Behavioral and neuroimaging studies on language processing in Dutch speakers with Parkinson's disease
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2.1 Introduction

The motor disabilities of Parkinson’s disease (PD) patients are the result of abnormalities of basal ganglia (BG) function. This chapter highlights the consequences of dopamine loss in the BG, which may be held responsible for the emergence of motor and some non-motor symptoms in PD. We start this chapter by considering the basic neuroanatomy of the BG. A detailed review of the anatomy, physiology, and biochemistry of the BG is beyond the scope of this thesis and can be found in for example DeLong and Wichmann (2007, 2010), Bartels and Leenders (2009) or Wichmann and DeLong (2007). However, the description that follows is intended to be sufficient for readers to understand the proposed role of the BG in language processing. The BG are known to be organized into circuits that influence cortical functioning, and the current models on the cortico‐striato‐pallido‐thalamo‐cortical circuits are briefly discussed. Unraveling the micro-level of the circuits, each BG circuit contains at least three separate pathways: the direct, indirect and hyperdirect pathway. After describing the neuromodulation within these separate pathways, BG function in health and disease is described in more detail. The section on the hypothesized roles of the BG in the cognitive domain is concluded with the presentation of evidence of cognitive impairments in PD patients without dementia.

2.2 Basic neuroanatomy of the basal ganglia

The human BG are a system of grey matter structures located bilaterally deep in the brain, and include mainly the striatum, the pallidum, the subthalamic nucleus (STN), and the substantia nigra. Most of these nuclei also consist of subnuclei. The striatum encompasses three subnuclei: the nucleus caudatus (or also caudate nucleus, Caud), the putamen (Put) and the nucleus accumbens (Acb); the pallidum also consists of three subnuclei: the internal and external segments of the globus pallidus (GPI and GPe respectively) and the ventral pallidum (VP). Finally the substantia nigra (SN) consists of a pars compacta, containing dopaminergic neurons (SNc,) and a pars reticulata (SNr). The STN is a rather small nucleus that is not subdivided. The ventral tegmental area (VTA), located medial to the substantia nigra also contains dopaminergic neurons (Groenewegen & Van Dongen, 2007). Figure 2.1 shows the location of the most important parts of the BG from the lateral view.
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Figure 2.1: Macro-anatomy of the basal ganglia from a lateral viewpoint, the left cerebral hemisphere removed (Glubbegovic & Williams, 1980)

1. nucleus caudatus (Caud); 2. foot of lentiform nucleus (putamen, (Put) & Globus Pallidus); 3. putamen (Put); 4. gray connections between putamen (Put) and nucleus caudatus (Caud); 5. pulvinar of thalamus

Each of the structures in the cortico-striato-cortical circuits is composed of many \(10^4-10^{10}\) neurons and is characterized by complex spatio-temporal interactions (Bergman et al., 1998). Therefore we will here only illustrate schematically the most basic concepts of the anatomy of the BG.

As illustrated in Figure 2.2 (A and B), the striatum is the core input nucleus of the BG, and as such receives information from the cerebral cortex. The output side of the BG is formed by three other nuclei: the internal segment of the globus pallidus (GPI), substantia nigra pars reticulata (SNr) and ventral pallidum (VP). The output nuclei project to specific parts of the thalamus, which in turn project to different areas of the frontal cortex. The connections between the input and output structures of the BG are served by the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN) and are also called the ‘intrinsic nuclei’ of the BG (Martin, 2003) (see Figure 2.2 A and B).
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2.3 Cortico-striato-pallido-thalamo-cortical circuits

The connections of the BG and thalamus with the cortex are not yet fully understood. However, Alexander, DeLong and Strick (1986) were the first to publish a clear overview of the anatomy of these circuits. The BG are described as a site of anatomical convergence and divergence (Bergman et al., 1998) and are also seen as participants in five parallel ‘loops’ or ‘circuits’ with the cerebral cortex. According to the findings of Alexander et al. (1986) and also Bergman et al. (1998) the BG along with the thalamus and cortex make up the cortico-striato-pallido-thalamo-cortical circuits (abbreviated as cortico-striato-cortical circuits and from now on referred to as such). The flow of information within the circuits is topographically organized from the cortex through the BG to the thalamus and back to the frontal cortex.

Five different circuits have been described. These are the skeletomotor, oculomotor, anterior cingulate, dorsolateral prefrontal and lateral orbitofrontal circuits (Alexander et al., 1986). Two of these five circuits involve motor areas, that is, the skeletomotor and oculomotor areas of the cerebral cortex. The remaining three loops incorporate non-motor areas of the frontal cortex. These non-motor regions include the dorsolateral prefrontal cortex (Brodman Area (BA) 46), the lateral orbitofrontal cortex (BA 12), and the anterior cingulate/medial orbitofrontal cortices (BA 24 and 13). These frontal regions are known to be involved in planning, cognitive flexibility, working memory, rule-based learning, attention,
and other aspects of higher executive\textsuperscript{4} function (Middleton & Strick, 2000). Figure 2.3 illustrates the three main cortico-striato-cortical circuits.

In his review article, Cummings (1993)\textsuperscript{5} described the syndromes that derive from lesions of specific circuit structures. There were striking similarities in behavioral changes after frontal cortical lesions and lesions restricted to the BG, which were comprehensively illustrated with clinical evidence. In other words, damage to striatal structures that are part of a particular cortico-striato-cortical circuit can result in a deficit that was originally thought to be caused by a lesion of the frontal cortical area that is served by the circuit (see Figure 2.3).

\textsuperscript{4} The term executive function is used as a blanket term referring to a set of abilities that allow individuals to achieve goal-oriented behavior. These aspects of behavior can be regarded as top-down processes, in contrast to bottom-up processes that only represent stimulus driven processing. Lezak (1982) defines executive functions the following way: “those mental capacities necessary for formulating goals, planning how to achieve them, and carrying out the plans effectively” (p. 281). Executive functions will be discussed in more detail in section 2.8.2.

\textsuperscript{5} For a recent update see Tekin and Cummings (2002).
Figure 2.3: Schematic representation of the three main cortico-striato-cortical circuits regulating various aspects of motor control, cognition, emotion in humans, adapted from Groenewegen and Van Dongen (2007).
The BG outputs to the cerebral cortex are more widespread than originally thought. According to Middleton and Strick (2000, 2002) there must exist more than five circuits, since they found evidence for the existence of loops with the temporal and parietal cortex too. The loop structure has been conceptualized as a unilateral system, but cortical projections to the contralateral neostriatum, especially from the medial frontal cortex, also exist (Buchanan, Thompson, Maxwell, & Powell, 1994; Cowan & Wilson, 1994; Inase, Tokuno, Nambu, Akazawa, & Takada 1999; Morino, Mascagni, McDonald, & Hökfelt, 1994; Wang & Pickel, 1998).

The early findings on the circuits were mainly based on tracer studies in monkey brains (Alexander et al., 1986; Bergman et al., 1998; Middleton & Strick, 1994). By using Diffusion Tensor Imaging, Lehéricy et al. (2004) could demonstrate in a non-invasive way the existence of distinct cortico-striato-cortical circuits in humans that had till then only been hypothesized on the basis of primate-human extrapolations. In particular, Lehéricy et al. (2004) described a functional relationship between:

1) Putamen anterior > premotor cortex  
2) Putamen posterior > motor cortex  
3) Nucleus caudatus > prefrontal cortex  
4) Ventral striatum > orbitofrontal cortex

Summarizing, the general role for the distinct cortico-striato-cortical circuits is modulating through a system of anatomical convergence and divergence the operations of the frontal lobe.

2.4 The roles of the direct, indirect and hyperdirect pathway

Albin, Young and Penney (1989), Alexander and Crutcher (1990) and Crossman (1989) proposed the direct and indirect pathways model, explaining the connectivity of the BG system. Although drawbacks of the model (Parent, Levesque, & Parent, 2001) have led to more complex approaches, it is still the most widely accepted and used assumption.

As illustrated in the ‘box-and-arrow’ model in Figure 2.4, the input and output structures of the BG are either directly or indirectly (via intrinsic nuclei) connected to each other. The direct and indirect pathways involved in motor control are given as an exemplar in Figure 2.4.
Figure 2.4: Schematic diagram of the direct, indirect and hyperdirect pathways in relation to motor control.

Figure 2.4 shows that the motor cortices send activating signals to the Nucleus caudatus (Caud) and Putamen (Put). The cells of the direct pathway in the Nucleus caudatus and Putamen that receive these signals are inhibitory and, once they become activated, send inhibitory signals to the internal segment of the globus pallidus and substantia nigra pars reticulata (GPI/SNr output nuclei). In rest, these two nuclei send inhibitory signals to the ventral anterior nucleus of the thalamus, which prevents the development of significant activity in the motor cerebral cortices. However, on activation of the direct pathway, the net effect of the two successive inhibitory signals allows activation of the thalamus which, in turn, sends activating signals to the motor cortices. By way of an intermediary projection via the external segment of the globus pallidus and subthalamic nucleus (GPe-STN projection) the indirect pathway inhibits the excitatory neurons within the thalamus, which project to the motor regions of the cerebral cortices, and which subsequently results in reduced activity within the motor cortex. In this way the two pathways are in balance, with the direct being responsible for facilitation of action and the indirect for braking or switching from one action to the next.
Recently, a third pathway has been described, which is the hyperdirect pathway (see Figure 2.4), as the subthalamic nucleus (STN) not only receives inhibitory input from the external segment of the globus pallidus (GPe), but also excitatory input directly from cortical fibers (Crosson, Benjamin, & Levy, 2007; Groenewegen & Van Dongen, 2007; Martin, 2003; Nambu et al., 2000; Nambu, Tokuno, & Takada, 2002). The hyperdirect pathway is excitatory to the internal segment of the globus pallidus and substantia nigra pars reticulata (the GPi/SNr), but then inhibits the excitatory neurons within the thalamus (Crosson et al., 2007).

To summarize, the effect of the direct and indirect pathways are functionally opposite; the direct pathway enhances thalamic activation back to the cortex, while the indirect pathway suppresses activation. A third pathway called the hyperdirect pathway projects directly from the cortex to the subthalamic nucleus (STN) and has a suppressive effect on action.

2.5 Neuromodulation of the cortico-striato-cortical circuits

To gain real insight into the roles of the BG in language, a basic knowledge of the neurotransmitters utilized by the neurons of the cortico-striato-cortical circuits is essential. Figure 2.4 also describes in more detail the excitatory and inhibitory effects of the most important neurotransmitters within the cortico-striato-cortical circuits.

GABA or γ-aminobutyric acid is the major neurotransmitter of the BG and is inhibitory. The excitatory neurotransmitter glutamate is used by the corticostriatial neurons, the thalamic neurons and the projection neurons of the STN (Gerfen, 1992). Acetylcholine is another neurotransmitter in the BG and the neurons furthermore contain neuropeptides such as substance P and enkephalin. The striatum is densely innervated by dopaminergic fibers originating in the SNc and VTA. Within the striatum, two different classes of dopamine receptors (i.e., docking sites of dopamine) interact with dopamine and modulate subsequently the direct and indirect pathways; the D1 receptor modulates the direct (excitatory) pathway, while the D2 receptor modulates the indirect (inhibitory) pathway (Gerfen, 1992). In general, dopaminergic modulation influences the properties of neuronal representations of perceptual and cognitive events. Alterations in dopaminergic innervation can have profound effects on motor and cognitive function, and are implicated in diseases such as schizophrenia, Huntington’s disease, Tourette’s syndrome, and PD.

In daily life, there is a variety of learned actions in human beings, such as lacing shoes, writing words with a pencil, driving a car, preparing a meal etc. Each of these motor actions is composed of multiple individual movement elements arranged in a sequential fashion. The order and timing of this sequential arrangement needs to be constantly adapted and modified depending on situation or context.

The theory of Mink (1996) for motor control claims that only the selected motor program is initiated, executed and terminated at the appropriate timing, whereas other competing programs are inhibited. Like Mink (1996), most of today’s researchers accept that the BG form a system involved in selecting actions in response to both external and internal stimuli (e.g., Balleine, Delgado, & Hikosaka, 2007; Cohen & Frank, 2009; Frank, 2005; Humphries,
Stewart, & Gurney, 2006; Jueptner & Weiller, 1998; Redgrave, Prescott, & Gurney, 1999). Striatal neurons recognize activation patterns in their cortical inputs that represent well-known contexts. Upon detection of such a context, simultaneous transmission through the direct and indirect pathways leads to the competitive selection of activation patterns in the output structures. In the end, processing routines in the frontal cortex that have been rewarding in similar contexts are facilitated with the support of the BG. The prefrontal regions play a functional role in the integration of temporally separate events into purposeful action sequences and in the mediation of domain-specific representations of sequential event knowledge (Fuster, 1997; Goldman-Rakic, 1998; Grafman, 1989). Furthermore, the prefrontal cortex is connected to several cortical and subcortical areas, whose functions are related to higher order sensory processing (parietal cortex, association areas), memory (hippocampus), and motor control (premotor cortex, supplementary motor area and BG) (Wood & Grafman, 2003). Thus, the BG do not initiate or generate syntactic sequences themselves. They have a role in the implementation of the process, but the initiation and programming of the sequence occurs elsewhere in the brain (Aldridge & Berridge, 2003).

In conclusion, as part of the cortico-striato-cortical circuits, the BG support the encoding of goal-oriented action sequences through behavioral learning. And as such they are engaged in the retrieval, management, and constitution of these sequences (Graybiel, 1995a, 1995b, 1997).

2.6 Effects of PD on the function of the cortico-striato-cortical circuits

Degenerative neurological diseases like PD allow us to analyze the effects on behavior of poorly functioning, yet still engaged BG circuitry (Dubois & Pillon, 1995; Marsden & Obeso, 1994). In PD, dopaminergic afferents to the striatum are lost and striatal output via the direct and indirect pathways is altered (see Figure 2.5). According to the direct and indirect pathways model, dopamine deficiency leads to reduced inhibition by the indirect pathway and reduced excitation by the direct pathway, with the net result of an excessive activation of the globus pallidus internus (GPI) and substantia nigra pars reticulata (SNr) and inhibition of the thalamus, resulting in PD patients’ motor symptoms (i.e., hypokinesia) among other symptoms.

Harrington and Haaland (1999) and Brown (1999) both mentioned sequence learning deficits in PD patients, as has Dominey (Dominey, Arbib, & Joseph, 1995; Dominey, Ventre-Dominey, Broussolle, & Jeannerod, 1995; Dominey & Jeannerod, 1997). Recently, Carbon et al. (2004), investigated motor sequence learning during a positron emission tomography (PET) imaging study and concluded that sequence learning is normally associated with tight coupling between dopaminergic input to the caudate and thalamo-cortical functional activity. Early stage PD patients already demonstrated a loss of this coupling (Carbon et al., 2004).

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6 A discussion of every existing hypothesis on BG function in the motor domain is beyond the scope of this thesis. Therefore, I refer to the article of Gale, Amirnovin, Williams, Flaherty, & Eskandar (2008) that provides an in depth review on that matter.
In recent years the functioning of the cortico-striato-cortical circuits has become clear. Of course, many things are still unknown. Also caution is warranted in attributing behavioral functioning to this model, since it fails to explain all clinical findings in PD (e.g., tremor) and leaves a number of paradoxes. The most prominent example is the fact that therapeutic inactivation of the globus pallidus internus (GPi), whether by ablative surgery or by high-frequency stimulation, improves motor symptoms in PD \(^7\). Murdoch (2001) and Farrell Theodoros, Ward, Hall and Silburn (2005a and 2005b) concluded that pallidotomy in PD patients has not always had a similar effect on speech production, as on the motor functions of the limbs and trunk. The independent nature of the circuits that serve the orofacial musculature and the muscles of the limbs might be responsible for the divergent postoperative effects (Farrell et al., 2005; Murdoch, 2001). Although there is anatomical (Middleton & Strick, 2000) and physiological (Alexander, DeLong, & Strick, 1986; Mink, 1996) evidence for functionally segregated processing within the cortico-striato-cortical pathways, there is also evidence for significant overlap of information channels.

The degree of segregation between the different circuits that pass through the BG is still a matter of debate (Bergman et al., 1998).

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\(^7\) In a retrospective study York et al. (2007) found that PD patients receive significant long-term motor benefit from bilateral pallidotomy without significant short-term cognitive consequences. However, on the long term, bilateral pallidotomy impaired both language and executive functioning scores.
The role of the BG has been characterized in detail in motor control, but as yet it is unclear what the role of the BG with regard to cognitive functions is. In the following section, theories on the hypothesized roles of the BG in the cognitive domain are discussed (see Saint-Cyr, 2003 for a recent review).

2.7 Role of the basal ganglia in higher cognitive functions

The discussion above might have given the impression that the BG are exclusively associated with motor functions. However, anatomical (Middleton & Strick, 1994) and neuroimaging data (e.g., Dagher, Owen, Boecker, & Brooks, 2001; Grahn, Parkinson, & Owen, 2008; Owen, Doyon, Dagher, Sadikot, & Evans, 1998) have shown that they are also involved in higher cognitive functions.

The neurobiological study by Middleton and Strick (1994) broadened the view on the function of the BG from strictly motor to also include “cognitive processes such as working memory, rule-based learning, and planning future behavior” (p. 460). Marsden and Obeso (1994) linked the function of the BG in motor control explicitly to thought processes, “particularly if thought is mental movement without motion.” (1994, p. 893). In their view, the BG support the execution of routine actions, by facilitating the intended cortically driven action and by suppressing unwanted actions. Secondly, the BG can modify an ongoing action in novel or changed circumstances, including the reorganization of cortically driven motor (e.g., walking) or cognitive (e.g., talking) behavior. Graybiel (1995) stated that the BG are “critical structures involved in action planning – both motor actions and mental actions” (p. 62). Accordingly, Graybiel (1997) termed the BG “cognitive pattern generators” and suggested that by analogy to the central pattern generators of the motor system, these pattern generators operate to organize neural activity underlying aspects of action-oriented cognition. The direct and indirect pathways model suggests that both pathways control the initiation, switching, modulation and termination of actions that are aspects of serial processing (Saint-Cyr, 2003).

It is generally accepted that controlled processing is voluntary, requires attention, and is relatively slow, as opposed to automatic processing, which is assumed to be involuntary, does not require attention, and is relatively fast. A theoretical model which differentiates between controlled processing and automatic processing and which includes suggestions about the role of the BG in cognition was developed by Norman and Shallice (Shallice, 1988; Norman & Shallice, 1986). The conscious selection of goals must be attributed to the cortex, while the situational context (e.g., a rewarding testing environment) is possibly encoded by the BG (Saint-Cyr, 2003). However, context may be implicitly encoded by the BG, so that the context recognized by the cortex cues the striatum to evoke dopamine-potentiated rules (Wise, Murray, & Gerfen, 1996). Subsequent simultaneous transmission through the direct and indirect pathways leads to the selection of frequently successful (rewarding) activation patterns in the output structures, which facilitate processing routines in the frontal cortex.

Recently, Koerts, Leenders and Brouwer (2009) presented a comprehensive mental schema framework that is an adaptation of the dual-process model of Norman and Shallice (1986). Later in this thesis, the framework of Koerts et al. (2009) will be considered for the interpretation of the linguistic data in PD patients and healthy control (HC) subjects.
described in Chapters 4 and 5. Within this framework, it is interesting to address the automatic and controlled processing involved in language tasks, and more in particular morpho-syntactic processes in verb production (Chapter 4) and sentence comprehension (Chapter 5).

In the remainder of this section, first the influential dual-process theory of Norman and Shallice is sketched and then the framework of Koerts et al. (2009), which is illustrated schematically in Figure 2.6, is described. In the next section, I will provide a brief overview of automatic and controlled processing in PD based on the cognitive literature.

**Norman and Shallice’s model**

Behavior can be defined as all actions in response to external or internal stimuli. Norman and Shallice propose two basic mechanisms that determine our behavioral responses (Shallice, 1982, 1988; Norman & Shallice, 1986).

A first mechanism involves *automatic processing*, which is called ‘contention scheduling’. Contention scheduling is involved in routine situations in which actions are triggered automatically by stimuli in the environment or conceptual thought (Grafman, 1995). For example, seeing a red traffic light makes you ‘automatically’ stop. In routine situations automatic processes rely on previously established and learnt relationships between situational context and behavioral patterns. These context-specific behavioral patterns are commonly assumed to be stored in memory and are also known as ‘schemata’ (Norman & Shallice, 1986). Schemata consist of complex series of actions that are familiar to the individual (e.g., preparing coffee). As such, a schema contains sequential knowledge about the action to be performed. The BG are assumed to be involved in the processing of sequences of actions at this level, as discussed in the section on the role of the BG in higher cognitive functions (section 2.7 of this chapter). Consequently, contention scheduling depends upon the integrity of the BG, as suggested by Norman & Shallice (1986).

The second mechanism which regulates behavior proposed by Norman and Shallice is the ‘supervisory attentional system’ (SAS), involved in *controlled processing*. It depends upon the prefrontal cortex, which is reciprocally connected to the striatum (Alexander & Crutcher, 1990). The SAS can be broadly conceptualized as overseeing all conscious activities. It operates in situations where it is necessary to override the automatic contention scheduling mechanism. The SAS consists of a number of distinct subfunctions (Norman & Shallice, 1986), like monitoring, planning and cognitive flexibility. Additionally, declarative memory and working memory also assist in the planning, implementation and application of new schemata.

To summarize, contention scheduling executed by the BG is involved in situations where schemata are automatically activated. By contrast, in non-routine situations, the SAS, which is situated in the frontal lobes, modulates a known schema or plans a new schema to solve a problem.
The mental schema framework of executive functioning of Koerts, Leenders and Brouwer (2009)

The framework of Koerts et al. (2009) (depicted in Figure 2.6) is a more elaborated version of the Norman and Shallice model and is divided in two parts: first of all, the SAS used in non-routine situations above the horizontal bar and secondly, the routine selection of behavior (i.e., automatic processes) below the horizontal bar.

![Figure 2.6](image)

**Figure 2.6:** Schematic representation of subprocesses of automatic and controlled behavior (after Koerts et al., 2009, adapted from the Framework of Brouwer and Schmidt, 2002)

In this framework monitoring, inhibition, mental effort, planning, working memory and flexibility are important elements of controlled processing by the SAS. Importantly, the two parts of the system are not independent from each other but interact. Consequently, a deficit in the SAS affects automatic processing, and an impairment in automatic processing influences controlled processing or executive functioning as well.

### 2.8 Cognitive processing in Parkinson’s disease

Neuropsychological deficits frequently occur in PD. Neuropsychological research in non-demented PD patients showed impairments in several cognitive domains such as language, executive functions, memory, and visuospatial skills, even in the early stages of the disease (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Dubois & Pillon, 1997; Green et al., 2002; Pillon, Czernecki, & Dubois, 2003). More in particular, non-demented PD patients demonstrated impairments in set switching (also called ‘shifting’ or ‘cognitive flexibility’), planning, working memory, inhibition and declarative memory (Cools, Barker, Sahakian, &
Robbins, 2001; Green et al., 2002; Muslimovic, Post, Speelman, & Schmand, 2005; Schneider, 2007; Van Beilen et al., 2008, Wientraub et al., 2005). The described deficits in PD resemble those of patients with frontal lobe lesions (Daum, Schugens, Spieker, Poser, Schönle, & Birbaumer, 1995; Gotham, Brown, & Marsden, 1988; Lange et al., 1992; Lange, Paul, Robbins, & Marsden, 1993; Taylor, Saint-Cyr, & Lang, 1986, 1990), who also demonstrate severe problems in the control and regulation of behavior in their daily lives. Comparative neuropsychological studies of prefrontal patients and PD patients demonstrated that a lesion in the prefrontal cortex is responsible for impairment in the sequential ordering of events and in respecting sequence boundaries and hierarchies, while PD patients fail to establish the contextual importance of each event within the planning activity (Zalla et al., 2000).

Godbout and Doyon (2000) examined the effects of BG dysfunction on the mental representation of familiar activities using a script generation task. To this end, a group of non-demented PD patients was compared to a group of matched HC subjects on the production of six familiar scripts (e.g., going to the cinema, going to a doctor’s office, going to a restaurant, etc.) in a forward condition (i.e., routine situation) and two others in a backward condition (i.e., non-routine situation). PD patients produced incomplete structures of the scripts in both forward and backward conditions. This demonstrates that patients with PD not only have impaired controlled, but also impaired automatic information processing (see also Koerts, Leenders, & Brouwer, 2009; Koerts, 2009).

### 2.8.1 Automatic processing in Parkinson’s disease

PD patients do not only have problems in skilled behavior, but also have problems with automatic behavior. These are most evident in their motor symptoms, such as gait abnormality, which is a highly learned and automatized procedure. Automatic processing is the end result of extensive training. Similar automatic processing is involved in the motor, cognitive and language domain. An example for the latter is the transition from novice to skilled reader.

PD has also been described as a de-automatisation disorder (Saling & Phillips, 2007), which may be compensated for by relying more on controlled processing than HC subjects (Koerts et al., 2009). In addition, it is evident that PD patients do not only have problems with automatic behavior achieved early in life, such as walking or talking, but are also poor in learning new skills. In other words, they have problematic procedural learning skills (Myers et al., 2003; Swainson et al., 2000). As will be discussed in more detail in Chapter 3, researchers investigating production of nouns and verbs in PD patients have reported a selective deficit for verb processing (Bertella et al., 2002; Boulenger et al., 2008; Péran et al., 2003, 2009). More in particular, the deprived production of regular past tense of the verb in PD (Almor et al., 2002; Longworth et al., 2003, 2005; Penke et al., 2005; Terzi et al., 2005; Ullman et al., 1997; Ullman, 2001) has been explained as a deficit in the automatic procedural memory system that regulates grammar.
2.8.2 Controlled processing in Parkinson’s disease

PD patients often show deficits in controlled processing or executive functioning. PD patients consistently fail tests measuring executive functions (Dujardin, Defebvre, Grunberg, Becquet, & Destée, 2001). Two distinct neurobiological mechanisms have been proposed to underlie the executive dysfunctions in PD: 1) disruption of fronto-striatal circuitry resulting from nigrostriatal dopaminergic deficit (Dagher, Owen, Boecker, & Brooks, 2001; Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, Doyon, Dagher, Sadikot & Evans, 1998; Rinne et al., 2000) or 2) dysfunction of the frontal lobe due to hypofunctioning of the mesocortical dopaminergic system (Mattay, Tessitore, Callicott, et al., 2002). In both explanations, the malfunctioning of the BG contributes to the deficit.

Executive functions are subcomponents of the SAS (see Figure 2.6, above the horizontal bar). However, in the literature on cognition there is no consensus on the number and the nature of these subcomponents. We will discuss only the major impairments of executive function in PD that are relatively well defined in a theoretical sense and have already been subject to experimental investigation. The following section will center on impairments in attention, set-switching, working memory, inhibition and declarative memory in PD patients.

Attention

The results of auditory and visual selective attention tasks in PD patients show increased interference by distractor items or irrelevant aspects of stimuli (Levin, Llabre, & Weiner, 1989; Maddox & Filoteo, 1999; Sharpe, 1992), and more intrusion into working memory (Sharpe, 1990, but see Lee, Wild, Hollnagel, & Grafman, 1999 for a contrasting finding). On dual tasks (i.e., tasks testing divided attention), PD patients experience increased interference between tasks (Brown & Marsden, 1991; Fournet, Moreaud, Roulin, Naegle, & Pellat, 2000; Malapani, Pillon, Dubois, & Agid, 1994). Dual task impairments have been ascribed to limited attentional resources. Partiot et al. (1996) showed that PD patients had difficulty re-engaging their attention after a shift, and then keeping it focused on the required cues.

To sum up, there is evidence for an attentional deficit in PD, which in turn interferes with executive functions such as set-switching and working memory. Both functions will be discussed separately in the following sections.

Set-switching

Set-switching refers to the control processes involved in the flexible shift of attention and response preparation from one set of stimulus-response rules to another (Heyder, Suchan, & Daum, 2003). Many researchers have reported set-switching impairments or decreased flexibility in PD (e.g., Cools et al., 2001; Green et al., 2002; Muslimovic et al., 2005).

In clinical practice, cognitive flexibility is assessed with standard neuropsychological tests such as the Trail Making Test parts A and B (TMT A & B, Reitan, 1992), the Odd Man Out Test (OMO-Test, Flowers & Robertson, 1985) or the Wisconsin Card Sorting Test (WCST, Grant & Berg, 1948), in which subjects must rapidly switch between different cognitive sets to solve
the problem.\(^8\) However, in interpreting the results, one needs to bear in mind that such tests address a wide range of distinct cognitive functions in addition to set-switching and suffer from poor specificity and selectivity (Cools et al., 2001). In order to measure set-switching in isolation from other cognitive functions, Cools et al. (2001) developed a set-switching paradigm that controlled for the factors of rule learning and working memory (WM). It was concluded that cognitive flexibility is genuinely impaired in PD, specifically when interference between competing task sets is present. In a later study it was furthermore shown that Levodopa can alleviate cognitive flexibility impairments in PD (Cools et al., 2003). These data show that not only the frontal cortex is involved in set-switching, but also the cortico-striato-cortical circuits, which are obviously disrupted in PD. In accordance with these findings, neuro-imaging studies in HC subjects showed fronto-striatal activity when receiving a signal that a switch was needed (Monchi et al., 2001) and a lack of activation in the fronto-striatal circuit in PD patients (Monchi et al., 2004).

**Working memory**

WM is assumed to operate whenever information has to be retained and manipulated for a short period of time (Baddeley, 1986; Goldman-Rakic, 1995; Petrides, 1995). Figure 2.6 shows that WM is an aspect of executive functioning, since information needs to be activated during and also after the formation of a plan and selection or manipulation of schemata. PD patients usually have reduced WM capacity and encounter more problems with tasks that require manipulation of information (Gabrieli, 1996; Lewis, Dove, Robbins, Barker, & Owen, 2003; Gilbert, Belleville, Bherer, & Chouinard, 2005). The frontal-striatal circuits are involved in a WM task as shown during an fMRI study by Lewis et al. (2003). Cognitively impaired PD patients showed reduced activation in the striatum and frontal cortex during the manipulation of information relative to maintenance of information.

**Inhibition**

As shown in Figure 2.6, inhibition is an important subprocess that enables us to stop ongoing behavior, whether automatic or controlled. For the motor domain, Mink (1996) suggested that the BG inhibit competing motor mechanisms that potentially interfere with the desired movement. Furthermore, the BG also ‘disinhibit’ to allow an intended movement to proceed. PD patients are known to have problems with the prototypical task that measures inhibition, that is, the Stroop Color Word Test (Stroop, 1935).\(^9\) During this task, the most familiar response of reading a word aloud needs to be inhibited, as it is, in the terminology of the SAS model, the strongest schema in the contention scheduling. Hence, PD patients have difficulties with inhibiting the more familiar reading of the words in favor of the less common naming of the ink color in which the words are printed. However, inhibition deficits are not always present and have mainly been reported after subthalamic nucleus-deep brain stimulation (Hershey et al., 2004; Schroeder et al., 2002).

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\(^8\) See Appendix C for a brief description of these set-switching tasks.

\(^9\) See Appendix C for a brief description of the Stroop task.
Declarative memory

Our declarative memory contains our knowledge about facts (semantic knowledge) and events (episodic knowledge). This can include plans or rules from previous experiences. Declarative memory depends primarily on medial temporal lobe structures such as the hippocampal region (Squire & Knowlton, 2000), which is relatively intact in PD patients. Studies by Green et al. (2002) and Muslimovic et al. (2005) report that PD patients are impaired in recalling information from declarative memory, which is interpreted as a selection problem in a situation of competition. However, PD patients do show enhanced hippocampal activity during a planning task, suggesting that they rely more on their declarative memory during planning than healthy controls (Dagher et al., 2001) because this may be impaired.