Bari and Robbins 2013b).

In PD patients without ICD, the SSRI citalopram decreased impulsivity, as measured by the stop-signal reaction time, and enhanced task-related brain activation of the inferior frontal gyrus (Ye et al. 2014a). Nevertheless, this effect was only observed in PD patients in a more advanced disease stage, possibly because of pathologically induced individual differences in the integrity of the serotonin system. Almost no studies have been conducted on the association between serotonin and ICD in PD patients. In a single small-scale study in PD patients an association between polymorphisms in the 5-HT2a receptor gene and ICD was observed (Lee et al. 2009). Studying the serotonergic system in relation to ICD in PD does seem worthwhile, since evidence suggests that SSRIs are efficacious in improving at least some aspects of impulse control. Although admittedly speculative, SSRIs might therefore be considered as an adjuvant treatment to dopamine replacement therapy, more specifically dopamine agonists, to prevent the risk of ICD development in susceptible patients, e.g. those with depressive symptoms (Vriend et al. 2014c).

To date there are no studies that specifically addressed the association between the serotonergic system and anxiety in PD. Although in clinical practice SSRIs are often prescribed to anxious PD patients because of their efficacy in non-PD patients with anxiety disorders (Lenze et al. 2005), there is currently no evidence-based pharmacological treatment available for anxiety in PD (Seppi et al. 2011). Clinical trials on the treatment of PD-related anxiety disorders – some of the most prevalent neuropsychiatric disorders in PD – are therefore urgently needed.

In short, although there is evidence that the serotonergic system undergoes alterations during the course of PD, studies on the involvement of serotonin dysfunction in neuropsychiatric symptoms and how the serotonergic and dopaminergic systems interact are still limited. Most evidence is available for an association between serotonin signaling and impulse control, but its role in the development of clinically significant ICD warrants further investigation. The serotonergic system may prove to be an interesting target for pharmacological intervention for ICD in PD.
**Noradrenaline**

As discussed above for the serotonergic system, the Braak neuropathological staging of PD implies that alpha-synuclein pathology accumulates earlier in the locus coeruleus (stage II) than in the substantia nigra (stage III) (Braak et al. 2003). Although this view gets support from post-mortem studies (Braak et al. 2003; Zarow et al. 2003), a nuclear imaging study using Fluorodopa found no differences in monoamine availability in the locus coeruleus between early-stage PD patients and healthy controls (Pavese et al. 2011). Conversely, striatal monoamine availability — primarily reflecting dopamine availability — was decreased in PD patients versus healthy controls. Locus coerulear monoamine availability did, however, decline progressively over the course of the disease (~8% annually). This suggests that during the early stages of the disease the locus coeruleus is still relatively preserved. Nevertheless, Fluorodopa is a non-specific radioactive tracer and this study needs to be replicated with a tracer with high and selective affinity for the noradrenaline transporter.

The noradrenergic and dopaminergic systems exhibit extensive (and complex) interactions. For one, they share a biosynthetic pathway, where noradrenaline is formed by hydroxylation of dopamine by dopamine-β-hydroxylase in the noradrenergic synapse (Benarroch 2009). Noradrenaline also facilitates dopamine release through its efferent projections towards the substantia nigra and ventral tegmental area (Rommelfanger and Weinshenker 2007). In animal models of PD, chemical lesions of the substantia nigra that give rise to motor symptoms are exacerbated by an additional lesion of the locus coeruleus (Mavridis et al. 1991; Fornai et al. 1997) and reduced by knock-out of the noradrenaline transporter, which increases extracellular noradrenaline concentrations (Rommelfanger et al. 2004). It is currently unknown whether these effects depend on neurotransmission through noradrenergic receptors. Noradrenaline can actually also act as a paracrine factor, has antioxidative effects against reactive oxygen species (ROS), and activates anti-inflammatory factors, each of which may protect against PD-related neurodegeneration of the substantia nigra (Rommelfanger and Weinshenker 2007). Nevertheless, interpretation of the effects of locus coeruleus ablation is confounded by the fact that it does not only lead to loss of noradrenaline but also of a number of cotransmitters (e.g. brain-derived neurotrophic factor [BDNF] and the neuropeptide galanin) that may also possess neuroprotective properties (Rommelfanger and Weinshenker 2007).

Studies on the association between noradrenergic signaling and neuropsychiatric symptoms in PD are scarce. At post-mortem examination, PD patients who suffered from depression exhibited increased neuronal loss and gliosis in the locus coeruleus, but not raphe nuclei, compared with PD patients without depression (Frisina et al. 2009). A nuclear imaging study with [11C]RTI-32 showed a negative correlation between the severity of depressive symptoms and monoamine availability in the locus coeruleus (Remy et al. 2005). Tricyclic antidepressants (TCAs), which block reuptake at both the level of the serotonin...
and noradrenalin transporter, are more effective in treating depression in PD than SSRIs (Troeung et al. 2013). Nevertheless, because of their less favorable side-effect and safety profile compared with SSRIs, and because SSRIs are also used to treat co-occurring anxiety, SSRIs are still the first-line treatment. The selective serotonin and noradrenaline reuptake inhibitor (SNRI), reboxetine (Pintor et al. 2006), but not atomoxetine (Weintraub et al. 2010b), was efficacious in treating depression in PD. Additional support for a role of noradrenaline in the pathophysiology of depression comes from preclinical animal studies. Knock-out of the noradrenaline transporter that increase extrasynaptic noradrenaline availability leads to reduced depression-like behavior and resilience against stressors (Perona et al. 2008; Haenisch et al. 2009). See (Haenisch and Bonisch 2011) for a review on the effects of modulating the noradrenergic system on depressive-like behavior in animal models.

The noradrenergic system has not been studied in relation to ICD development in PD. In PD patients without psychiatric disorders, however, atomoxetine was able to increase inhibition-related activity in the inferior frontal gyrus (Ye et al. 2014b). In correspondence with a study in healthy controls (Nandam et al. 2011), atomoxetine had no overall effect on behavioral performance, but was associated with behavioral improvement in those subjects that showed a more pronounced increase in inferior frontal gyrus activation (Ye et al. 2014b). In a double-blind placebo controlled study in PD patients, atomoxetine was able to improve action cancellation accuracy and reduce reflection impulsivity and risk taking (Kehagia et al. 2014). The role of the noradrenergic system in impulsive behavior has been studied more extensively in preclinical animal models. Overall it can be stated that increases in noradrenergic signaling improve impulse control (Chamberlain et al. 2007a; Robinson et al. 2008; Baarendse et al. 2013), but the mechanism is still unknown and is partly dependent on the subtype of impulsive behavior being studied (see Bari and Robbins 2013b for a review).

Anxiety in PD has also not been previously associated with (dysfunction of) the noradrenergic system. There is, however, some evidence from clinical trials on depression in PD that TCA’s and atomoxetine also improve co-occurring anxiety (Troeung et al. 2013). In mice, overexpression of alpha-synuclein in noradrenergic neurons in the locus coeruleus interferes with the regulation of dopamine-β-hydroxylase – the enzyme that converts dopamine into noradrenaline – and is associated with increased anxiety-like behavior in mutant compared with wild-type mice (Kim et al. 2014). Furthermore, combined depletion of dopamine and noradrenaline but not depletion of either neurotransmitter alone, increased anxiety-like behavior in rats (Delaville et al. 2012).

In summary, the role of the noradrenergic system in PD has so far received very little scientific attention and has been neglected as a potential therapeutic target for both motor and neuropsychiatric symptoms (‘a red-headed stepchild’ (Rommelfanger and Weinschenker 2007)). Nevertheless, based on the available empirical evidence, the noradrenergic system seems to be an interesting
target to pursue, particularly for impairments in impulse control. Whether the noradrenergic system is directly involved in the development of neuropsychiatric symptoms or through modulation of dopamine signaling is currently unknown and deserves further investigation.

Is Parkinson’s disease a functional disconnection syndrome?

As reviewed in Chapter 5, dopaminergic denervation of the striatum leads to a hypofunctioning of CSTC circuits that seems to, at least partly, underlie the motor, cognitive and neuropsychiatric symptoms of PD. This is supported by functional resting-state imaging studies showing decreased functional connectivity between cortical and striatal areas compared with healthy controls (Luo et al. 2014; Szewczyk-Krolikowski et al. 2014; Wei et al. 2014). This decreased connectivity correlates with disease severity (Wei et al. 2014), integrity of the striatal dopamine system (Baik et al. 2014), and normalizes after a dose of dopamine replacement therapy (Szewczyk-Krolikowski et al. 2014). Based on these findings, PD can be conceptualized as a functional disconnection syndrome, a term first coined in the 1970’s and also used to describe the pathophysiology of schizophrenia (Friston 1999) and autism (Melillo and Leisman 2009). The functional decoupling between the striatum and cortex in PD may also be partly due to reduced integrity of white matter tracts connecting the (pre)frontal cortex and striatum (Meijer et al. 2013; Kamagata et al. 2014; Rosskopf et al. 2014). Functional disconnection of CSTC circuits is relevant for, among other, response inhibition, executive functioning and emotional processing. PD-related dysfunction of these processes is discussed in more detail below. Although response inhibition can also be seen as an executive function, for the purpose of this discussion we consider it separately.

Response inhibition

Response inhibition is often used as an experimental operationalization of impulsivity (Aron 2011). As reviewed in Chapter 7, response inhibition depends on (mostly right-lateralized) brain areas within CSTC circuits with key functions for the inferior frontal gyrus, pre-supplementary motor area and subthalamic nucleus (Chambers et al. 2009; Aron 2011; van Velzen et al. 2014). In Chapter 6 we showed that early-stage medication-naïve PD patients in comparison with matched healthy controls exhibit behavioral deficits in response initiation but not action cancellation. PD patients also showed reduced activation of the bilateral inferior frontal gyrus and inferior parietal lobule during inhibition. Activation of the inferior frontal gyrus correlated negatively with disease severity and positively with DaT availability in the bilateral ventral striatum, suggesting a link between degeneration of the midbrain dopamine neurons in PD and impulsivity. It needs to be stressed that the correlation between DaT availability and activation of the IFG
was conducted in a smaller subset of our sample and did not survive the statistical correction for age. This finding therefore needs to be interpreted with caution and awaits replication. Nevertheless, the importance of the dopamine system in impulsivity is well established (Volkow et al. 1998; Nandam et al. 2011; Dalley and Roiser 2012; Ghahremani et al. 2012; Nandam et al. 2013). In Chapter 7 we provided an extensive review of the literature on response inhibition in PD and compared this with studies on other disorders that are characterized by inhibitory deficits, i.e. obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), trichotillomania and Tourette’s syndrome. In all discussed disorders, inhibitory deficits as well as some of the disorder-specific symptoms seem to stem from dysfunction of CSTC circuits. Because of the importance of dopamine in these circuits, we tentatively postulated that dysfunction of the dopamine system might be a common feature among all these disorders and underlie the inhibitory dysfunction. We postulated that the relation between dopamine and inhibitory control follows an inverted U-shape curve (Figure 7.2 and 7.3) where both decreases and increases in dopamine signaling relative to the optimum lead to deficits in inhibitory control. Dopamine degeneration in PD leads to decreases in dopamine, CSTC circuit dysfunction and inhibitory deficits, whereas dysfunction of CSTC circuits and inhibitory deficits in the other disorders is most probably related to neurodevelopmental changes in dopamine signaling. What these changes are depends on the disorder and may entail changes in dopamine receptor availability, DaT availability or the metabolization of dopamine (Prince 2008; Olver et al. 2009; Steeves et al. 2010). Other neurotransmitters, such as serotonin and noradrenaline, likely also contribute to aberrations in inhibitory control, either through modulation of dopamine signaling or signaling through their own afferent projections (Boureau and Dayan 2010; Cools and D’Esposito 2011; Dalley and Roiser 2012; Bari and Robbins 2013a; de Bartolomeis et al. 2013).

The study of response inhibition in PD may be particularly valuable to understand the pathophysiology of ICD in PD. Nevertheless, as reviewed in Chapter 7, very few studies have so far investigated response inhibition in PD patients with ICD and no neuroimaging studies have yet been conducted. Because multiple studies have shown that response inhibition impairments are observable in both OCD patients and their unaffected siblings (Menzies et al. 2007; Chamberlain et al. 2008a; de Wit et al. 2012), it has been suggested that response inhibition failures constitute an endophenotype of OCD (Chamberlain and Menzies 2009). An endophenotype is defined as a measurable or observable trait (i.e. biomarker) between genotype and phenotype that is heritable and is associated with an increased risk for the development of a particular disorder (John and Lewis 1966; Gottesman and Gould 2003b). Response inhibition impairments may also constitute an endophenotype of ICD in PD, or may at least be seen as a valuable biomarker for ICD development in PD patients after they commence dopamine replacement therapy. Genetic association studies have shown that ICD in PD is associated with polymorphisms in genes coding for the dopamine D3 receptor (DRD3), serotonin 2A receptor
(HTR2A) and the glutamate N-methyl D-aspartate receptor subtype 2B (GRIN2B) (Lee et al. 2009; Vallelunga et al. 2012). These results mimic those obtained in patients with ICD in the general population where ICD development has been associated with polymorphisms in all layers of the dopamine and serotonin signaling cascade, and in glutamate receptors (see Cormier et al. 2013; Leeman and Potenza 2013 for reviews). Because polymorphisms in a number of the same genes that are associated with ICD are also associated with performance of response inhibition tasks (see Chapter 7), response inhibition might be a useful endophenotype to study the risk for ICD development in PD. In the (near) future, response inhibition might also be used as a tool to screen PD patients for the risk for ICD development.

**Executive functioning**

There is considerable evidence that supports a role of CSTC signaling and dopaminergic neurotransmission in executive functioning (Chudasama and Robbins 2006; Leh et al. 2010; Yuan and Raz 2014). It is therefore not surprising that PD patients exhibit deficits in executive functioning, including deficits in cognitive flexibility, planning, attention, learning and working memory (Kehagia et al. 2010). Executive dysfunction in PD may influence the ability to cope with real-life problems and stressors (Hurt et al. 2012) in a continuously changing environment, and thereby forms an important modulator in the development of neuropsychiatric symptoms. Furthermore, cognitive problems also make behavioral and cognitive interventions less feasible as treatment options. PD-related executive dysfunction is sensitive to treatment with dopamine replacement therapy but the effect depends highly on the specific task and endogenous dopamine concentrations. Reviews on the effects of dopaminergic medication on cognitive functioning are provided by (Vaillancourt et al. 2013) and (Robbins and Cools 2014).

Neuroimaging studies in PD patients have shown an association between alterations in brain areas that are part of the associative CSTC circuit and deficits in executive functioning. Morphometric studies have shown that reductions in gray-matter volume of frontostriatal brain areas correlate with executive deficits in PD (O’Callaghan et al. 2013a; Gerrits et al. 2014a; Lee et al. 2014a; Mak et al. 2014). PD patients also showed decreased recruitment of among others the dorsolateral prefrontal cortex (DLPFC) and caudate nucleus compared with healthy controls during performance of a working memory task (N-back) (Ekman et al. 2012). The task-related activation of the caudate nucleus correlated positively with DaT availability in the same region. In our own lab we showed that compared with matched healthy controls, early-stage drug-naïve PD patients hyperactivated the DLPFC and caudate nucleus during performance of the N-back task, but at the same time showed decreased functional connectivity between the DLPFC and precuneus, superior, and inferior frontal gyrus (Trujillo et al. 2014). On average, behavioral performance was still relatively preserved but correlated positively
with dopamine content (as measured by DaT availability) in the anterodorsal striatum.

The DLPFC plays a critical role in cognitive flexibility, working memory and planning and is the main cortical target of the associative CSTC circuit (Cohen et al. 2009; Leh et al. 2010; Aupperle et al. 2012). In PD, boosting DLPFC activation using transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) improved performance on the trail-making task (i.e. attention and switching) (Doruk et al. 2014), N-back task (working memory) (Boggio et al. 2006) and Tower of London task (planning) (Srovnalova et al. 2012). Similarly, inhibiting the DLPFC with repetitive TMS in healthy controls results in decreased performance on the Tower of London task (van den Heuvel et al. 2013) and set-shifting task (Gerrits et al. 2014b) with concomitantly decreased task-related activity. Comparing set-shifting performance between healthy controls and early-stage drug-naive PD patients showed that task-related activation of the ventrolateral prefrontal cortex was decreased but compensated for by increased activation of the parietal, superior frontal and superior temporal gyrus that probably underlay the observed preservation of set-shifting performance (Gerrits et al. 2015). Other studies, however, in medicated PD patients at more advanced disease stages have observed more set-shifting errors and decreased task-related activation compared with healthy controls (Monchi et al. 2007; Rustamov et al. 2014).

In short, deficits in executive functioning are common in PD and are associated with alterations in activation and connectivity of brain areas that are related to the associative CSTC circuit, particularly the DLPFC. Cognitive functions are a relevant study subject matter in the investigation of neuropsychiatry in PD because they are necessary for the correct recognition and appraisal of emotions (see below) and changing the activation of the associative CSTC circuit might therefore constitute a possible treatment target for neuropsychiatric symptoms.

**Emotional processing**

The CSTC circuits are also involved in the processing of emotional stimuli (Fusar-Poli et al. 2009b; Peron et al. 2012). Numerous studies have shown that PD patients exhibit deficits in recognizing emotional stimuli across modalities (i.e. visual and vocal stimuli; negative more than positive emotions) and show a blunted psychological as well as physiological reaction to these stimuli (see Peron et al. 2012 for a review). Based in part on these results, it has been suggested that PD patients suffer from alexithymia (Costa et al. 2010); see box 8.1. Dopamine also seems to play an important role in emotional processing. Pharmacological studies in healthy controls have shown that administration of dopamine (ant) agonists affects the ability to recognize emotional stimuli and alters concomitant task-related activity in CSTC-related brain areas (see Salgado-Pineda et al. 2005 for a review). PD patients exhibit reduced brain activity in these same brain areas, particularly those of the limbic CSTC circuit, while viewing emotional stimuli. One
study showed that orbitofrontal cortex volume correlated with the ability to recognize emotional faces in PD patients (Ibarretxe-Bilbao et al. 2009). Emotional stimuli also elicited a blunted activation of the ventrolateral prefrontal cortex that correlated with the degree of putaminal dopaminergic denervation (Lotze et al. 2009). Two other studies have observed reduced amygdalar activation (Tessitore et al. 2002; Yoshimura et al. 2005) while processing emotional stimuli. This amygdalar hypoactivation was partly restored by dopamine replacement therapy (Tessitore et al. 2002).

It has been well established that the amygdala plays an important role in the processing of emotional stimuli and its dysfunction is linked to the development of affective disorders. In Chapter 2 we showed that the severity of anxiety symptoms, mainly the severity of psychological symptoms, correlates negatively with volume of the left amygdala. This left-lateralization was not associated with the lateralization of motor symptoms. The left amygdala seems to be more involved in the processing of negative emotional stimuli and sustained emotional processing compared with the right amygdala (Fusar-Poli et al. 2009a). Since this was a cross-sectional study and only the first to study the volumetric correlates of anxiety symptoms in PD, we have to be careful about drawing conclusions on the directionality. Nevertheless, we tentatively speculate that PD-related neurodegeneration of the amygdala constitutes a risk factor for the development of anxiety symptoms. Supporting evidence stems from studies showing reduced in vivo volume (Bouchard et al. 2008; Ibarretxe-Bilbao et al. 2009; Morgen et al. 2011) and increased amygdalar neuronal loss at post-mortem examination (Braak et al. 1994; Harding et al. 2002) in PD patients versus matched healthy controls and that (surgical) damage to the amygdala is associated with the development of anxiety (Truitt et al. 2009; Assefa et al. 2012; Knutson et al. 2013). Alternative interpretations, such as that the reduction in amygdalar volume occurs secondary to the development of anxiety symptoms or that individuals with a premorbid smaller amygdala – independent of the development of PD – already have an increased risk of developing anxiety symptoms cannot not be ruled out. These alternative hypotheses can only be discounted or confirmed with prospective longitudinal studies. Such studies should also investigate what the link is between dysfunction in emotional processing and the development of anxiety, depression or apathy, something that is still incompletely understood (Peron et al. 2012). So far, correlations between performance on emotional processing tasks and severity of affective symptoms have provided mixed results with some studies showing a positive correlation (Kan et al. 2002; Clark et al. 2008) while others do not (Dujardin et al. 2004; Lawrence et al. 2007; Dara et al. 2008).

In summary, processing of emotional stimuli is disturbed in PD and seems to be governed by dysfunction of dopamine signaling and reduced activity in the limbic CSTC circuit, particularly in the amygdala. Dysfunction of the amygdala also seems to be relevant for the development of anxiety symptoms in PD patients but whether this depends on PD-related pathological alterations or not remains
to be determined by future studies. These studies should also investigate the link between dysfunction of emotional processing, alexithymia and the development of neuropsychiatric symptoms.

**Box 8.1 - Alexithymia in Parkinson’s disease**

Alexithymia is defined as an inability to identify and describe one’s feelings and distinguish between feelings and bodily sensations of emotional arousal (Taylor et al. 1991). Although alexithymia is considered a personality trait, there is evidence that the prevalence is approximately twice as high in PD compared with the general population (Costa et al. 2010). Degeneration of dopaminergic mesolimbic and mesocortical projections has been suggested as the possible cause for this increased prevalence (Costa et al. 2010). Neuroimaging studies have also shown decreased activation of the prefrontal, parietal and anterior cingulate cortex during emotional processing in alexithymic males compared with non-alexithymic males (Berthoz et al. 2002; Kano et al. 2003). The lack of emotional self-awareness that alexithymics seem to suffer from might be associated with the development of neuropsychiatric disorders. Associations between the severity of alexithymia and depression, apathy or anxiety in PD have provided mixed results with some studies showing positive correlations (Costa et al. 2010; Goerlich-Dobre et al. 2014), while another showed no association (Bogdanova and Cronin-Golomb 2013). Similarly, studies in the general population showed that alexithymia was associated with higher anxiety scores in late adolescents (Karukivi et al. 2014), but was not associated with depression in the elderly (Mooi et al. 2010). Recently, it was shown that the severity of alexithymia in PD patients, mainly difficulty in identifying and describing feelings, is associated with the severity of ICD (Goerlich-Dobre et al. 2014), a result that has also been observed in the general population (Mitrovic and Brown 2009). The authors suggested that patients with alexithymia do not know how to deal with negative emotions and therefore perform impulsive-compulsive behavior as a compensatory mechanism to alleviate the distress (Goerlich-Dobre et al. 2014). It also seems that alexithymia and ICD are at least partly associated with dysfunction of the same brain areas (Berthoz et al. 2002; Kano et al. 2003; Vriend et al. 2014). In short, alexithymia might be an interesting construct to take into account in the study of neuropsychiatric disorders in PD. On a side note; if the main symptom of alexithymic patients is that they have difficulty describing feelings, how reliable are (self-report) rating scales for the severity of neuropsychiatric symptoms?
Interaction between cognition and emotion: dorsal vs. ventral systems

In the general population, dysfunction of CSTC circuits is well documented in several neuropsychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia and obsessive-compulsive disorder (Phillips et al. 2003a; van den Heuvel et al. 2011). In 2003, Mary Phillips and colleagues postulated a theoretical framework for the neurobiological underpinnings of emotion dysfunction in major depressive disorder, bipolar disorder and schizophrenia (Phillips et al. 2003a; Phillips et al. 2003b). This model was updated in 2008 to include six emotion regulation subprocesses proposed by Ochsner and Gross (Ochsner and Gross 2007) and applied to explain the results of neuroimaging studies in bipolar disorder (Phillips et al. 2008) and major depressive disorder (Rive et al. 2013). To review all these subprocesses would defeat the purpose of this section and interested readers are therefore referred to the reviews of (Phillips et al. 2008) and (Rive et al. 2013). In general terms, the model specifies that emotion dysfunction arises due to an imbalance between a ventral ‘emotion perception and generation’ system and a dorsal ‘emotion regulation’ system. The ventral system is responsible for identification and appraisal of the emotional significance of a certain stimulus and generation of a specific affective state and awareness (i.e. bottom-up influence of emotion). The dorsal system’s function is to regulate these affective states and control emotional behavior (i.e. top-down cognitive control). Figure 8.3 provides an illustration of these systems. The ventral system comprises the amygdala, insula, ventral striatum, ventral anterior cingulate cortex, ventromedial prefrontal cortex and orbitofrontal cortex, while the dorsal system includes the hippocampus, dorsal anterior cingulate cortex and dorsolateral and dorsomedial prefrontal cortex (Phillips et al. 2003b; Phillips et al. 2008). These ventral and dorsal systems are nearly equivalent to the limbic and associative CSTC circuits with presumptive roles in emotional processing and executive functioning, respectively (Alexander et al. 1986; Vriend et al. 2014c). There is substantial evidence from studies in animal models, lesion and neuroimaging studies to suggest that aberrations in brain areas of the dorsal or ventral system are associated with neuropsychiatric disorders (Phillips et al. 2003a; Phillips et al. 2008; van den Heuvel et al. 2011; Rive et al. 2013). Neuropsychiatric symptoms are thought to occur when regulation of emotional behavior by the dorsal system is decreased and/or sensitivity of the ventral system to emotional stimuli is increased (Phillips et al. 2003a). Although this model was based on findings in neuropsychiatric disorder in non-PD samples, it might also be applicable to the development of neuropsychiatric symptoms in PD. Nevertheless, whereas the etiology of ventral/dorsal system imbalance in non-PD samples should probably be sought for in neurodevelopmental processes, the imbalance in PD patients is likely due to neurodegenerative processes (e.g. degeneration of dopaminergic, serotonergic and noradrenergic systems). There is substantial evidence for dysfunction of the dorsal associative system in PD patients that is commonly linked to deficits in executive functioning
see above. The ventral limbic system seems to be relatively well preserved early on in the disease but may start to show dysfunction with progression of the disease (O’Callaghan et al. 2014) or after dopamine suppletion, either because of over-dosing the ventral limbic circuit (Cools 2006) or due to denervation-induced dopamine receptor supersensitivity ((Gerfen et al. 2002); Chapter 5). Studies on neuropsychiatry in PD using the theoretical framework of Phillips and colleagues are limited and this field deserves further attention. One study already showed, however, that boosting the activity of the DLPFC (part of the dorsal system) with repetitive TMS had antidepressant effects similar to the SSRI fluoxetine (Cardoso et al. 2008), suggesting that increasing the activation of the cognitive dorsal system can improve neuropsychiatric symptoms in PD.

Conclusion – is PD a functional disconnection syndrome?

Based on the above reviewed literature it is evident that response inhibition, executive functioning and emotional processing in PD are at least partly related to a functional disconnection of the striatal and cortical areas that leads to dysfunction of CSTC circuits. A relative imbalance in activity between CSTC circuits by which unconstructive emotions are insufficiently regulated by cognitive processes is associated with emotional dysregulation and the development of neuropsychiatric disorders. Our understanding of these disorders in PD can greatly improve by further studying the neural correlates of response inhibition, executive functioning and emotional processing and studying the hypothesized imbalanced activation of dorsal and ventral CSTC circuits.

Methodological Considerations

The studies reported in this thesis need to be interpreted bearing some limitations in mind. Most of the reported studies were conducted on data derived from a database of PD patients that visited the outpatient clinic for movement disorders of the VU University medical center between 2008 and 2012. This outpatient clinic is a tertiary referral center and approximately 50 percent of the patients are referred to this clinic for a second opinion. These patients may therefore not be a perfect reflection of the overall PD population, thereby hampering generalization. Furthermore, although this thesis focused on the pathophysiology of neuropsychiatric disorders in PD, none of the PD patients were formally diagnosed (e.g. according to DSM criteria) with such a disorder within the context of our studies. Rather we used (self-report) rating scales—validated for use in PD—to determine the severity of neuropsychiatric symptoms and correlated them with neuroimaging parameters. Due to the use of these rating scales our samples also included patients with subclinical neuropsychiatric symptoms that may have different neurobiological underpinnings than full-
Blown neuropsychiatric disorders. However, given the fact that all our regression analyses showed linear relations between the severity of neuropsychiatric symptoms (i.e. anxiety, depression and ICD) and changes in neuroimaging parameters (i.e. volume, DaT availability or brain activation), this is unlikely. Furthermore, the range of scores of our samples on the rating scales extended well beyond the published cut-off scores for clinically significant symptoms and patients with these score would probably have met the diagnostic criteria for clinical diagnoses of depression, anxiety and ICD.

In hindsight, there are a couple of things that, given the opportunity, I would
have done differently. For one, I would like to have had a measure for the severity of apathy. Unfortunately, such a questionnaire was not part of the battery of questionnaires utilized in our outpatient clinic for movement disorders. As reviewed in Chapter 5, apathy shows both phenomenological and neurobiological overlap with depression and such a measure would have allowed us to (partly) disentangle the neural correlates of these related motivational disorders. The set of questionnaires also did not include a measure of the severity of ICD symptoms (e.g. the questionnaire for impulsive-compulsive disorders in Parkinson’s disease-rating scale; QUIP-RS). The QUIP-RS was not available at the time we started data collection in 2008. We therefore did not have a baseline measure for the severity of ICD in our study reported in Chapter 4 that would have allowed us to see the effects of commencing dopamine replacement therapy on the development of ICD symptoms. Furthermore, healthy controls and non-PD patients with neuropsychiatric symptoms were not included in our studies except for the study reported in Chapter 6. Measurements in these subjects could have been valuable in disentangling the contributions of the PD pathology and neurobiological alterations associated with the development of neuropsychiatric symptoms unrelated to PD pathology.

Clinical implications and future prospects

The ultimate goal of all clinical research is to advance our knowledge of the pathophysiology of a disease and its symptoms and (thereby) improve care for patients. The research discussed in this thesis focused on the neurobiological aspects of three neuropsychiatric disorders, not on therapeutic interventions. Therefore our findings cannot directly be applied to clinical practice. Nevertheless, in addition to advancing our knowledge of the pathophysiology of neuropsychiatric disorders in PD, this thesis also provides several leads for future screening methods and potential therapeutic interventions. The implications for clinical practice and directions for future studies are discussed below.

Implications for depression and ICD in PD

Depression and ICD are a major source of distress in PD patients, yet the neurobiological risk factors for their development are still largely unknown. Our research on the association between depressive symptoms and DaT availability in the caudate nucleus supports the role of a loss of dopamine in the limbic and associative CSTC circuit in the pathophysiology of PD-related depression and suggests that optimizing dopamine replacement therapy deserves consideration as a first step in the treatment of PD-related depression. This was also captured by our model presented in Chapter 5.

This thesis also suggests that DaT SPECT imaging may be useful for other
purposes than just for the differential diagnosis of movement disorders. Imaging of the integrity of the striatal dopamine system with \([123I]\text{FP-CIT SPECT}\) may for example be used to identify PD patients at risk of developing ICD after commencing dopamine replacement therapy. Further support from prospective longitudinal studies is of course needed before this approach can be put into clinical practice. In our department we are currently conducting a prospective longitudinal study in which we follow 60 PD patients from diagnosis and start of dopaminergic suppletion until four years into the disease to monitor the development of ICD symptoms and progression of motor, cognitive and other neuropsychiatric symptoms. All PD patients will undergo \([123I]\text{FP-CIT SPECT}\) scanning at baseline. We hypothesize, as we did in our study in Chapter 4, that PD patients at risk of developing ICD symptoms will have lower striatal \([123I]\text{FP-CIT}\) binding at baseline compared with not-at-risk PD patients. Before \([123I]\text{FP-CIT SPECT}\) scanning can be used in clinical practice for ICD risk prediction in individual patients, however, specific cut-off values (e.g. using machine learning) first need to be defined. Studies should also investigate whether reduced \([123I]\text{FP-CIT}\) binding relates to downregulation of the DaT or increased dopamine degeneration by in vivo dual imaging of DaT and VMAT2, to provide support for our theory or the ‘overdose’ theory on the development of ICD, as mentioned previously. Studies in animal models can also shed more light on the effect of dopamine denervation on impulse control. At the Anatomy & Neuroscience department we are currently investigating the role of dopamine denervation of the ventral and mediodorsal striatum (with sparing of the sensorimotor part of the striatum) in impulse control in a rat model of PD. After the rats are treated with 6-hydroxydopamine (6-OHDA) to dopamine deplete these striatal areas we will compare their performance on the stop-signal task (the animal variant of the paradigm we used Chapter 6) with the performance of sham-lesioned animals. The rats will subsequently be treated with dopamine replacement therapy (levodopa or agonists) to study the effects of dopamine suppletion on impulsivity in Parkinson-like (i.e. 6-OHDA lesioned) and sham-lesioned rats. This design will allow us to test the validity of the model presented in Chapter 5 for the interaction between ventral striatal dopamine depletion and dopamine suppletion, and the subsequent development of ICD (figure 5.2). In this animal model we can also study the potential therapeutic effects of serotonergic and noradrenergic agents on impulse control.

In Chapter 5 we suggested to study the temporal relation between symptoms of depression and ICD, symptoms that frequently co-occur in PD but seem to be associated with contrasting symptomatology and limbic brain activation patterns. The Experience Sampling Method is a technique that can be used to study everyday occurrence and fluctuations of symptoms by prompting patients to answer specific questions related to mood, motor symptoms, medication status, etc., at specific time points throughout the day by means of paper-and-pencil or—a more recent introduction—with smartphone applications (Bolger
et al. 2003). This technique can be a valuable tool to determine the situations in which patients experience depressive or ICD symptoms, the temporal relation between these symptoms and thereby provide clues to the environmental, psychological and neurobiological factors that contribute to them. Studying the neurobiological and clinical factors that underlie depression and ICD is something I will actively pursue in the coming years.

Our study in drug-naïve PD patients on response inhibition shows that the stop-signal task is sensitive to subtle impairments of inhibition-related neural activity, even without clinically relevant ICD. Although this hypothesis is as of yet untested, it is conceivable that individual PD patients that already show behavioral and functional deficits during performance of the stop-signal task in a drug-naïve state have an increased risk of developing ICD symptoms after commencing dopamine replacement therapy. We are currently conducting follow-up analyses on our cohort of drug-naïve PD patients to test the validity of this hypothesis and to see whether the stop-signal task is valuable as a risk assessment tool.

Lastly, future studies can make comparisons – as we did in our review in Chapter 7 – between ICD in PD and other disorders within the impulsive-compulsive spectrum, such as OCD, to find common as well as distinct biomarkers for impulsive and compulsive behaviors, focusing on goal-directed learning, habit formation, response inhibition and cognitive control functioning that involve signaling in the various parallel CSTC circuits.

Implications for anxiety in PD

As previously mentioned, there is great paucity in our understanding of the pathophysiology of anxiety in PD, and evidence-based treatments for this disorder are currently not available. Our study suggests involvement of the amygdala, similar to anxiety in non-PD patients. Other studies suggest a role of dopamine denervation, but at this point there is not much more empirical evidence available. The lack of studies on anxiety in PD is in part because until recently there was a lack of validated scales to accurately diagnose and measure the severity of anxiety in PD (Leentjens et al. 2011a; Leentjens et al. 2014). Since there are no evidence-based treatments for anxiety disorders in PD, clinical trials need to be conducted. Given the (unpublished) success of SSRI’s in treating anxiety in PD patients in clinical practice, this class of pharmacotherapeutics deserves the primary attention. By extension, the serotonergic system should be considered in the pathophysiology of PD-related anxiety and examined using nuclear imaging techniques employing tracers specific for the serotonin transporter (e.g. [11C] DASB) and serotonin receptors (e.g. [18F]MPPF). Wearing-off anxiety, on the other hand, may depend more on dopamine dysfunction and require a different type of treatment. This type of anxiety is often associated with dopaminergic undertreatment and can be remedied by increasing the dose, shortening the dose intervals, or prolonging drug release to reach longer-lasting steady-state dopamine levels (Stacy et al. 2005). Increasing or prolonging doses is, however,
not always feasible due to the risk of developing dyskinesias. Furthermore, a number of patients suffers from wearing-off anxiety that arises unpredictably and does not correspond to plasma dopamine levels (van Laar 2003), suggesting that dopamine does not provide the full story for these fluctuations. Although there are questionnaires available that score wearing-off symptoms, these do not capture hour-to-hour fluctuations, thereby hampering associations with clinical information. The Experience Sampling Method likely provides the best method to study these fluctuations and provide clues to the pathophysiology of wearing-off anxiety.

**The need for prospective studies**

This thesis is largely based on cross-sectional and retrospective studies. As mentioned previously, there is a dire need for prospective and longitudinally collected data. Many research questions cannot be adequately answered using study samples obtained by just a single center. This is increasingly being realized and therefore (inter)national collaborations such as the Parkinson’s Progression Marker Initiative (PPMI; http://www.ppmi-info.org/) and the Oxford Parkinson’s Disease Centre (OPDC; http://opdc.medsci.ox.ac.uk/) have been set up. The goal of these cohorts is to identify markers for disease progression and develop new strategies for early diagnosis and intervention. In the Netherlands we are currently setting up the Netherlands Parkinson Cohort (NPC), which is a joint venture of seven Dutch University Medical Centers and several non-academic centers to collect data from PD patients with a focus on neuropsychiatry and cognition (http://www.parelsnoer.org/).

**Conclusions**

The aim of this thesis was to gain a better understanding of the underlying neurobiological mechanisms of PD-related anxiety, depression and ICD, using multiple neuroimaging modalities and analytical tools. Overall, our results showed that the severity of these symptoms is linked to imaging measures of the neurodegenerative process in PD. Anxiety symptoms were associated with reductions in amygdala volume. We further showed that degeneration of striatal dopamine projections is associated with the severity of depressive symptoms and the development of ICD symptoms after patients commence dopamine replacement therapy. Moreover, (functional) deficits in impulse control may already be evident prior to the start of dopamine replacement therapy, but it remains to be determined whether or not these deficits increase the risk of later developing full-blown ICD. In this thesis, we also present two neurobiological models revolving around dysfunction of the midbrain dopamine system as a major contributor to the development of PD-related depression and ICD, as well as inhibitory dysfunction in PD and other disorders within the impulsive-
compulsive spectrum. This thesis furthermore provides possible leads for future clinical and preclinical studies, particularly the investigation of risk factors of and treatment alternatives for ICD. Also, I strongly argue for more research on the pathophysiology and treatment of anxiety and the contributions of the serotonergic and noradrenergic systems to PD-related neuropsychiatric disturbances. With initiatives such as the PPMI, the OPDC and the establishment of the Netherlands Parkinson Cohort, research on the pathophysiology of PD has taken a tremendous leap forward and holds promise for further elucidation of the intricate puzzle that is the pathophysiology of PD-related neuropsychiatry. Increased understanding of this pathophysiology will ultimately lead to better prediction, recognition and treatment of these highly detrimental disorders. All in all, exciting times lie ahead for research and treatment of PD-related neuropsychiatry.