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The role of the basal ganglia in auditory language processing: Evidence from ERP lesion studies and functional neuroimaging

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In der vorliegenden Arbeit wurde die Beteiligung subkortikaler Strukturen wie der Basalganglien bei syntaktischer, lexikalisch-semantischer und emotional prosodischer Verarbeitung mit Hilfe ereigniskorrelierter Potentiale (EKP) und funktioneller Magnetresonanztomographie (fMRT) untersucht. Die zentrale Frage, die innerhalb der Untersuchungsreihe im Vordergrund stand, war, ob die Beteiligung der Basalganglien bei der Wahrnehmung sprachlicher Subprozessen funktionsspezifisch ist oder eher generelle kognitive Prozesse reflektiert (z. B. Aufmerksamkeit).

Patienten mit Hirnschädigung der Basalganglien, Parkinson Patienten sowie Alterskontrollen stellten die primäre Untersuchungsstichprobe bei den EKP-Untersuchungen dar. Probanden, die an funktionellen Kernspinuntersuchungen teilnahmen, waren Studenten der Universität Leipzig. Experimente zur syntaktischen Verarbeitung basierten auf syntaktischen Strukturen, die in ihrer Komplexität variierten. Neben Phrasenstrukturen wurden auch Morphosyntax und Verbargumentstrukturen in einem Verletzungsparadigma getestet. Die Ergebnisse zeigen, dass eine sprachspezifische Komponente, die P600, die mit Reanalyse syntaktischer Strukturen zusammenhängt, bei Patienten mit Hirnschädigungen der Basalganglien reduziert ist oder ausfällt.

In einem weiteren Schritt wurde nachgewiesen, dass dieses Defizit ein sprachspezifisches Defizit sein kann, da im direkten Vergleich mit einem nichtsprachlichen Aufmerksamkeitsparadigma Basalganglienpatienten eine vergleichbare Hirnreaktion auf Erwartungsverletzungen zeigten wie Alterskontrollen. Untersuchungen zur lexikalisch- semantischer Verarbeitung in den beiden Patientengruppen deuten an, dass die zeitliche Verarbeitung dieser Information im Vergleich zu Alterskontrollen betroffen ist, jedoch im Vergleich zu syntaktischen Prozessen weniger stark betroffen zu sein scheint.

Die Tatsache, dass die Basalganglien auch in Aktivierungsstudien bei lexikalisch-semantischer und emotional prosodischer Verarbeitung aktiviert werden, legt die Schlussfolgerung nahe, dass diese Gehirnstruktur bei auditiver sprachlicher Verarbeitung eine entscheidende Rolle spielt. Zu klären bleibt, ob die bislang unter-

schiedlichen Beeinträchtigungen bei der Verarbeitung syntaktischer und lexikalisch-semantischer Verarbeitung in den Patientenstichproben qualitativer oder quantitativer Natur sind.

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Chapter I

Introduction

I Introduction

In a recent review, Saint-Cyr (2003) pointed out that a functional specification of the basal ganglia in the motor and non-motor domains remains difficult. One of the main reasons is that subcortical functions cannot really be understood isolated from cortical functions. While the connectivity to frontal areas has been extensively investigated in primate studies (e.g., Wise, Murray & Gerfen, 1996) there has been paucity to investigate the basal ganglia and their connectivity to other cortical areas such as the temporal cortex (but see Yeterian & Pandya, 1998). Furthermore, the investigations exploring possible connections between the basal ganglia and the temporal cortex have been limited to the visual domain, in particular to the visual circuitry connecting the basal ganglia to area TE in the inferior temporal cortex (see Middleton & Strick, 2000). Thus, while the main focus of the current thesis will be on the structural and functional differentiation of the basal ganglia, a framework for further research will be proposed. This framework consists of a model on auditory input and output connections between the basal ganglia and the superior and middle temporal cortex. The model is based on non-human primate investigations as well as a small set of functional imaging evidence, and specifically, it describes cortico-subcortical input and subcortical-cortical output connections that provide the groundwork for understanding the role of the basal ganglia in auditory language processing. In addition, cortico-cortical connections between the left rostral superior temporal gyrus (STG)/superior temporal sulcus (STS) and left inferior frontal brain areas are considered as part of a network engaged in auditory language processing. To this end, I will present in this thesis a more extended model for auditory language processing based on non-human primate evidence, human imaging evidence, and by my own event-related potential (ERP) and functional magnetic resonance imaging (fMRI) investigations of different language processes (syntactic, lexical-semantic, and emotional prosodic) in the auditory modality in both healthy and brain-damaged populations.

In the following chapter (Chapter II), particular focus will be given to the basal ganglia and associated structures. An extensive overview on the structure, connectivity, neurochemistry, and diverse function of the basal ganglia system (BG) will be presented. Chapter III provides a distinction between non-language and language functions of the basal ganglia. Chapter IV introduces the methods (behavioural lesion, ERPs, and fMRI) applied in the current investigations of the basal ganglia. In order to understand the critical role of the basal ganglia and their connections in auditory language processing, the use of lesion studies presents a first attempt to understand the structure-function relationship underlying this cognitive function. Thus, specific focus in Chapter IV will be given to the introduction of the lesion technique and critical data supporting the basal ganglia function in auditory

language processing. With the help of ERPs, specific language processes (phonology, lexical-semantics, syntax, and prosody) can be investigated online in a millisecond time range allowing the separation of language sub-processes. In relation to this, Chapter IV4 will also provide a brief methodological description as well as a description of ERP components correlated with specific language processes. Last, the fMRI method is introduced in Chapter IV as a tool to investigate the neural functional underpinnings of the basal ganglia during auditory processing in healthy participants.

Chapter V summarises my own work. A series of experiments that substantiate the role of the basal ganglia in auditory language processing will be presented and discussed. Chapter VI presents an attempt to correlate auditory language processes within a cortico-subcortical auditory network and provides an outlook on further research to substantiate the proposed model.

Chapter II

Basal ganglia and associated structures

II Basal ganglia and associated structures

2.1 The BG system

Let me begin with a description of the basal ganglia and their associated structures that form the basal ganglia system. With the application of modern anatomical tracing techniques and fine-grained physiological analysis starting in the mid 1970s, a better understanding of the cortical afferents of the basal ganglia has been pursued. However, only recently investigations of projections via the thalamus back to the cortex were successful in identifying subcortical efferents. Using markers via neurotrophic viri, Middleton & Strick (2000) reported a differentiation of efferents from the dorsal pallidum to the dorsolateral prefrontal cortex and the ventral pallidum to the motor cortex. Such differentiation not only allows the segregation of parallel circuits, but also specifies the functional role of the basal ganglia supporting both motor and non-motor functions. However, before discussing the current state of functionally diverse circuitries, I will provide a structural description of the basal ganglia and functionally associated areas.

The basal ganglia comprise a grey matter subcortical structure positioned deep within the telencephalon region of the brain and consist of the corpus striatum (*striped body*) and the pallidum. More specifically, Parent (1986) described the dorsal striatum (caudate nucleus, putamen), the ventral striatum (nucleus accumbens and part of the olfactory tubercle), and pallidum as the core structures. The substantia nigra consisting of the pars compacta (rich in dopamine) and the pars reticulata (low in dopamine), the subthalamic nucleus (STN), the ventral anterior (VA) nucleus, the ventrolateral nucleus (VL), and the centromedial nucleus of the thalamus have a strong functional connection to the basal ganglia, were not always viewed as part of the basal ganglia structure. They have been termed associated structures. Together, the core and associated structures are now viewed as the basal ganglia system (see Figure 2-1). More recently, Parent & Hazrati (1995a, 1995b) further specified the intrinsic organisation of the basal ganglia into a “main axis” including the striatum, pallidum, and substantia nigra. As “control structures”, the authors described the subthalamic nucleus together with the pars compacta of the substantia nigra, the centro median/parafascicular thalamic complex, dorsal raphe and the pedunculopontine modulation (Parent & Hazrati, 1995b).

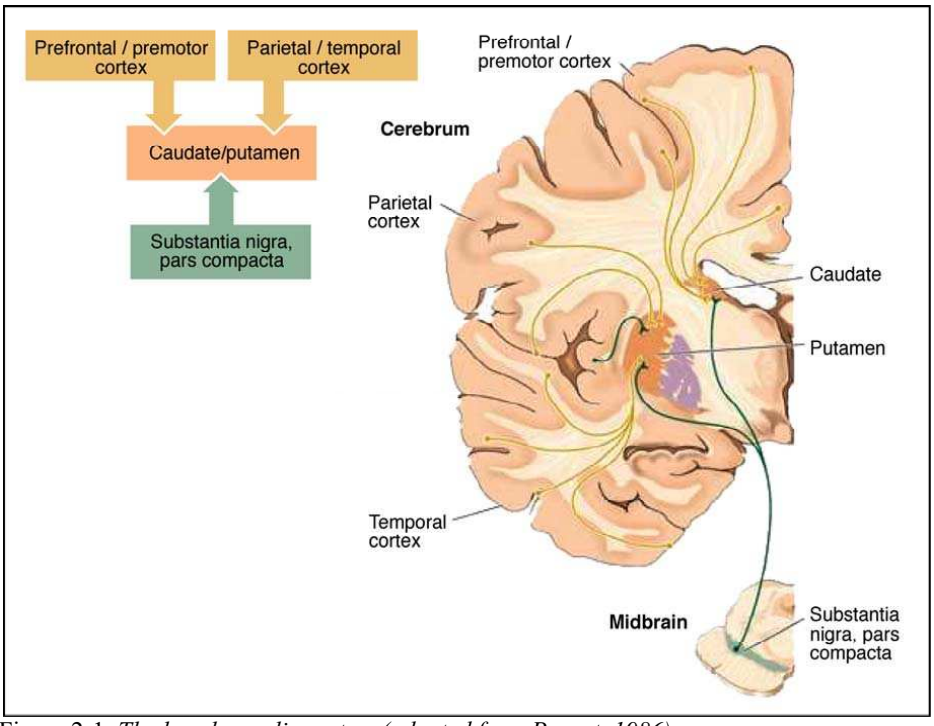

Figure 2-1. *The basal ganglia system (adapted from Parent, 1986).*

The *caudate nucleus* is divided into head (*caput*), body (*corpus*) and tail (*cauda*). The head forms a convexity into the anterior horn of the lateral ventricle. The body forms the lateral wall of the body of the lateral ventricle, and the tail curves and lies in the roof of the inferior temporal horn of the lateral ventricle. The *putamen* is separated from the caudate nucleus by the anterior limb called the capsula interna. Together, the caudate nucleus and putamen form the *corpus striatum*. The corpus striatum contains two types of neurons: spiny neurons (projection) that constitute almost all of the striatal neurones (90%) and consist of GABA, taurine and neuropeptides; and aspiny neurones (interneurones; see Houk, 1995). Aspiny neurones can be either large or small. The large neurones contain acetylcholine, while the small neurones contain GABA. Due to the acetylcholinesterase of the neurones, the striatum is divided into weakly reactive patches called *striosomes* and interspersed with strongly reactive patches called *matrix*. The two patch types differ in their input, output, neurotransmitters, and neuromodulators (e.g., immunohistochemical distribution of several markers including acetyl cholinesterase, enkephalin, substance P, dopamine, opiate receptors and calcium-binding protein (e.g. Gerfen, 1988, 1992; Graybiel, 1990). Furthermore the patches are viewed as the com-

partmental rather than the functional organisational principle of the striatum (see Graybiel, 1995).

The *pallidum* is a structure between the putamen and posterior limb of the internal capsule. The pallidum includes the internal segment of the globus pallidus (GPi), the external segment of the globus pallidus (GPe), and the substantia nigra pars reticulata (SNr) that project back to the cerebral cortex via specific thalamic nuclei. While anatomically close, the globus pallidus and the putamen are functionally different (e.g., Wise et al., 1996; Haber, 2003). The caudate nucleus and the putamen are considered to be *input* nuclei, while the globus pallidus is thought to be an *output* nucleus. All three nuclei lie below the insula. They are separated from the grey matter of the insula by the extreme capsula, the claustrum, and the external capsula. GPi and the SNr are morphologically and chemically similar. Most of their neurones are multipolar projection neurones that contain GABA. Interneurons are rare in these structures.

The *substantia nigra* (SN) is an elongated nucleus positioned medial to the basis pedunculi throughout the rostrocaudal extent of the midbrain. As a component of the brainstem, it is considered to be part of the basal ganglia system due to its reciprocal connections with the basal ganglia. There are two functionally and neurochemically distinct parts to the SN: the *pars reticulata* whose neurones use GABA and project primarily to the thalamus (ventral anterior, ventral lateral, and dorsomedial nuclei) and the brain stem (superior colliculus, pedunculopontine nucleus). The SNr also receives striatal input via GABA (and substance P) that is inhibitory. The second part of the SN is the *pars compacta* (SNc) whose neurones take up dopamine and project primarily to the neostriatum.

The *pedunculopontine tegmental nucleus* (PPTg) is a mesopontine nucleus that lies in close association to the ascending limb of the superior cerebella peduncle bordering the substantia nigra interiorly, the parabrachial nucleus posteriorly, the cuneiform and deep mesencephalic nuclei dorsally, and the pontine reticular nucleus ventrally (see Canteras, Simerly & Swanson, 1992). The structure has been associated with a variety of functions that cannot be easily reconciled, though two functions have been identified. First, the structure is confirmed as an outflow receptor of the basal ganglia for motor output and as an outflow receptor of the ventral-striatal-ventral pallidal axis for reinforcement and incentive-motivation (Inglis & Winn, 1995), thus potentially creating a neural interface between the limbic and the motor system (Olmstead, Munn, Franklin & Wise, 1998). Second, the PPTg seems to function as a "subsidiary", returning information to sites of striatal input (substantia nigra) and striatal output (thalamus; Ingles & Winn, 1995).

The *nucleus accumbens* (NAcc) together with the olfactory tubercle is described as a medial extension of caudate-putamen. The nucleus accumbens is also known as the *ventral striatum* and divided into a "core" and a "shell" part that is cy-

toarchitectonically, physiologically, and pharmacologically distinct in the rat and primate brain. The core resembles the caudate-putamen (see review of Joel & Weiner, 1999). The NAcc is a recipient of limbic (hippocampus and amygdalar) inputs (MacLean, 1990) and through its projections to the ventral pallidum and substantia nigra, it is often regarded as the key motor-limbic interface (Morgenstern et al., 1980). The NAcc is also related to the limbic parts of the forebrain (the median forebrain bundle, anterior cingulated gyrus). While the *amygdala* is not classified as part of the basal ganglia system, it is attached to the tail of the caudate nucleus and is considered part of the limbic system. Caudate, putamen, and globus pallidus are sometimes referred to as *neostriatum*, while nucleus accumbens, olfactory tubercle, and ventral pallidum are called *paleostriatum*. The *subthalamic nucleus* is a subcortical nucleus that comprises the extrapyramidal system. It is located between the cerebral peduncle and the thalamus and looks like a biconvex lense.

2.2 Morphometry of the BG

Quantitative brain morphometry has been used as a descriptor of the organizational principles of the brain and has been applied mainly to cortical structures. However, its application to subcortical structures such as the basal ganglia has been sparse and mainly realised by subtractions from cortical volume. Two representations of brain structure exist to date: *surface representation* as a spatial mapping dimension for functional processing in a structure; and *volumetric representation,* which may reflect global constraints on neural proliferation, cell density, and number of neurons (see Caviness, Kennedy, Bates & Makris, 1996). Two studies by Allen and colleagues (Allen, Damasio & Grabowski, 2002, 2003) as well as others (see references linked to particular morphometric aspects below) describe that: (1) the anatomical landmarks of the basal ganglia can be easily identified on coronal slices of the brain; (2) the total volume of the basal ganglia along with the thalamus is equivalent to about 5% volume of the frontal and parietal lobes; (3) while not specifically discussed, basal ganglia volume may be larger in men than women; (4) basal ganglia G/W ratio (grey/white matter ratio), in contrast, may be higher in women than men (Allen et al., 2003); (5) subregions of the basal ganglia such as the globus pallidus and lentiform nucleus show a consistent leftward asymmetry (Raz, Torres & Acker, 1995) and the putamen a rightward asymmetry (Husain, McDonald, Doraiswamy, Figiel, Na, Escalona, Boyko, Nemeroff & Krishnan, 1992); (6) the subthalamic nucleus (STN) and the globus pallidus internus (GPi) reveal a high degree of individual variability with men, showing a stronger lateral localization of the STN and GPi than women (Zhu, Hamel, Schrader, Weinert, Hedderich, Herzog, Volkmann, Deuschl, Müller & Mehdorn, 2002); and (7) loss of neurons in the putamen and caudate nucleus and volume reduction of the caudate and lentiform nuclei are age-dependent.

2.3 BG pathways and their neurochemical regulations

As described above, a diversity of neurotransmitters and neuropeptides can be traced in the basal ganglia. Within the basal ganglia nuclei, GABA, a γ-aminobutyric acid, plays a central role as the neurotransmitter of most striatal neurones. As an inhibitory transmitter, GABA regulates inhibitory connections between the corpus striatum and the pallidum, between the pallidum and the subthalamic nucleus, and between the pallidum and the nuclei of the thalamus. Glutamate, as an excitatory neurotransmitter, regulates external projections from cortical areas and the subthalamic nucleus. Consequently, glutamate initiates inhibitory GABA reactions in the striatum via its release in cortical areas. A mixture of GABA and diverse neuropeptides determines the activation of the *direct* or *indirect* pathway. For example, a mixture of GABA and substance P (high concentrations in the medial segment of the globus pallidus and the caudate nucleus) and Dynorphine activates the direct pathway from the GPi to the thalamic nuclei. In contrast, a combination of GABA and Enkephaline projects via the indirect pathway (GPe, subthalamic nucleus) to the thalamic nuclei.

Two major pathway – the direct and indirect – traverse through the basal ganglia (see Figure 2-2). The direct pathway is inhibitory in nature and projects monosynaptically from the putamen to functionally specific regions of the GPi and the SNr. This is the release of the *inhibitory* GABA in the striatum after *excitatory* glutamate projections from the cortex causes inhibition. The indirect pathway is both inhibitory and excitatory. Projections from the putamen to the GPe and from the GPe to the subthalamic nucleus are inhibitory, while projections to the Gpe and SNr are excitatory. Diverse indirect pathways are initiated via GPe inhibition as a result of GABA release in the striatum. For example, the disinhibition of the subthalamic nucleus results in the release of excitatory glutamate in GPi, which in turn release GABA from the GPi to the thalamic nuclei, causing thalamic inhibition.

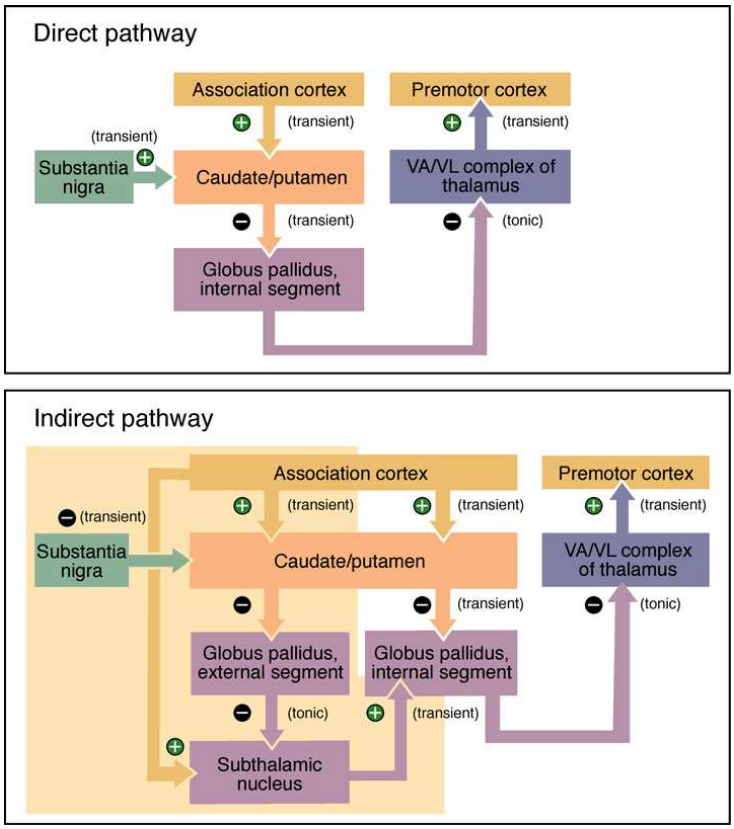

Figure 2-2. *A schematic illustration of direct and indirect basal ganglia pathways (adapted from Wichmann & DeLong, 1996).*

Both the ventral and dorsal portions of the corpus striatum receive strong glutaminergic (*excitatory/+*) input from the cortex and project gabaergic (*inhibitory/-)* neurones to thalamic nuclei. Here, the two main pathways are also direct or indirect. The direct pathway consists of gabaergic neurones that engage the GPi and the SNr as relay stations. The indirect pathway modulates two gabaergic projections, one to the GPe and from the GPe to the subthalamic nucleus. From there the neuronal chain is continued to the GPi by means of glutaminergic neurones and from the GPi via gabaergic projection to the thalamus. These two types of neural regulations render the direct pathway as an excitatory and the indirect pathway as an inhibitory input to the thalamus from the striatum. Projections from the thalamus to the cortex are glutaminergic**.**

In addition to the GABA, Dopamine (DA) is another prominent neurotransmitter in the basal ganglia. Different subclasses of dopaminergic receptors, D1 and

D2, are associated with the direct and indirect pathways that regulate motor behaviour. DA is found in the substantia nigra, from which it is projected to the dorsal striatum (nigro-striatal pathway). DA is also found in the mesolimbic pathway that projects from the ventral tegmental area to the nucleus accumbens, olfactory tubercle, amygdala, septal areas, and the prefrontal cortex. Other dopaminergic neurones, which are less numerous, are found in the hypothalamus (hypothalamus-hypophysis circuitry), in the retina (amacrine cells), in local circuits of the olfactory tubercle, and in the corpi quadrigemini projecting to the hypothalamus.

2.4 BG connectivity

2.4.1 Cortical and subcortical input structures

In order to understand the connectivity between the basal ganglia system and the cortex, one needs to differentiate between input and output sites and mechanisms. Three major sites have been identified as input structures: almost all of the cerebral cortex, the thalamus, and the mesencephalic dopamine sites. Identified output structures include GP, SNr, and the ventral pallidum. In the following, both input and output structures will be defined individually.

Cortico-striatal projections originate from *most cortical areas* and reach the neostriatum in two ways: (1) directly via the internal and external capsule and the subcallosal fasciculus; or (2) indirectly through the thalamus or as collaterals of cortical projections to the pons and medulla. Another input structure is comprised of the *centromedian and parafascicular nuclei* of the thalamus. While the centromedial nucleus mainly projects to functionally specific territories in the putamen, the parafasciculus projects to the caudate and the ventral striatum. Principal mesencephalic (dopamine) projections to the striatum come from the *SNc*. Dopamine facilitates striatal projections to the GPi and inhibits projections to the GPe.

2.4.2 Output structures within the BG system

The following subcortical output structures receive input from other subcortical structures: projections of the neostriatum; the subthalamic nucleus; the GPe and GPi; and SNr and the ventral pallidum. GP also receives projections from the putamen, while the SNr receives fibres from the caudate nucleus.

The GPi and the SNr utilise two pathways to project to the VA, VL, and dorsomedial nuclei of the thalamus, the ansa lenticularis and the lenticular fasciculus. Between the subthalamic nucleus and the GPe, there is a reciprocal connection. The subthalamic nucleus receives its main input from the cortex (BA 4 and BA 6), the GPe, the thalamus, and from the reticular formation and outputs to both GP compartments and the SNr.

The ventral striatum receives input from the hippocampus, amygdala, cingulate gyrus, temporal cortex, and orbitofrontal cortex. The output direction of this structure is the ventral pallidum, which in turn sends axons to the dorsomedial thalamic nucleus that has strong prefrontal interconnections.

2.4.3 Organisation of cortico-striato-thalamo-cortical loops

Several anatomical models describing the nature of the connections between the basal ganglia and cortical areas have emerged in recent years. Through the development and use of refined tracer techniques in animal models, it has been established that the cortico-subcortical-thalamo-cortical connections are highly topographic. However, dispute persists as to whether the cortical input to the basal ganglia is convergent or *open*, i.e., more than one cortical area can project to a given region within the corpus striatum (Graybiel & Kimura, 1995), or whether there is a *closed* loop, i.e., one topographically mapping cortical area connects to one particular region in the corpus striatum (Alexander, DeLong & Strick, 1986; Strick, Dum & Picard, 1995). In addition, the number of loops and their corresponding functional specificity (e.g., cognitive, emotional) has vastly expanded, and other cortico-subcortical loops besides the classical fronto-striatal motor loop have been described (e.g., Middleton & Strick, 1996, 2000). Last, in an attempt to map clinically complex symptoms that do not fit a simple closed loop model of the basal ganglia circuitry, work by Joel and Weiner (1994, 1997, 2000) has introduced the combined open and closed circuitry model called *split* circuitry. In the following these models will be described and discussed.

In their seminal work, Alexander and colleagues (1986) described five basal ganglia-thalamo-cortical connections with parallel organisation. These include motor, oculomotor, dorso-lateral prefrontal, lateral orbito-frontal, and limbic circuitry. The motor circuit originates in the supplementary motor area and the oculomotor circuit in the frontal eye fields, while the three prefrontal circuits project from the dorso-lateral, orbito-frontal cortex and the anterior cingulate. Each circuit is described as functionally segregated and has no interaction with the other circuits (Alexander & Crutcher, 1990), thus creating five closed circuitries. The five circuit model was refined and revised by Parent and Hazrati (1995a, 1995b) who postulated that only three functional regions within the basal ganglia system project back to cortical sites that functionally and topographically map the striatal output region. They described a *sensorimotor* area in the putamen projecting back to motor cortices (primary motor cortex, SMA, premotor cortex), an *associative* or *cognitive* area in the dorsal caudate nucleus projecting to the prefrontal cortex, and a *limbic* or *emotional* area in the ventral striatum projecting to the anterior cingulate cortex and medial orbito-frontal cortices.

Middelton and Strick (1996, 2000, 2001) following the concept of closed circuitry functionally specified a multiple closed loop model with cortical sites as afferents and efferents from and to topographically mapping areas in the corpus striatum. They extended the number of loops originally described by Alexander and colleagues by describing the following: a total of seven skeletomotor loops; up to three oculomotor loops; a dorso-lateral prefrontal loop with specified cortical areas (dorsal 46, ventral 46, medial 9, lateral 9, dorsal 10) receiving output from four subcortical channels; a lateral orbito-frontal loop (SN output only to lateral 12 and orbital 12); a medial orbito-frontal loop (projections from area 13 to ventro-medial caudate and ventral striatum); anterior cingulate loops (input areas 24, 24a, and 24b on cingulate gyrus and 24c on ventral bank, fundus of anterior portion of cingulate sulcus); and finally, infero-temporal/posterior parietal loops. The latter loops are interesting for two reasons. First, they are considered to be part of the basal ganglia input system, but not as cortical output targets of the basal ganglia. Second, they establish that cortical areas besides the frontal lobe utilise basal ganglia circuitry. Initially, it was assumed that these cortical areas use the basal ganglia system simply to influence executive functions in the frontal lobe. However, Middleton and Strick (1996) were able to show with viral tracing that the inferio-temporal area TE is targeted by projections from SNr via the VAmc of the thalamus.

Middelton and Strick (2000) concluded that the output of the basal ganglia system could influence a vast range of behaviour via projections to multiple cortical sites. This in turn could explain how widespread damage to the basal ganglia can produce a broad array of motor, cognitive, limbic, and sensory dysfunction. However, one major drawback of the closed loop models as described above is that cortical and subcortical dysfunction (under the assumption of topographic mapping between cortical and subcortical sites) does not always result in the same type of dysfunction. Furthermore, taking Parkinson's disease (PD) as a model of dysfunction, there are often reports of multiple deficits that cannot be explained under the assumption of closed circuitry.

Recently, including an open loop concept has extended the concept of parallel closed cortico-striato-thalamo-cortical circuitry. Open loops allow striatal projections to a cortical area that does not project to the corpus striatum itself, and open loops also support communication between closed circuitry. In the work of Joel and Weiner (1994, 1997, 2001; see Figure 2-3) a combination of open and closed circuitry is described as split circuitry. Such a split circuit contains one fronto-cortical-striatal pathway and two striato-fronto-cortical pathways passing through the basal ganglia output nuclei and the thalamus. One of the striato-fronto-cortical pathways returns to the original fronto-cortical region (closed loop), while the second ends in a different fronto-cortical region where it may connect to a different circuit (open loop). The authors described the associative circuit consisting of a closed loop (as-

sociative striatum, SNr, the VA and MD thalamic nuclei, and associative prefrontal cortex) and an open associative loop (associative striatum, associative region of GPi, VA thalamic nucleus, and premotor cortex to the motor cortex). Similarly, the motor circuit contains a closed motor circuit (motor striatum, motor GPi, the VA thalamic nucleus, premotor and primary motor cortex, and supplementary motor cortex) and an open motor circuit (motor striatal projections to the SNr, motor prefrontal cortex). The limbic circuit contains a closed limbic circuit (limbic striatum including ventral caudate and putamen, ventral or limbic pallidum, MD thalamic nucleus, limbic orbitofrontal cortex, anterior cingulate, and limbic prefrontal cortex) and the open limbic circuit (limbic striatal projections to the SNr, associative prefrontal cortex). The split circuitry adheres to the principle of direct and indirect pathways. Two types of indirect pathways are described: a *closed indirect* pathway ending in the same GPi/SNr subregion as the direct pathway and an *open indirect* pathway that terminates in a different GPi/SNr subregion. Thus all three-split systems (motor, associative, and limbic) are interconnected via their open pathways or routes. Split circuitry may explain why damage to one station in a closed loop may result in selective motor, cognitive, and emotional behavioural symptoms, i.e., similar symptoms that may result from damage to either topographically mapping cortical or subcortical sites. However, split circuitry also allows one to explain combinations of motor, cognitive, and emotional symptoms as a result of damage to a station in an open loop.

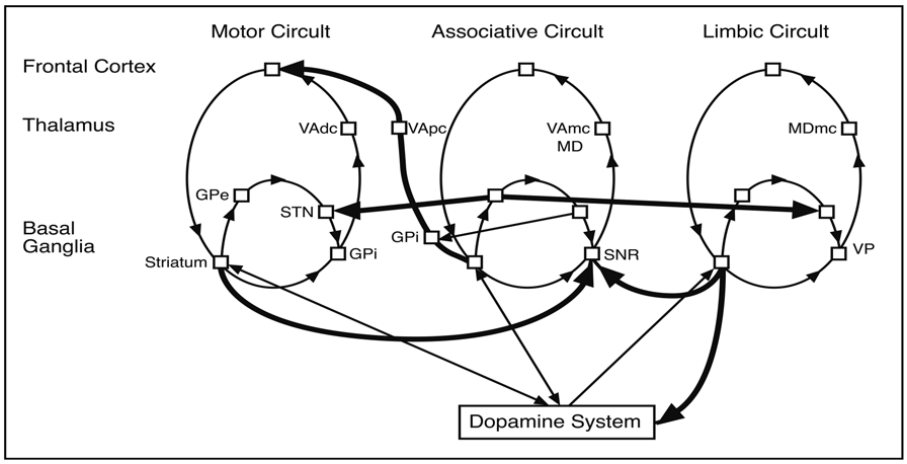

Figure 2-3. *Diagram summarising the structural organisation of the motor, associative, and limbic split circuits. Abbreviations stand for: MD (medio-dorsal thalamic nucleus); VA (ventral anterior thalamic nucleus; dc = dencicellular subdivision; pc = parvicellular subdivision); GPe (globus pallidus external segment); STN (subthalamic nucleus); VP (ventral pallidum); and SNr (substantia nigra pars reticularis; adapted from Joel & Weiner, 1997).*

Chapter III

Language and non-language functions of the BG

III Language and non-language functions of the BG

As has become apparent in the previous chapters, the basal ganglia play a most prominent role in the motor domain. However, based on the multitude of circuitries that have been described in the non-human primate literature and in the neuropsychological literature on Parkinson's and Huntington's diseases, non-motor functions have also entered the limelight.

One major assumption about the functionality of the basal ganglia is that due to the parallel and circular organisation of circuitries, the basal ganglia are involved in the reconfiguration of cortical activation patterns. That is, they collect cortical information, funnel it, and then converge it at cortical output areas through the enervation of thalamic nuclei (e.g. Kemp & Powell, 1971). Why the basal ganglia are involved in such reconfiguration and whether this procedure is domain-specific or -general is still unclear.

Saint-Cyr (2003) addressed the status of domain specificity in the following way: "Basal ganglia efferents provide the cortex with an attentional and domain specific focus in preparation of action, and also instruct the evolving behavioural pattern according to the outcome". From this statement one can conclude that the basal ganglia may establish, monitor, and readjust domain- specific behaviour according to variable input and environments. Saint-Cyr bolsters this statement by reporting both primate and neuropsychological results that provide evidence that the basal ganglia are engaged in attentional and preparatory function, implicit learning, forming of response habits, procedural learning, skill learning, rule learning, associative learning, and some forms of cognitive skill acquisition. The role of neurotransmitters in the regulation of these functions has yet to be defined. Only dopamine and its key role in reinforcement seems to be well understood.

In the following, a brief summary of functional evidence in the language and non-language (i.e., classically described as non-motor) domains will be summarised in order to establish context for the proposed hypothesis that the basal ganglia may play a computational role in auditory language processing.

3.1 Language functions of the BG

Language is a complex, yet highly automated system that can be subdivided into linguistic sub-processes such as phonology, syntax, lexical-semantics, prosody, and pragmatics. While the role of cortical structures in language processing has been well investigated for decades in lesion studies and recently in neuroimaging studies (ERPs, fMRI, and positron emission tomography (PET) studies), the role of subcortical structures in language processing has been less explored and rather controver-

sial. One of the reasons may be that subcortical aphasia is often not a persistent phenomenon (see Vallar, Perani, Cappa, Messa, Lenzi & Fazio, 1988) and primarily coincides with production deficits that could be motoric in nature. For example, the phenomenon of pallalia, realised by arbitrary repetitions of syllables, words, and word combinations, may be produced with increasing speed during production in PD patients. However, such a phenomenon is usually seen as a motor planning deficit rather than a speech production deficit per se. In addition, Wallesch and Blanken (2000) suggest that comparable to *recurring utterances* in global aphasia, this type of speech automatism can also occur in patients with basal ganglia lesions or their connecting pathways. However, as in the case of pallalia, the authors conclude that speech automatisms are linked to a pre-articulatory deficit based on the reduced capacity to inhibit appropriate target expressions. While production deficits (primarily prosodic) have been reported in PD patients, it has been argued that linguistic processes such as phonology, lexical-semantics, and syntax in language perception are not affected. Rather, these processes may appear deficient, but may be secondary to attentional and/or working memory deficits. Often these deficits mimic frontal cortical phenomena such as verbal working memory or verbal fluency deficits (Wallesch, 2003). In an early information-processing model, Wallesch and colleagues (Wallesch, 1985; Wallesch & Papagno, 1988) proposed that a cortico-striato-pallido-thalamo-cortical loop regulates response preparation and response selection. According to this model, multiple lexical alternatives (i.e., response alternatives) are produced and released in the posterior perisylvian cortex, then carried to the anterior perisylvian cortex and the striatum in parallel modules. Thus, the striatum may monitor various types of lexical alternatives (situational, emotional, motivational, semantic) and play an immanent role in the selection of a contextually appropriate lexical candidate. Structurally, the model can be criticised as basal ganglia lesions often include white matter lesions thus are not exclusive lesions.

Next to the striatum, the thalamus has been discussed as the subcortical structure that may be engaged in language processing. Lesions of specific thalamic nuclei can produce word finding deficits and paraphasia. Wallesch (2003) described three anatomical models that assign a potential role to the thalamus during language processing (see also Nadeau & Crosson, 1997). First, the ventral thalamic nuclei VA and VL are part of the cortico-striato-pallido-thalamico-cortical loop that regulates speech production. Second, the pulvinar as the largest thalamic nucleus projects mainly to the posterior temporal language cortex. Third, lesions of unspecific thalamic nuclei can disrupt the connection between the ascending reticular activation system (cerebellum) and the cortex, resulting in attentional, motivational, and consciousness deficits that may supersede language deficits. According to these proposed models, the striatum and the thalamus are plausible, but not necessary,

structures regulating language processing. Language deficits may therefore be an epiphenomenona of attentional and/or working memory deficits.

Last, besides the critical functional contribution of the basal ganglia in language production and comprehension, the structural contribution has also been at dispute. Aphasia resulting from a left-hemispheric basal ganglia lesion may result from focal lesions, but also from pathway lesions that in turn cause cortical deficits within the same hemisphere (see Nadeau & Crosson, 1997). Weiller, Willmes, Reiche, Thron, Isense, Buell and Ringelstein (1993) pointed out that large striatal lesions could also include cortical insula lesions that affect the blood supply system of the arteria cerebri media, resulting in aphasia. In conclusion, it appears that the relative structural and functional contribution of the basal ganglia to language processing is still a highly controversial topic and deserves further investigation.

3.1.1 Language production

Early evidence on subcortical language production deficits included reports of naming deficits and paraphasias after pallidectomies (Svennilson, Torvika, Lowe & Leksell, 1960) and reports of reduced sentence production after electrical stimulation of the caudate nucleus (Van Buren & Ojemann, 1966). Speech production after putaminal lesions has often been described as hypophone or dysarthric and can result in a foreign accent. Cappa and Abutalebi (1999) have reviewed cases of aphasia after striatal lesions and the surrounding white matte. They reported aphasic deficits comprised mainly of non-fluent production and lexical-semantic deficits. However, fluent aphasia, perseverations, and echolalia have also been described in conjunction with subcortical lesions. Word finding difficulties and written language deficits frequently occur (Cappa, Cavalotti, Guidotti, Papagno & Vignolo, 1983). One case of bilingual subcortical aphasia points to a switching mechanism effective during language output in bilinguals (Abutalebi, Miozzo & Cappa, 2000). Taking up the concept of declarative and procedural learning, Ullman and colleagues (Ullman, Corkin, Coppola, Hickok, Growdon, Koroshetz & Pinker, 1997; Ullmann, 2001) reported that PD patients show deficits in the production of regular morphological forms during verb participle production, while patients with neurodegenerative changes in the temporo-parietal cortex show deficits of regular verb forms. The author proposed that regular, or default, verb forms can be composed in real-time by grammatical/procedural computations subserved by a basal ganglia-frontal lobe circuitry. However, a language production study with PD patients reported no confirming evidence for increased morphological errors but smaller amounts of grammatical sentence production (Murray, 2000). The latter result has found further support very recently in a study by Longworth and colleagues (Longworth, Keenan, Barker, Marslen-Wilson & Tyler, 2005), who describe that neither Parkinson's nor Huntington's patients display a selective impairment for grammatical rule application in

both verb tense production and comprehension. Last, striatal as well as thalamic contribution to language processing has been reported in electrophysiological studies (Abdullaev & Menichuk, 1997) and in PET production studies (e.g., Demonet, Price & Wise, 1994; Friston, Frith, Liddle & Frackowiak, 1993). From the combined production data, it is apparent that the basal ganglia seem to play a role in the production of both prosodic and grammatical form. What remains unclear, however, is whether the underlying function deficit observed during the production of both forms in patients with neurodegenerative change or lesions of the basal ganglia is in fact functionally specific or not.

3.1.2 Language perception

The summarised evidence clearly supports a functional role, albeit yet to be defined, of the striatum in language production as evidenced by lesion, neurodegenerative, and imaging data. However, recent patient and imaging results have shown that parts of the basal ganglia system may also be actively engaged during language reception.

3.1.2.1 Syntax

Receptive language was investigated during syntactic processing in a PET (Moro, Tettamanti, Perani, Donati, Cappa & Fazio, 2001) and an fMRI study (Friederici, Rueschmeyer, Hahne, & Fiebach, 2003a). Both studies reported activation of the left striatal complex during syntactic computation. Other evidence shows that the basal ganglia may modulate working memory processes during the computation of syntactically complex sentences (Grossman, Carvell & Gollomp, 1991; Grossman, Carvell, Stern, Grollomp & Hurtig, 1992; Grossmann, Carvell, Gollomp, Stern, Reivich, Morrison, Alavi & Hurtig, 1993a; Lieberman, Friedman & Feldman, 1990; Lieberman, Kako, Friedman, Taichman, Feldman & Jiminez, 1992; Natsopoulos, Grouios, Bostantzopoulou, Mentenopoulos, Katsarou Logothetis, 1993; Pickett, Kuniholm, Protopapas, Friedman & Lieberman, 1998). Grossmann et al. (1993a) in particular argued that grammatical processing deficits in PD might result from an attentional deficit, not a grammatical deficit per se. More recently, Grossman, Zurif, Lee, Prather, Kalmanson, Stern, and Hurtig (2002) attributed grammatical comprehension deficits in PD patients to slowed lexical access. In an attempt to study whether the basal ganglia are essential for rule-governed language processing, Longworth et al. (2005) tested inflectional morphology in a primed lexical decision task in both PD and Huntington's patients. Morphological priming was impaired, but was independent of verb regularity in both patient groups compared to controls. In conclusion, the authors propose that basal ganglia disorders are not specifically associated with difficulties in comprehending regular past tense formation.

Similar to the case in grammatical production, the perception of syntactic processes also has a deficit in the amount of data pointing to a clear functional specification of the basal ganglia in conjunction with these processes. In summary, the grammatical system utilized during language production or perception seems to rely on the basal ganglia. However, several questions remain as to whether the deficits observed in BG patients are functionally specific, i.e., purely grammatical in nature, or whether they are non-functionally specific as they result from attentional, working memory-related, or temporal deficits.

3.1.2.2 Lexical-semantics

Taking a structural standpoint, lexical-semantic processes may not be regulated primarily by the striatum, but by another subcortical structure, namely the thalamus. Crosson (1985; proposed a model of subcortical language production in which the basal ganglia, along with the thalamus, may be engaged in the selection of covertly produced speech segments after semantic verification in a striato-thalamico-cortical network. Nadeau and Crosson (1997) suggested that the thalamic part of this loop is regulated by the frontal cortex and engaged during selection in semantic tasks. Crosson (1999) argued that the posterior thalamus (including the pulvinar) is involved in a "selective engagement system" that might, next to semantic selection, be involved in working memory processes. He points out that the nature of the thalamic language function hinges critically on the cortical connectivity of the thalamus. Moreover, he suggests that the thalamus is "involved in multiple processes which directly or indirectly support cortical language function". Kraut and colleagues (Kraut, Calhoun, Pitcock, Cusick & Hart, 2003; Kraut, Kremen, Moo, Segal, Calhoun & Hart, 2002) extended this proposition by suggesting that the pulvinar is the critical structure in semantic feature binding during object recognition. This model is supported by thalamic lesion data (e.g., Cappa & Vignolo, 1979; Crosson, 1985; Crosson, Rao, Woodley, Rosen, Bobholz, Mayer, Cunningam, Hammeke, Fuller, Binder, Cox & Stein, 1999; Raymer, Moberg, Crosson, Nadeau & Rothi, 1997).

While such propositions on the role of the thalamus in the lexical-semantic network need to be followed up with carefully controlled lesion and imaging studies, recent lesion data and neuroimaging studies have provided ample evidence for decreased (in the case of PD and BG lesion patients) and increased basal ganglia activation during lexical-semantic processing. Activation increase in the basal ganglia has been correlated with semantic judgement and categorisation (Abdullaev, Bechtereva & Melnichuk, 1998; Binder, Frost, Hammeke, Cox, Rao & Prieto, 1997; Mummery, Patterson, Hodges & Price, 1998; Pilgrimm, Faili, Fletcher & Tyler, 2002; Price, Moore, Humphreys & Wise, 1997), semantic anomaly judgement (Kuperberg, McGuire, Bullmore, Brammer, Rabe-Hesketh, Wright, Lythgoe, Williams

& David, 2000; Ni, Constable, Mencl, Pugh, Fulbright, Shaywith, Shaywith, Gore & Shankweiler, 2000), semantic working memory (Crosson et al., 1999), lexical decision (Abdullaev et al., 1998), lexical decision as a function of word frequency (Fiebach, Friederici, Müller & von Cramon, 2002), and of semantic priming (Kotz, Cappa, von Cramon & Friederici, 2002; Rossell, Bullmore, Williams & David, 2001). Furthermore, Copland and colleagues (Coplan, Chenery & Murdoch, 2000a, 2000b, 2001) reported controlled lexical ambiguity priming deficits in patients with basal ganglia lesions and PD while automatic facilitation was intact. In a recent paper, Copland (2003) provides further evidence for such a semantic deficit in PD and BG lesion patients and functionally links the basal ganglia to semantic inhibition comparable to inhibition in motor function (Mink, 1996; see also Kotz, Frisch, von Cramon, & Friederici, 2003a) for a similar analogy in terms of controlled syntactic processing).

This conclusion has been supported by PD data. Gurd and Oliveira (1996) reported that PD patients have difficulties in selecting a target word in the context of semantic distracters in a word search task. Watters and Patel (2002) investigated semantic ambiguity in a neural network simulation of PD and also report semantic inhibition problems. Further evidence comes from semantic set-shifting in PD patients (McDonald, Brown & Gorrell, 1996; for similar results on selecting salient information see Brown, Corcos & Rothwell, 1997; Levin, High, Williams, Eisenberg, Amparo, Quinto & Evert, 1989). As this brief review shows, a major aim of further investigations will have to tackle the respective roles of the basal ganglia and the thalamus (in particular the pulvinar) in lexical-semantic processes. It is clear, though, that in comparison to grammatical function, the functional specification of the basal ganglia and thalamus in lexical-semantic processing is more advanced. As is the case for the basal ganglia's role in grammatical function, the domain specificity of lexical-semantic processing as well its nature (e.g. automatic vs. controlled) in the basal ganglia has yet to be specified.

3.1.2.3 Prosody

To extend the potential multifunctional role of the basal ganglia in language processing, there has been a recent revival in investigating linguistic and non-linguistic prosody. As described above, there have been early reports on prosodic production deficits primarily after putaminal lesions. A note of caution needs to be raised as to whether such prosodic deficits are motoric in nature or actually reflect a deficit in realising basic acoustic properties of prosody such as fundamental frequency, duration, and intensity. This, of course, also applies to the perception of prosody. PD has been proposed as a model to understand how the basal ganglia contribute to the processing of linguistic or non-linguistic prosodic tone

Recently, a number of laboratories published neuroimaging and lesion evidence that describes a highly distributed network involving both cortical and subcortical structures during the perception of emotional tone (Adolphs, Damasio & Tranel, 2002; Baum & Pell, 1999; Buchanan, Lutz, Mirzazade, Specht, Shah, Zilles & Jäncke, 2000; George, Parekh, Rosinsky Ketter, Kimbell, Heilmann, Herscovitch & Rost, 1996; Kotz, Meyer, Alter, Besson, von Carmon & Friederici, 2003b; Morris, Scott & Dolan, 1999; Wildgruber, Hertrich, Riecker, Erb, Anders, Grodd & Ackermann, 2004; Wildgruber, Pihan, Ackermann, Erb & Grodd, 2002). However, not all of the imaging studies reported activation of the basal ganglia (see Buchanan et al., 2000; George et al., 1996), and the contribution of the basal ganglia in decoding prosodic cues has often been reported as secondary to cortical deficits or to impairments in decoding the finer temporal suprasegmental structure of auditory input (Lieberman, 2001). Still, some neuropsychological studies have reported discrimination and recognition deficits of emotional prosody after focal basal ganglia lesions (Brådvik, Dravins, Holtas, Rosen, Ryding & Ingvar, 1991; Breitenstein, Daum & Ackermann, 1998; Breitenstein, Van Lancker, Daum & Waters, 2001; Cancellier & Kertesz, 1990; Pell & Leonard, 2003; Starkstein, Federoff, Price, Leiguarda & Robinson, 1994; Wedell, 1994). In a series of studies, Pell and Leonard (2004) systematically investigated the perception of emotional prosody utilising discrimination, identification, and emotional feature rating tasks in PD patients and age-matched controls. In comparison to the controls, PD patients showed an overall reduction in the perception of emotional prosodic cues. The authors took these results as evidence that the basal ganglia play a regulatory role in "predicting the value of cue sequences within a temporal sensory event" (see also Lieberman, 2001 for an elaborative standpoint on this view).

In conclusion, non-linguistic and linguistic prosodic processing seems to be modulated by the basal ganglia. However, in comparison to grammatical and lexical-semantic processing, the present evidence seems to point to a non-domain specific function of the basal ganglia in these processes, a role involving the temporal encoding of linguistic or non-linguistic cues in an auditory sequence.

3.2 Non-language functions of the BG

3.2.1 Sequencing

Graybiel (1995) established the view that "the basal ganglia are critically involved in building up sequences of behaviour into meaningful, goal-directed repertoires." As a consequence, Graybiel (1997) termed the basal ganglia "cognitive pattern generators" and suggested that by analogy with the central pattern generators of the motor system, these pattern generators operate to organise neural activity underlying aspects of action-oriented cognition. Brown (1999) elaborated on this idea and ar-

gued that the basal ganglia regulate sequential processing. This view has been neurologically and functionally supported via the direct and indirect pathways that control initiation, switching, modulation, and termination of serial processes. Behavioural evidence for this model comes from PD studies that investigated sequencing as a function of motor behaviour (Martin, Phillips, Iansek & Bradshaw, 1994), learning (e.g., Harrington, Haaland & Hermanowicz, 1998), temporal coupling (Malapani, Dubois, Rancurel & Gibbon, 1998), temporal ordering (Sagar, Sullivan, Gabrieli, Corkin & Growdon, 1988; Harrington et al., 1998), or temporal discrimination that is Dopamine (DA)-dependent (Rammsayer & Classen, 1997). In addition, Graybiel (1998) has shown that the basal ganglia are involved in the chunking of action sequences. Last, the learning of sequences (Dominey, Arbib & Joseph, 1995a; Dominey, Ventre-Dominey, Brousolle & Jeannerod, 1995b; Dominey & Jeannerod, 1997) as well as sequential information processing (e.g., Beiser & Houk, 1998; Berns & Sejnowski, 1996; Hikosaka, 1999) has been reported as a basal ganglia function.

Which circuitries actually do support sequencing? Miyachi, Hikosaka, Miyashita, Karadi and Rand (1997) described that carbachol injections into the anterior caudate and putamen in monkeys prevented the learning of new movement sequences, while injections into the middle-posterior putamen disrupted well-learned sequences. Matsumoto, Kasri and Kooken (1999) reported that the monkey striatum and niagral afferents are involved in the encoding of new motor information and in subsequent retrieval. However, as shown in PD-induced monkey models, relearning is possible. Thus, the authors concluded that encoding of sequential processes must be regulated by a cortico-striatal circuitry.

3.2.2 Neural timing

Within the neural circuitry involved in timing, two systems have been differentiated and supported by the following number of dissociating factors: duration range (millisecond and multisecond intervals; Gibbo, Malapani, Dale & Gallistel, 1997); modulation by pharmacological agents (e.g., Rammsayer, 1993; 1999); differential impairment by task demands (Rammsayer & Lima, 1992); and specific brain lesions (Clarke, Bellmann, Ribaupierre & Assal, 1996). In particular, it has been suggested that intervals in the millisecond range engage an automatic circuitry independent of overt attention, while intervals in the multisecond range are modulate by controlled, attended processes and are perceived as discrete entities (see Lewis & Miall, 2002 for a meta-analysis). The automatic timing system, with intervals less than a second, mainly engages SMA bilaterally, sensorimotor cortex as well as the frontal operculum, STG, thalamus and right cerebellum. In contrast, the left basal ganglia is only involved when short intervals were presented continuously or defined by movement (Larsson, Gulyas & Roland, 1996; Parsons, 2001; Schubotz & von Cramon, 2001).

Lewis and Miall (2002) concluded that while many of these regions belong to the motor system, activation must be genuinely linked to timing, as the task engaged was covert decision not relying on the motor system per se. The neural network supporting controlled timing has often been elicited by controlled tasks, thus engaging working memory and attention (e.g., Petrides, 1994; Smith & Jonides, 1999). The structures involved include the dorso-lateral prefrontal cortex, ventro-lateral prefrontal cortex, bilateral intra-parietal sulcus, and inferior partietal region. The right basal ganglia only came into play for long time intervals when the presentation was non-continuous and not related to movement (Meck & Benson, 2002).

In a review article on timing in speech, Schirmer (2004) briefly described the role of the basal ganglia in speech perception and production. In an adaptation of a described interval timing dysfunction in PD patients (Mangels, Ivry & Shimizu, 1998; Meck, 1983; 1996), Schirmer lists evidence that PD patients have problems detecting temporal cues in speech (Breitenstein et al., 2001), problems in production with speech acceleration being too fast (Canter, 1963) or too slow (Gräber , Hertrich, Daum, Spieker & Ackermann, 2002), and problems using pauses in the speech stream (Canter & Van Lancker, 1985; Fraïle & Cohen, 1999). Thus, the general role of the basal ganglia in timing in speech appears to deserve specific emphasis.

3.2.3 Implicit and procedural learning

Double dissociations between declarative (medial temporal-diencephalic memory system) and procedural learning and memory (basal ganglia system) systems have been reported early on (e.g., Cohen & Squire, 1980; Mishkin, Malamut & Bachevalier, 1984; Saint-Cyr, Taylor & Lang, 1988). However, the specification of the procedural learning system regulated by the basal ganglia (cf. Gabrieli, 1998; Squire, Knowlton & Musen, 1993) has been heavily debated (e.g., Wise et al., 1996) as lesions in the monkey striatum have not resulted in complete elimination of procedural learning but only in a reduction of learning efficiency. Still, ample evidence from PD studies on procedural learning deficits have supported the role of the basal ganglia in procedural learning (e.g., Haaland, Harrington, O'Brien & Hermanowicz, 1996; Harrington & Haaland, 1999; Vakil & Herishanu-Naaman, 1998; Westwater, McDowall, Siegert, Mossman & Abernethy, 1998). More specifically, some evidence points to the fact that maintenance of not yet automated routines (Patriot, Verin, Pillon, Teixeira-Ferreira, Agid & Dubous, 1996) as well as automatic processing (Faglioni, Botti, Scarpa, Ferrari & Saetti, 1997) are deficient in PD patients. An interesting concept proposed by Pascual-Leone and colleagues (Pascual-Leone, Grafman & Hallett, 1994) could help in the understanding of why artificial grammar and category learning is not clearly affected in PD patients (Reber & Squire, 1999). The authors claim that the basal ganglia regulate the timely access and transfer of

information from a working memory buffer to the prefrontal cortex, while the cerebellum may order events in time. The involvement of the cerebellum during skill and implicit learning has been recently supported by imaging evidence (e.g., Gabrieli, Singh & Stebbins, 1996; Juetpner & Weiller, 1998; Pascual-Leone et al., 1994).

3.2.4 Reinforcement learning

The most seminal model on reinforcement learning was proposed by Wise and colleagues (1996). In this model, the basal ganglia are described as a DA-based system that regulates rule potentiation and learning of context. This proposition implies that potentiation of rules as a result of reinforcement happens in the direct pathways (see e.g., Contreras-Vidal & Schultz, 1999), while the indirect pathways facilitate future rule potentiation based on previously established patterns (Wise et al., 1996). Furthermore, it has been argued that a combination of DA-dependent reinforcement and competition learning rules reduces the amount of information transferred from the cortex to the basal ganglia (Bar-Gad & Bergmann, 2001). This reduces the capacity to select and respond from/to ambiguous information (Saint-Cyr, 2003). Next to the amygdala, one particular structure within the ventral striatum, the nucleus accumbens, has been ascribed to reward or anticipation of reward (e.g., Rolls, Critchley & Treves, 1996; Tremblay & Schultz, 1999; Bowman, Aigner & Richmond, 1996), especially in relation to the orbitofrontal cortex (Rolls, 2000).

3.2.5 Attention

Cognitive textbooks describe attentional control as an ability to focus on a target, to maintain attention in a distracter context, and to release attention due to internal or external cues. The basal ganglia model by Brown and Marsden (1998) describes the basal ganglia as a system that regulates the synchronisation of brain potentials in order to focus attention. The model is supported by attentional control deficits in PD patients who are incapable of carrying out dual tasks, or self-monitoring (e.g., Brown & Marsden, 1991; Brown, Soliveri & Jahanshahi, 1998) and of carrying out simultaneous actions (Taylor, Saint-Cyr & Lang, 1986). In addition, PD patients also have problems with covert (Downes, Roberts, Sahakian, Evenden, Morris & Robbins, 1989) and overt attentional priming (Bennett & Castiello, 1996) and with set-shifting (Hayes, Davidson, Keele & Rafal, 1998; Hsieh, Hwang, Tsai & Tsai, 1996; Owen, James, Leight, Summers, Marsden, Quinn, Lange & Robbins, 1992). For example, Hayes and colleagues (1998) reported that treatment of motor-symptoms with l-dopa medication results not only in improvement of motor-behaviour, but also in attentional set-shifting. This implies that dopamine plays a regulatory role in both motor and attentional control. Loss of striatal dopamine also prevents sufficient encoding and appropriate selection of ambiguous information

and impairs predictive control, i.e., the ability to use current information to adapt future behaviour (Graybiel, 2000; Graybiel Aosaki, Flaherty & Kimura, 1994). Saint-Cyr (2003) speculates that the deficit in attentional control may result from two disrupted pathways: the thalamo-cortical pathway and the thalamic nuclei under the control of the pallido-nigral projections. Also, according to Steriade and Llinas (1988), direct projections from the GPe to thalamic reticular shell nuclei may be essential as this mechanism modulates the signal-to-noise ratio of information processing. A clear separation of attentional mechanisms and working memory will not be attempted here, but it is apparent from the PD literature that working memory is under the scrutiny of some attentional mechanisms. According to Baddeley (1986), working memory involves several capacities such as self-monitoring, short-term-memory, delayed response, and problem solving. Several authors have reported that PD patients show deficits related to these capacities. To name a few, deficits in conditional associative learning (e.g. Taylor et al., 1990; Vriezen & Moscovitch, 1990), some forms of procedural cognitive learning (Saint-Cyr et al., 1988; Saint-Cyr, Taylor, Trépanier & Lang, 1992), spatial/non-spatial working memory (Owen, 1997), and cognitive planning (Owen, 1997) have been reported.

Chapter IV

Methods used to investiagte BG functions

IV Methods used to investigate BG functions

4.1 Lesion technique and lesion behavioural studies

Functional studies of the basal ganglia in humans have used different methods over the past hundred years. In this section, I briefly describe these. More than a hundred years ago first descriptions of functional cognitive deficits due to brain lesions were reported (Broca, 1961; Lichtheim, 1884; Wernicke, 1874). The French neurologist Paul Broca (1861) described that lesions of a left frontal brain region (Broca's area) affect language production, but not language perception. Several years later, the German neurologist Carl Wernicke (1874) noted that lesions of the left posterior temporal region result in language comprehension deficits with intact language production (e.g., Goodglass & Kaplan, 1972). Wernicke argued that a separation of anterior (frontal) and posterior (temporal) language areas substantiates a functional separation of production and perception, but not of linguistic sub-processes per se. At the beginning of the 1970s, systematic and theoretically motivated behavioural experiments started to investigate specific language deficits as linguistic phenomena. A similar development can be reported for the investigation of other cognitive functions. However, a couple of critical aspects remain to be explained as they carry particular weight for the current investigations on patients with focal lesions of the basal ganglia. (1) What are the implications of such focal lesions for functional deficits, and (2) What are the functional correlates of subcortical structures such as the basal ganglia, considering the clinical evidence over the last thirty years?

Addressing the question how focal lesions correlate with functional deficits, Damasio and Damasio (1997) pointed out that localisation of damage should not be equated with localisation of function. More likely, specific cognitive functions engage a neural network and neurophysiology that do not allow for a simple linear interpretation of cognitive function as residual performance and compensation during recovery are often found. Therefore, the authors postulate that the lesion technique allows to formulate hypotheses about the relative involvement of an anatomical region as a "processing unit" (see Damasio & Damasio, 1997) within a network supporting cognitive function. This, of course, can go hand in hand with fMRI investigations that aim to confirm the relative contribution of particular structures within an anatomical network supporting cognitive function.

Based on this hypothesis, I have taken a triangle approach to investigate cognitive function in the basal ganglia. First, by utilizing both fMRI and ERPs in healthy populations, the basic neuroanatomical network as well as the temporal resolution of language function was delineated by previous research in our laboratory and my own investigations (see Exp. 5 & 6, Chapter 5). Second, by investigating both patients with focal basal ganglia (BG) lesions and patients with Parkinson's disease (PD), the contribution of one particular structure within the functional

neuroanatomical network of language function was investigated. Using ERPs with these populations, one can look at the effect of structural and neurodegenerative deficits on the temporal dynamics of language function. To this end, a brief summary as to why the basal ganglia are an interesting player in language processing should be sketched out. In a brief excerpt, Damasio (1985) listed three factors that are in close agreement with the current series of investigations on the basal ganglia in the auditory language domain. First, Broca's patient Monsieur LeBorgue ("TAN") did not have a localised lesion in Broca's area but an extended lesion including the frontal operculum and most of the putamen and caudate (see Figure 4-1). Therefore, the functional role of subcortical structures such as the basal ganglia deserve further investigation.

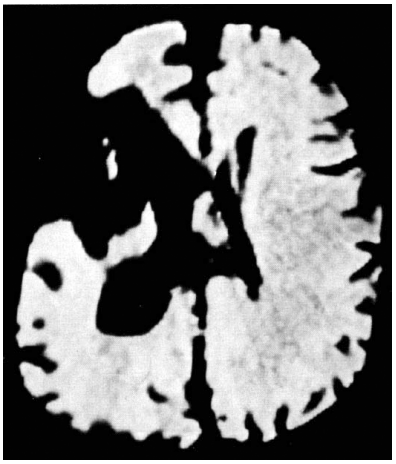

Figure 4-1. *CT-scan of original brain of Broca's patient Monsieur LeBorgue (adapted from Castaigne, Lhermitte, Signoret & Abelanet, 1980).*

Secondly, it has been reported that haemorrhages (Alexander & Lo Verme, 1980; Hier, Davis, Richardson & Mohr, 1977), but also vascular lesions in the basal ganglia result in language deficits (Brunner, Kornhuber, Seemüller, Suger & Wallesch, 1982; Damasio, Damasio, Rizzo, Varney & Gersh, 1982; Naeser, Alexander, Helm-Estabrooks, Levine, Laughlin & Geschwind, 1982). In particular, the dorsal half of the caudate head, the anterior limb of the internal capsule, and the anterior and dorsal part of the putamen seem to be responsible for language dysfunction (Damasio, 1983). While articulatory deficits in speech production have been described as Broca-like, there are also reports of fluent aphasia and in particular, severely impaired auditory comprehension. This suggests that the picture of deficits resulting from basal ganglia lesions is far from being conclusive. Damasio (1983) raises the intriguing question how lesions within the neostriatum cause auditory verbal processing deficits and points to sparse primate evidence implying that specific sensory projections to the caudate may shed some light onto this question. For example, a rhesus monkey model describes massive projections from the auditory

association cortex, next to projections from the frontal cortex, to the head of the caudate (via anterior limb of capsule and anterior putamen; Damasio, Damasio & Van Hoesen,1982; Van Hoesen, Yeterian & Lavizzo-Mourey, 1981). Damasio (1985) speculates that lesions to these areas could cumulatively result in an acoustic analysis deficit. Last, anatomical and physiological animal studies (see also outlook Chapter 6) extend the primary motor function of the basal ganglia to other functions by describing differentiated cellular components in the primate neostriatum (Yeterian & Van Hoesen, 1978; Goldman-Rakic, 1982). For example, Rolls and colleagues (Rolls, Baylis& Hasselmo, 1984) have proposed that response preparation, and attending and orienting towards pattern changes of a stimulus may be guided by the striatum. The extent to which these speculations and functional specifications from primate research translate into functional specification and deficits related to the basal ganglia in the human brain will be elaborated on in Chapter 5.

4.2 Event-related brain potentials (ERPs)

Studies of brain-damaged patients as well as fMRI and PET studies have provided helpful evidence in understanding the neuroanatomical organisation of both language and other cognitive functions. However, these methods are limited by their low temporal resolution as compared to electrophysiological measures such as event-related brain potentials (ERPs). Thus, ERPs offer a meaningful extension to methods with high spatial resolution. ERPs are measured as voltage fluctuations time-locked to sensory, motor, or cognitive events in the ongoing electroencephalogram (EEG, Hillyard & Picton, 1987). These stimulus-dependent voltage fluctuations are manifested in a continuous temporal course of positive and negative peaks (or components) that are too small to be isolated from the ongoing EEG. Signal-averaging of similar stimulus types extract the stimulus-triggered ERP from the EEG or background noise.

The modulation of scalp recorded brain potentials results from depolarisation of neuronal- and gliacellmembran (Hillyard & Picton, 1987). Changes in the ionic conductance cause a balance between positive and negative current or vice versa (Nunez, 1995). These patterns of electrical fields are called dipoles. Transmembran potentials or dipole sources produce field potentials in extracellular fluid that can be registered at the scalp. However, field potentials with local current cannot be registered at the scalp. These closed fields are normally generated by one dipole. Overlap of dipoles as a result of synchronised activation and spatial ordering of cell groups allows the electrical activity to pass cell borders. The resulting open fields are the source of ERPs that can be measured at the scalp surface.

The topographic distribution of scalp ERPs can provide some information about the source of neural generators of a potential, though inferences about the location of such generators are limited (Hillyard & Picton, 1987; Nunez, 1981; 1995).

First, each spatio-temporal potential at the scalp can be the sum of more than one source configuration. Furthermore, smearing or low-pass filtering of potentials can result from the electrical current running from the brain to the scalp. Last, the direction of the dipole source defines the pattern of scalp ERPs. Therefore, it is possible that an ERP with a lateralised right hemispheric distribution is generated in the left hemisphere.

Given the restrictions of spatial localisation, ERPs still provide a number of beneficial aspects. The method is non-invasive and can be measured passively, which makes it an excellent measure for both healthy and brain-damaged populations. For example, patients with motoric restrictions can be measured without being required to make a task-dependent response via a button press. However, a combination of ERPs and behavioural measures is preferable, as the modulation of components should clearly show a component change based on an aphasic or non-aphasic symptom rather than merely an average of correctly and incorrectly detected information. Two main advantages of ERPs should be mentioned: high temporal resolution (ms range) and continuous measurement. These are particularly relevant for the measurement of auditory language processes, as language comprehension occurs in real time. In comparison, reading and reaction times as well as eye movement measures are fixed in time and cannot provide information about sequential, online processes. In addition, ERPs are three-dimensional as characterised by latency (onset of activation), amplitude (extent of activation), and topography (pattern of brain activity; see McCarthy & Wood, 1985). These dimensions are both physiologically and functionally defined aspects of an ERP component (Donchin, Ritter & McCallum, 1978; but see also Coles & Rugg, 1995). In particular, changes in these dimensions in patient populations reveal the modulating character of a particular brain structure that is engaged in a cognitive process.

Components are subdivided into exogenous and endogenous components based on the type of manipulation. Exogenous components seem to reflect physical features of a stimulus, while endogenous components are influenced by the cognitive state of a participant as well as by specific testing conditions and procedures. Endogenous components thus give insight into the neural basis of cognitive processes. On a critical note, Heinze and colleagues (Heinze, Luck, Mangun & Hillyard, 1990) reported that spatial attention modulates the P1, while the P2, which is thought to be an endogenous component, is sensitive to sensory aspects of a stimulus (Ritter, Simson & Vaughan, 1983). Therefore, it appears that a clear separation of exogenous and endogenous components is not clear-cut.

In the following, a brief description of ERP components should prime the reader to all components that can be elicited during language processing. While the current thesis will not elaborate on early ERP components, these will be briefly introduced as some of these components have been found to be sensitive to brain

damage. However, relevant to the thesis, specific focus will be given to the late language-related components such as the N400 and the P600 as well as to the non-linguistic, attention-related P300.

Early components (P1, N1)
As described above, early components are thought to specifically reflect physical stimulus features (Luck, Hillyard, Mouloua, Woldorff, Clarke & Hawkins, 1994; Mangun & Hillyard, 1990). However, both the P1 (90-120 ms post-stimulus onset) and the N1 (200 ms post-stimulus onset) have been reported to reflect modality-specific processing sensitive to attentional direction (e.g., Mangun & Hillyard, 1990). The two components are functionally correlated with different attentional aspects. While enhanced P1 amplitude seems to reflect sensory "gating", the N1 amplitude seems to correlate with enhanced perceptual processing at an attended location (e.g., Luck et al., 1994). There are multiple speculations about the neural generator of the N1, while the plausible generator of the P1 is the secondary visual cortex (Gomez Gonzalez, Clark, Fan, Luck & Hillyard, 1998).

P2
A functional classification of the P200 component is complicated due to sparse and controversial evidence. Some investigations have proposed that the P200 is an exogenous component as the P200 is elicited by stimulus complexity (Ritter et al., 1983). However, Luck and Hillyard (1994) have shown that the P200 results from detection of task relevant deviants. This renders a functional interpretation of the P200 impossible, partially explaining the lack of investigations locating a neural generator of this component.

N2 – N2b and N2c
This component is endogenous with a peak latency of 270 to 310 ms and reflects selective attentional processing. The N2 has been differentiated into the N2b and the N2c. In the auditory domain, the N2b is labelled MMN with an onset as early as 100 ms post-stimulus presentation (Näätänen, 1992). The MMN can be evoked pre-attentively. In the visual modality, the N2b occurs at around 270 ms and clearly guides selective attention (Näätänen & Picton, 1987). In addition, the N2b has been linked to stimulus selection and response in multidimensional selection tasks (Smid, Jakob & Heinze, 1999). It has been speculated that the prefrontal cortex is a prime generator candidate of the N2 (Lange, Wijers, Mulder & Mulder, 1998).

E(L)AN – LAN
Within the domain of language, there have been reports on early negativities correlated with syntactic aspects of language processing in both the auditory and visual

modality. The early anterior negativity (E(L)AN) is a response to phrase structure violations that cause a biphasic pattern of an early negativity followed by a late positivity (Friederici, Hahne & Mecklinger, 1996; Friederici, Pfeifer & Hahne, 1993; Hahne & Friederici, 1999; Maess, Friederici, Damian, Meyer & Levelt, 2002; Neville, Nicol, Barss, Forster & Garrett, 1991). Another early negativity (LAN) with a longer latency has been reported in response to agreement violations (Deutsch & Bentin, 2001; Gunter, Friederici & Schriefers, 2000; Stowe & Mulder, 1997; Penke, Weyerts, Gross, Zander, Münte & Clahsen, 1997). The latency of the early negativity does not only vary as a function of violation, but also where the violation occurs in the critical word (onset or offset of word; see Friederici, Gunter, Hahne & Mauth, 2004). It has been argued that the early negativity is automatic in nature as proportion manipulations did not affect the amplitude of this negativity (Maess et al., 2002). Neural source candidates of the early negativity have been investigated with current source density mapping (Knösche, Maees & Friederici, 1999), dipole modelling (Friederici, Hahne & Saddy, 2002), fMRI (Friederici et al., 2003a) and ERP lesion studies (Friederici, Hahne & von Cramon, 1998; Friederici, von Cramon & Kotz, 1999; Kotz, Frisch, von Cramon & Friederici, 2003a). There is converging evidence that early syntactic structure-building is supported by the deep frontal operculum and the anterior superior temporal gyrus (see for further discussion Friederici & Kotz, 2003).

P300 – P3a and P3b

The P300, or more precisely the P3a and P3b, have been correlated with discrimination and detection processes. While the P3a seems to be a specific response in automatic novelty detection, the P3b has been correlated with voluntary attention to target stimuli. The P3b is elicited in a classical detection paradigm, the so-called "odd-ball" paradigm. Participants passively (silent counting) or actively (button press) respond to a deviant target that elicits a parietal positivity between 300-500 ms post-stimulus onset and is multimodal in nature. P3b amplitude and latency vary as a function of probability, stimulus meaning, and task relevance. Functionally, the P3b has been correlated with inhibition processes involved in the processing of expected targets (Heit, Smith & Halgren, 1990; Schupp, Lutzenberger, Birbaumer, Miltner & Braun, 1994) and context updating in working memory and attention (Donchin, Ritter & McCallum, 1988; Ruchkin, Johnson, Canoune, Ritter & Hammer, 1990).

The P3a is elicited in the so-called "novelty oddball" paradigm and consists of standard and deviant stimuli as well as low probability novelty stimuli. Involuntary response to a novel stimulus elicits a P3a, which is maximal at fronto-central electrode-sites, has an earlier onset than the P3b (60-80 ms) and habituates with stimulus repetition (Solanti & Knight, 2000). This component has been interpreted

as reflecting an orienting response towards novel events (Yamaguchi & Knight, 1991).

Evidence from intracranial recordings shows that the P3a engages the inferior parietal, cingulate, dorso-lateral prefrontal, and postero-medial temporo-frontal cortices, while the P3b has been elicited from the superior parietal lobe and the medial temporal lobe (Halgren, Baudena, Clarke, Heit, Liegeois, Chauvel & Musolino, 1995a; Halgren, Baudena, Clarke, Heit, Marinkovic, Devaux, Vignal & Biraben, 1995b). In addition, lesion data show a reduction of the P3b as a result of temporo-parietal lesions (including the temporo-parietal junction and the posterior STS) mainly in the auditory and somatosensory domains and to a lesser degree in the visual domain. Furthermore, P3b reductions after prefrontal lesions correlate with task complexity, while P3a reductions in the same patient group are independent of task complexity during novelty detection in all modalities. P3a amplitude reduction also results from posterior lesions, leading to the conclusion that this brain area is involved in phasic attention independent of stimulus novelty. It appears, then, that prefrontal and posterior association brain areas interact during voluntary and involuntary attention and working memory processes.

P600

The P600 has been elicited in a variety of syntactic contexts: in syntactic violations requiring repair (see Friederici, 2002 for a comprehensive review) or in temporarily ambiguous sentences that require syntactic reanalysis (Osterhout & Holcomb, 1992; 1993; Osterhout, Holcomb & Swinney, 1994; Mecklinger, Schriefers, Steinhauer & Friederici, 1995). The P600 has been viewed to reflect controlled processing (see Coulson, King & Kutas, 1998b; Gunter et al., 1997) as the P600 is sensitive to probability, but the functional interpretation includes the following: indexing syntactic processing in general (Hagoort, 1993); secondary processing of repair or reanalysis (Osterhout & Holcomb, 1992; Osterhout et al., 1994; Friederici & Mecklinger, 1996); and syntactic integration cost (Kaan, Harris, Gibson & Holcomb, 2000; Kaan & Swaab, 2002). In addition to the classical P600 with a peak latency of 600 milliseconds post-stimulus onset, a second positivity with a shorter latency and a more frontal distribution has been reported for diagnosis before reanalysis (Mecklinger et al., 1995; Friederici, 1998) in more complex syntactic structures and to revisions of hierarchically structured linguistic information (Bornkessel, Schlesewsky & Friederici., 2002).

Due to its centro-parietal distribution and susceptibility to target expectancy, the P600 component has been viewed as part of the P300 family (see Coulson et al., 1998b; Gunter et al., 1997). However, latency differences and the fact that the two components behave in additive fashion when syntactic and physical violations are combined (Osterhout et al., 1994) have raised arguments about the functional simi-

larity of the two components. Differences in latency between the two components have been explained by target complexity of linguistic stimuli. This, however, cannot account for a functional differentiation between the P300 and P600 as the P300 latency varies as a function of target category (Kutas, McCarthy & Donchin, 1977). However, it is agreed that a dissociation of the two components with regard to a neural generator could help to settle the dispute. This aspect will be discussed further in Chapter 5.

N400

Investigations to substantiate the functional underpinnings of the N400 were realised in the auditory and visual domain using semantic anomalies (e.g., Kutas & Hillyard, 1980a, 1980b), semantic cloze probability (e.g., Kutas & Hillyard, 1984), context manipulation (Van Petten & Kutas, 1990), and semantic priming (e.g., Holcomb, 1988) in word lists and sentence paradigms. All results point to the fact that the N400 component reflects the integration of semantic processes (Chwilla, Brown & Hagoort, 1995; Holcomb, 1993; Kutas & Hillyard, 1984; Van Berkum, Hagoort & Brown, 1999; see also Kutas & Federmeier, 2002 for a modified interpretation of the N400).

The N400 is also elicited by pseudowords, but not by nonce words in classical lexical decision tasks (Holcomb & Neville, 1990). Furthermore, there has been evidence that the N400 is not language specific as the N400 can be elicited in the following situations: cross-modal paradigms in which either emotional prosodic or musical context facilitates visual targets (Schirmer, Kotz & Friederici, 2002; Koelsch, Kasper, Gunter & Friederici, 2004); in priming studies with pictures (Barrett & Rugg, 1990; Holcomb & McPherson, 1994); and cross-modally with words/sentences and pictures (Ganis, Kutas & Sereno, 1996; Nigam, Hoffman & Simons, 1992). However, an N400 is not elicited by incongruent musical sequences or incongruent geometrical figures (Besson & Macar, 1987; Besson & Faita, 1995; Paller, McCarthy & Wood, 1992), physical variations (Kutas & Hillyard, 1980a), or grammatical violations (Kutas & Hillyard, 1983). Recent evidence, however, shows that the N400 is elicited in a "syntactic context" type of violation when thematic role assignment is impossible due to case violations (Bornkessel, 2002; Frisch & Schlesewsky, 2001) or in verb-argument violations (Friederici & Frisch, 2000; Frisch, Hahne & Friederici, 2004).

The nature of the N400 has been a matter of a long-lasting debate. While some priming evidence with short SOAs and low proportion manipulations point to an automatic processing dynamic underlying the N400, most of the evidence presented above supports the notion that the N400 is integrative in nature. Furthermore, studies utilising masked priming, a paradigm used to investigate automatic processing, has resulted in controversial evidence (Brown, Jahanshahi & Marsden, 1993;

Deacon, Hewitt, Yang & Nagata, 2000; Kiefer & Spitzer, 2001). Thus, a final functional interpretation of the N400 is still outstanding. Neural generators of the N400 have been investigated with intracranial studies (Halgren, Dhond, Christensen, Van Petten, Marinkovic, Devaux, Vignal & Biraben, 2002; McCarthy & Nobre, 1995; Nobre & McCarthy, 1995), fMRI studies (Kotz et al., 2002; Rossell et al., 2001; Rossel, Price & Nobre, 2003), and lesion studies (Kotz & Friederici, 2003; Kotz, Meyer & Paulmann, in press; Swaab, Brown & Hagoort, 1997; Swaab, Brown & Hagoort, 1998). Some of this evidence postulates that the left inferior anterior temporal lobe, but potentially also the basal ganglia could be part of a neural network generating the N400 (see discussion below). A matter of debate, though, is whether modality specific contributions come from the inferior (visual) and superior (auditory) part of the anterior temporal lobe.

4.3 Functional magnetic resonance imaging (fMRI)

The development of modern imaging techniques has enabled the measurement of brain activity while participants do a task. While magnet resonance tomography (MRI) has been widely used to image anatomical structures, functional MRI (fMRI) is a relatively new procedure used to localize neuronal activity in an indirect, non-invasive manner. fMRI is based on local, neuronally defined changes of metabolistic activity. In comparison to positron-emissions-tomography (PET), fMRI is currently the only option that allows for the demonstration of repeated activation in the human brain without the use of ionised rays (for extended literature on fMRI, see Jezzard, Matthews & Smith, 2001; Buxton, 2002).

Due to its non-invasive nature as well as its relatively easy accessibility in clinics and research institutes, the method has gained a critical position in clinical neuroscience. The combination of structural and functional MRI allows for new insights into the cause, development, and treatment of neurological disease in comparison to both structural and functional investigations in the healthy brain.

Functional magnetic resonance tomography – Biological bases

fMRI measures regional blood flow changes that reflect neuronal activity in an indirect manner. This enables the identification of brain regions that are active during a given task. The cells demand increased energy during neuronal processing, resulting in increased oxygen use while oxygenised hemoglobin (Hb) is reduced to desoxyhemoglobin (dHb). Due to this not fully understood mechanism, vessels enlarge via neuronal activity and regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) increase. However, the increase of oxygenised blood is larger than the actual need of oxygen in the tissue (Bandettini and Wong, 1998). Due to this overcompensation the level of Hb is larger than dHB in a neuronally active region (Cohen und Bookheimer, 1994) than in a normally perfused region. In com-

parison to the magnetically neutral Hb, dHb creates a magnetically inhomogenous surrounding. Due to the larger portion of Hb relative to dHb, the tissue becomes magnetically homogenous. Consequently, a contrast, i.e., the oxygenised blood and the resulting changes in magnetic properties, can be measured. This contrast is called the **BOLD**-contrast (**B**lood **O**xygenation **L**evel **D**ependent; Ogawa & Lee, 1990; Belliveau et al., 1991). The BOLD-contrast influences the transversial dephasing of the T2*-weighted MR-signals, which results in different signal intensities. Blood that is strongly oxygenised interferes less with the dephasing of a signal, and this in turn increases the signal. On the other hand. increased dHb-concentration leads to stronger dephasing and a weaker signal. The linking to the hemodynamic response is the same for all metabolic measures. The hemodynamic response only indirectly reflects neuronal activity, is slow, and reduces itself relatively slowly. The BOLD-signal does not have an absolute value, but rather a relative meaning in relation to different activation states. Therefore, it is necessary to contrast different signal intensities against each other (e.g., stimulation against rest).

Spatial and temporal resolution

The spatial resolution of fMRI studies crucially depends on the size of the voxels measured and the resulting signal-to-noise ratio. In principle, voxels with a 3x3x4 mm dimension are measured. The smaller the voxels, the worse the signal-to-noise-ratio. Another restriction for the spatial resolution comes from the local blood supply in cortical structures. The complete capillary bed (intra- and extra-vascular region) as well as the venuous exit areas support the BOLD-signal. As a result, the spatial resolution is strongly linked to the local blood supply. Logothetis, Pauls, Augath, Trinath and Oeltermann (2001) were able to show that the BOLD-signal mainly correlates with local electrical field potentials that spatially extend beyond the expansion of the synaptic activity.

The temporal resolution of the fMRI is limited by the slowness of the BOLD-signals. After a brief stimulation, the BOLD-signal reaches its peak maximum after 4-6 seconds, and after 8-12 seconds, it is back to ~ 10% of its initial level. The temporal dynamic of the BOLD-signals occurs in the range of seconds, while real neuronal processes occur within milliseconds.

Temporally close processes elicit comparable BOLD-signals. These signals sum up in an almost linear fashion, thus increasing the amplitude of the signal. Therefore, an accumulation of processes elicited with short temporal spacing will lead to a larger signal change than single processes. This temporal dynamic of the BOLD-signals varies significantly between participants as well as between cortical areas. Unfortunately, this variability does not allow us to draw conclusions about the temporal characteristics of neuronal processes, making a direct comparison of different brain areas and participants difficult. However, it was demonstrated that

the BOLD-signal within one subject and within one brain area is extremely constant (Neuman, Lohmann, Zysset & von Cramon, 2003).

Due to susceptibility artefacts in the region of tissue transfer (e.g., air/cortex) the T2*- weighted signal in specific cortical regions is highly invariable. This is particularly true for the medial orbito-frontal cortex and the anterior temporal lobe. Due to the increased magnetic inhomogeneity of the region, the T2* signal quickly and significantly drops down, resulting in a signal wipeout. Studies that want to investigate such regions have to rely on specific fMRI recording sequences and techniques (see Jezzard et al., 2001; Norris, Zysset, Mildner & Wiggins, 2001; Deichmann, Gottfried, Hutton & Turner, 2003).

Chapter V

New evidence for the role of the BG in language processing

V New evidence for the role of the BG in language processing

5.1 Overview of empirical studies

As described above, the role of the basal ganglia during language processing may or may not be language-specific. Therefore, several venues need to be considered when looking at language-specific function and the basal ganglia. In terms of syntactic processing, the discussion has centred on the question of whether or not rule-based computation engages the basal ganglia as part of a fronto-striatal network (see Ullman, 2001; Ullman et al., 1997). If true, the automatic application of such rules should be impaired in patients with lesions or neurodegenerative changes of the basal ganglia. Alternatively, language deficits described in the literature have been described as secondary to attentional, timing, and working-memory related deficits (see work of Grossman, Kenny & Lee, 1999; Grossman, Kalmanson, Bernhardt, Morris, Stern & Hurtig, 2000; Grossman, Zurif, Lee, Prather, Kalmanson, Stern & Hurtig, 2002). In a series of auditory experiments, Kotz and colleagues (Friederici et al., 1999; Friederici et al., 2003a; Frisch, Kotz, von Cramon & Friederici, 2003; Kotz et al., 2003 a) investigated the syntactic function of the basal ganglia with different basal ganglia patient populations and with different syntactic structures varying in complexity. The main prerogative of these experiments was to: 1) test rule-based automatic syntactic processing in different patient populations (Experiments 1 & 2); 2) to dissociate a syntactic from a general cognitive deficit (Experiment 3); and 3) to investigate syntactic parsing of different complexities (Experiment 4).

Furthermore, the contribution of the basal ganglia to lexical-semantic processing was investigated in an auditory primed lexical decision fMRI experiment in a healthy population (Experiment 5) and in experiments including semantic selectional restriction and thematic violations in BG patients (Experiments 1 to 4; Kotz et al., 2002; Kotz & Friederici, 2003). The latter violation type allowed us to investigate the potentially semantic nature of verb arguments (Kotz et al., 2003 a). Given the variety of tasks applied to explore the relative contribution of the basal ganglia in lexical-semantic processing (see discussion in 3.1.2.2.), an obvious question was whether the core deficit linked to lexical-semantic information processing is in fact selection of lexical and/or semantic information. To answer this question, it is necessary to investigate a potential selection deficit in the context of automatic or controlled processing induced by the task and as a function of stimulus type (e.g., categorical or ambiguous). In a first attempt, automatic lexical-semantic processing was investigated at the word level (Experiment 5), while controlled semantic processing was tested at the sentence level (Experiments 1-4). Last, the basal ganglia in prosodic processing in the non-linguistic (e.g., emotional prosodic) and linguistic (sen-

tential prosodic) domains have been viewed as part of a neuroanatomical network (e.g. Adolphs et. al., 2002). This position indicates that the basal ganglia's contribution to prosodic processing may be relative. In particular, some evidence has linked the basal ganglia function in prosodic processing to one acoustic parameter in particular, i.e., the temporal encoding of prosodic cues in an auditory sequence (see Pell & Leonard, 2003). In a series of fMRI investigations (Kotz et al., 2003b; in press), we have followed up on how and under which circumstances the basal ganglia modulate emotional prosodic processes. Each specific language function and its relation to the basal ganglia will be discussed in turn, focussing on both published work as well as work in progress and preparation.

5.2 BG and syntactic processing

5.2.1 Experiment 1

Several theories have related subcortical structures such as the basal ganglia with syntactic processing. As discussed above, the approaches vary as a function of whether rule-based syntactic processing is directly linked to a fronto-striatal circuitry (Lieberman et al., 1990; Natsopoulos, Katsarou, Bostantzopoulou, Grouios, Mentenopoulos & Logothetis, 1991; McNamara et al., 1996) or whether it is part of an executive network necessary for the processing of complex syntax (e.g. Grossman et al., 1999). In order to understand the different processing levels implicated in these results, psycholinguistic modelling of syntactic processing provides a helpful framework. Frazier (1987) proposed that syntactic parsing occurs in two processing stages: an early automatic and a late controlled process. At the early stage, sentence information is structured on the basis of word category information, while at the second stage, all sentence information – syntactic and semantic – is integrated. In seminal ERP studies, Friederici and colleagues showed that these processing stages have psychophysiological reality (Friederici, 1995; Friederici et al., 1996; Hahne & Friederici, 1999). While detection of word category violations at the early stage elicits an early anterior negativity (E(L)AN), late syntactic processes correlate with a late centro-parietal positivity (P600). Thus, two syntactic processes can be linked to the fronto-striatal circuitry: 1) automatic syntactic processing, which is purely rule-based syntactic processing, and 2) controlled syntactic processing, which is dependent on attentional resources.

In 1997, Ullman and colleagues (see also Ullman, 2001; Pinker & Ullman, 2002) published a paper elaborating on the declarative/procedural model. Extending general rule-based behaviour to the application of grammatical rules, Ullman et al. (1997) reported that patients with Parkinson's disease show limited computational capacity to apply grammatical rules to past tense formation (e.g., *wash -ed*), while

patients with Alzheimer's disease display a problem with irregular past tense formation (e.g., *go – went*). Due to its unpredictable nature, past tense formation of irregular verbs is thought to be stored in memory rather than computed. Thus, Ullman's results imply that the basal ganglia are involved in rule-based grammatical behaviour. However, the question remains as to whether the basal ganglia are really a necessary structure in grammatical rule-based behaviour. For example, Friederici and colleagues reported ERP data from a frontal cortical lesion patient that did not show an E(L)AN in response to word category violations (Friederici et al., 1998). In addition, Ullman et al. (1997) and Tyler and colleagues (Tyler, de Morney-Davies, Anokhina, Longworth, Randall & Marslen-Wilson, 2002) reported that patients with perisylvian lesions with or without subcortical contribution have a deficit in regular past tense formation, also implicating cortical structures in grammatical rule application. Furthermore, Grossman et al. (2002) presented behavioural data of PD patients that showed intact automatic access to syntactic information. Thus, the contribution of the basal ganglia to automatic rule-based syntactic processing appears to be relative. This conclusion finds further support from the fact that neuroimaging data on syntactic sentence comprehension is not univocal on the involvement of the basal ganglia. While some studies link the basal ganglia to syntactic processing (Friederici et al., 2003a; Moro et al., 2001), others do not (Indefrey, Brown, Hellwig, Amunts, Herzog, Seitz & Hagoort, 2001; Inui, Otsu, Tanaka, Okada, Nichizawa & Konishi, 1998; Just, Carpenter & Keller, 1998; Stromswold, Caplan, Alpert & Rauch, 1996).

In a first experiment (Friederici et al., 1999) we therefore tested two patient groups (chronic stage), i.e., three patients with left fronto-cortical lesions and four patients with focal BG lesions in an auditory ERP sentence correctness judgement task. Data of the patients were compared to age-, gender-, and education-matched controls. We hypothesized that automatic rule-based syntactic processing should be affected in patients with fronto-cortical lesions. Furthermore, if the basal ganglia play a crucial rule in automatic rule-based syntactic processing, then patients with BG lesions should show a comparable deficit postulated for fronto-cortical patients. While controls showed the expected biphasic E(L)AN-P600 pattern elicited by word-category violations, patients with fronto-cortical lesions did not show an E(L)AN, but a P600 component. Crucially, patients with BG lesions did show an E(L) AN, but a reduced P600 component (see Figures 5-1 & 5-2). We therefore concluded that 1) automatic rule-based syntactic processing is primarily regulated by the left frontal cortex (including Broca's area), and (2) the basal ganglia do not play a necessary role in automatic rule-based syntactic processing. However, it appears that late syntactic processing may be affected in patients with lesions of the basal ganglia as the amplitude of the P600 component was reduced.

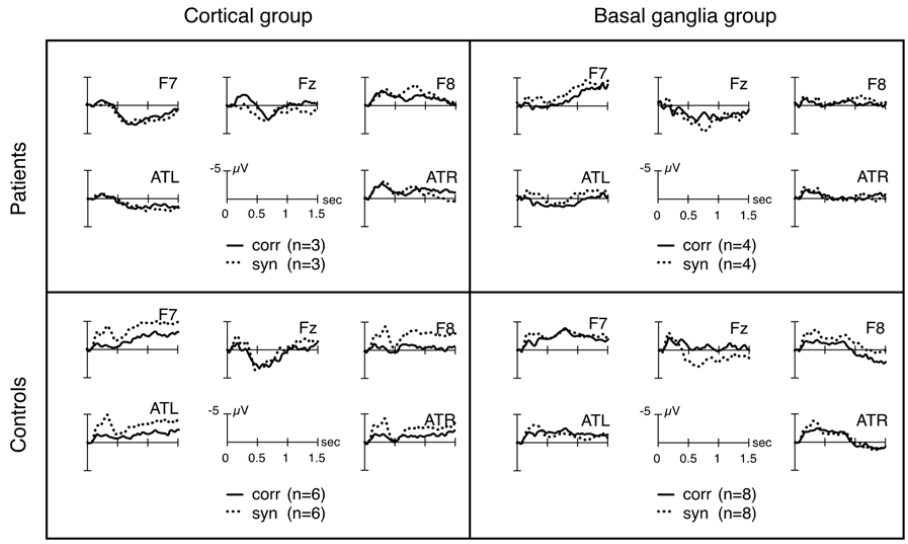

Figure 5-1. *Displayed are averaged automatic brain responses (E(L)AN) to syntactic phrase structure violations (dashed line) and correct syntactic phrase structure (straight line) at selected electrode sites for patients (top row; left: cortical patients: no E(L)AN; right: basal ganglia patients al., 1999).*

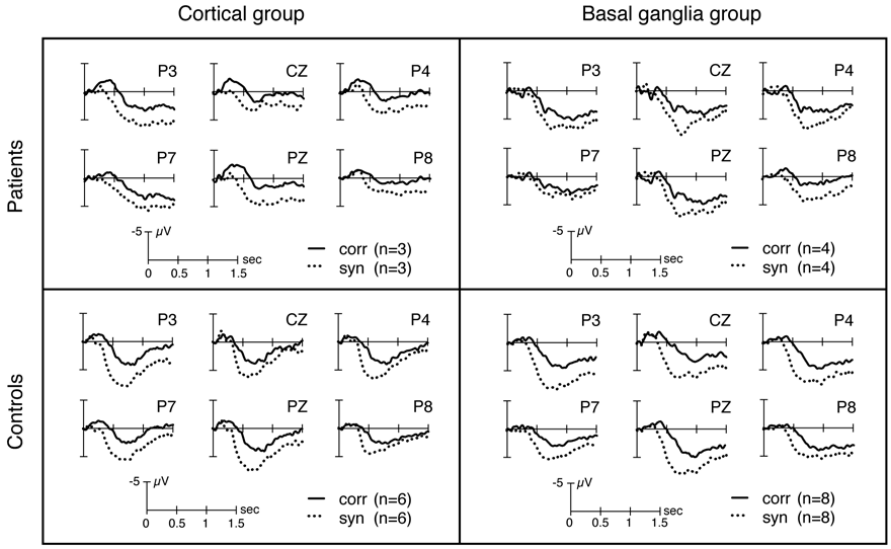

Figure 5-2. *Displayed are averaged controlled brain responses (P600) to syntactic phrase structure violations (dashed line) and correct syntactic phrase structure (straight line) at selected electrode sites for patients (top row; left: cortical patients; right: basal ganglia patients: reduced P600) and respective patient controls (bottom row; adapted from Friederici et al., 1999).*

What remains to be addressed are two critical issues. First, lesion patients may simply have a different neuronal dynamic underlying syntactic processing than patients with neurodegenerative disease such as Parkinson's disease (see Ullman et al., 1997). Second, if in fact automatic rule-based syntactic processing is not regulated by the basal ganglia, how can we explain the fact that controlled syntactic processing appears to be affected in patients with BG lesions? These questions were addressed in a second experiment.

5.2.2 Experiment 2

Following up the critical issues raised in the first experiment, we investigated the neural dynamics underlying syntactic processing in Parkinson's patients in a second experiment (Friederici, Kotz, Werheid, Hein & von Cramon, 2003). Patients who participated in the experiment were once again directly compared to age-, gender-, and education-matched controls in the same auditory sentence correctness judgement task used in Experiment 1. This allowed us to directly compare two aetiologies with the same paradigm. Parkinson's disease (PD) patients were selected by the following criteria: 1) on average, patients were in an early PD phase (on average, stage 2) as measured by the Hoehn & Jahr scale (1967); 2) all patients were L-Dopa medicated when participating in the experiment; and 3) none of the patients were either depressed or demented as measured by the GDS (Geriatric Depression Scale, Brink, Yesavage, Lum, Heersema, Adey & Rose, 1982; Yesavage, Brink, Lum, Huang, Adey & Leiter, 1983) and the MMSE (Mini-Mental State Examination). The latter two factors were important to control. While dementia could affect the patients' capacity to process lexical-semantic information, depression could affect prosodic perception of acoustic information and cause slowed down perception of information in general.

In comparison to patients with BG lesions, patients with PD were not required to respond to each trial with a button press. Rather, they were asked to listen to the sentences and to judge the correctness of the sentence covertly. This procedure was chosen to avoid possible interferences between language processing and motor demands due to motoric disabilities in all PD patients. On a critical note, one should mention that one major advantage of using ERPs in patient studies is that the method can be applied passively, thus reducing the physical demands on patients. On the other hand, a drawback of this approach is that trials cannot be averaged with only the correct responses included. Thus, no clear result on how well participants understood the critical trials correlated with a task can be achieved. However, in order to ensure that patients were able to understand the task and items at hand, we used an off-line paper and pencil task to test patients' comprehension of a subset of stimuli (20 incorrect and 20 correct items) used in the online ERP task. All pa-

tients were able to correctly identify correct and incorrect trials and to produce a correct version of the incorrect trials.

Results of the experiment revealed a similar pattern as in Experiment 1: PD patients showed an E(L)AN but no P600 effect for syntactic phrase structure violations (see Figure 5-3). These data further support both a functional and structural separation of automatic and controlled syntactic processes. While automatic syntactic processes seem to be regulated in fronto-cortical regions, late syntactic processes appear to be modulated by the basal ganglia.

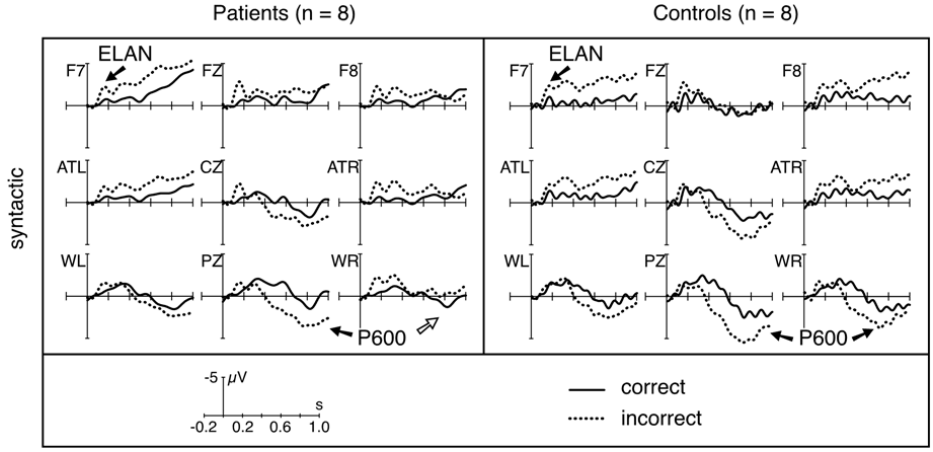

Figure 5-3. *Displayed are averaged automatic (E(L)AN) and controlled (P600) brain responses to syntactic phrase structure violations (dashed line) and correct syntactic phrase structure (straight line) at selected electrode sites for Parkinson patients (left; no P600) and controls (right; adapted from Friederici et al. , 2003c).*

Let me bridge these results to the two critical factors discussed above. Do different aetiologies affect syntactic processing in a similar way? How can we explain the fact that controlled syntactic processes are more affected than automatic syntactic processes? Comparing two different aetiologies with the same paradigm allows us to conclude that the emerging ERP pattern is the same for both aetiologies. Both patients with focal lesions of the BG as well as PD patients with neurodegenerative depletion of dopaminergic neurons in the BG show no deficit of rule-based syntactic processing. However, controlled syntactic processes that have been linked to syntactic processes in general (e.g., Hagoort, 1993; Osterhout & Holcomb, 1992), syntactic reanalysis or repair (Osterhout & Holcomb, 1992; Osterhout et al., 1994; Friederici, 2002; Friederici & Mecklinger,1996), or syntactic integration costs (Kaan et al., 2000; Kaan & Swaab, 2002) are clearly modulated in both patient groups. Independent of the functional interpretation of the P600 component,

the controlled syntactic processing impairment due to BG dysfunction needs to be explained.

Going back to the initial discussion at the beginning of the chapter, I would like to focus on two possible explanations. Grossman and colleagues discussed the role of the executive system in general (1999) and impaired processing speed for planning and inhibition (2002) during comprehension of syntactically complex sentences in PD patients. Both explanations for a syntactic comprehension deficit in PD patients link back to a more general cognitive deficit rendering language comprehension secondary to a primary cognitive deficit. However, the executive system encompasses both working memory and attentional mechanisms. Thus, it remains to be clarified whether, or to which extent, attention or working memory deficits modulate syntactic processing capacity. Second, if indeed a general cognitive deficit affects language comprehension in PD patients, we need to understand why controlled syntactic processes appear to be selectively impaired while controlled semantic processes are affected to a much lesser degree (for further discussion, see 5.3). Longworth and colleagues (2005) proposed that both syntactic and semantic processing may be impaired as a function of general impairment of inhibition. In fact, the authors cite investigations that postulate the role of the basal ganglia in inhibition of motor control (Mink, 1996), of cognition (Lawrence et al., 1998), masked priming (Aron, Schlaghecken, Fletcher, Bullmore, Eimer, Barker, Sahakian & Robbins, 2003), and reversal learning (Cools, Clark, Owen & Robbins, 2002). While this interpretation would be an intriguingly simple one, what inhibition means in the particular language context tested still needs to be specified. This will be discussed further in the context of semantic processing in Chapter 5.3. To follow up on Experiments 1 and 2, the next step described in the section below involved an attempt to dissociate the relative role of attention in language processing from controlled syntactic processing. In particular, we wanted to ensure that both syntactic and attentional processing was structurally simple to keep working memory demands low.

5.2.3 Experiment 3a and 3b

Along with my colleagues (Frisch et al., 2003), I explored whether the basal ganglia play a primary role in syntactic computation rather than a secondary role in an attentional deficit. In two experiments, we compared syntactic and attentional processing directly in patients with BG lesions. This investigation elaborated on an ongoing discussion about whether the P600 elicited during controlled syntactic processing is simply a P300b elicited by the detection of an unexpected, task-relevant target (Gunter et al., 1997; Coulson, King & Kutas, 1998a). This controversy results from the fact that the two components have a very similar centro-parietal scalp distribution, while the latency of the components may differ due to higher complexity

of linguistic versus non-linguistic stimuli. In the current context, testing BG patients with both a linguistic and a non-linguistic paradigm served two purposes. First, by potentially dissociating a P300 from a P600 component, we would be able to separate purely syntactic from general attentional processing. Second, by the same token, finding a P300 but not a P600 in the BG patients would support the existence of two functionally distinct components. Furthermore, if this dissociation was found, then at least one modulating structure underlying the generation of the P600 or P300, respectively, could be identified.

Patients with left lesions including the BG and patients with left lesions excluding the BG (primarily patients with temporo-parietal lesions) judged the grammaticality of correct and incorrect sentences that included a morphosyntactic violation and performed a non-linguistic oddball paradigm. Morphosyntactic violations were based on inflectional violations (e.g., *In the house it was often *to paint/painted*), while the oddball paradigm used a two-tone block with a standard 600 Hz tone occurring with a 0.8 probability and a deviant 660 Hz tone occurring with a 0.2 probability. The prediction was that patients with BG lesions should show no P600 based on previous evidence, while patients excluding BG lesions should show a P600. If the basal ganglia modulate controlled syntactic processes rather than attentional processes, both patient groups should show a P300 elicited in the non-linguistic oddball paradigm. Both predictions were confirmed (see Figure 5-4). While both patient groups displayed a P300 in the oddball task, no P600 was elicited by morphosyntactic violations in the patients with BG lesions.

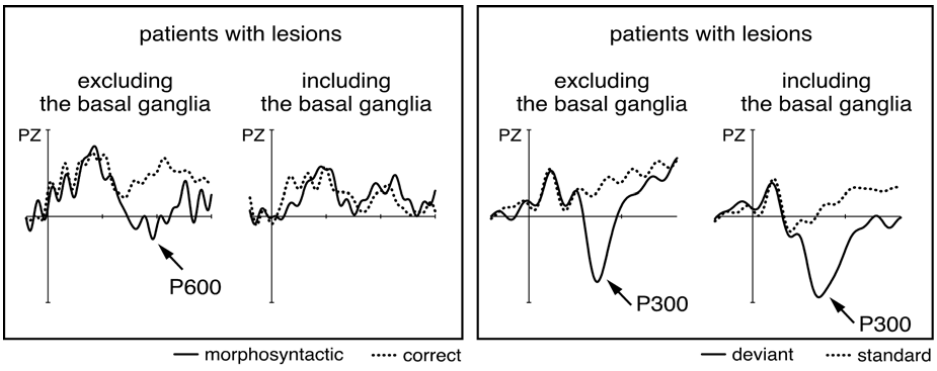

Figure 5-4. *Displayed are on the left side averaged controlled syntactic brain responses (P600) to morphosyntactic violations (straight line) and correct morphosyntax (dotted line) at a selected electrode site (PZ) for BG patients (left; no P600) and control patients (right). On the right hand side the P300 response to deviant tones (straight line) and standard tones (dotted line) is shown for BG patients on the left and control patients on the right (adapted from Frisch et al., 2003).*

Based on these data, we concluded that the basal ganglia play a modulatory role in the generation of the P600, a claim also made in a number of previous ERP studies with BG patients (Friederici et al., 1999; Friederici et al., 2003c). The fact that there was a clear dissociation between the P300 and P600 components in the BG patients suggests that general attentional processes are not affected in BG patients as otherwise, the P300 component would have been eliminated or reduced. Furthermore, we were able to add to the discussion as to whether the P600 is simply a P3b component. While there have been several attempts to identify the neural generators of the P300 (see discussion in Chapter 4.2.), the search for P600 generators is wide open.

In a first attempt, Friederici and colleagues (2001) with the help of a PCA analysis differentiated two positivities that partake in sentence revision when sentences are temporarily syntactically ambiguous: a centro-parietal positivity comparable to a P300 and an occipital positivity that responds specifically to syntactic aspects. Data from the patient investigation clearly show that the basal ganglia play a modulatory role in the generation of the P600, but not the P300. What remains to be clarified are several issues. First, the dissociation between linguistic and non-linguistic processing needs to be investigated with equal complexity of stimulus information. To be more specific, the P3 oddball task presents standard and deviant tones of the same consistent duration without building up a context. On the other hand, the P600 is elicited in sentence context, meaning that the component may be elicited as a function of expectancy and integration of both semantic and syntactic information. Furthermore, in the auditory modality, word duration is random. Thus, two factors varied between the linguistic and non-linguistic task: stimulus duration and context. Second, more complex syntactic structures should be investigated in order to test the relative contribution of working memory to syntactic processing. Last, as the discussion arose why controlled syntactic processes are affected specifically but controlled semantic processes to a lesser degree in BG patients, one should directly compare the relative contribution of the BG to these controlled processes. This is possible within one particular syntactic structure, namely verb-argument structure, which is reported next in Experiment 4.

5.2.4 Experiment 4

In sentence processing, the verb is characterized by the fact that it can or must take complements. These complements are both semantically and syntactically specified in the lexical entry of the verb. Semantically speaking, the verb *to visit* expresses an event in which one is visiting someone and one is being visited. In linguistic theory, these acting persons are termed *agent* (someone doing something) and *theme* (the one/thing something is done to). In linguistic terms, different participants are subsumed under different *thematic roles* (like agent, theme, etc.). Syntactically speak-

ing, the verb *to visit* needs two expressions as complements in order to form a grammatical sentence, namely two noun phrases. In sentence (1), these are the noun phrases *the little boy* and *the old man*.

(1) The little boy visits the old man.

Some verbs such as *to grin* are intransitive, i.e., they can only take an agent as an argument. If they are presented with an agent *and* a theme, the sentence becomes ungrammatical as in (2).
(2) * The little boy grins the old man.

In healthy participants, type (2) violations elicited a biphasic ERP pattern consisting of a negativity resembling an N400 component and a positivity interpreted as a P600 (Frisch & Friederici 1998; 1999; Frisch et al., 2004). This pattern suggests that verb-argument violations involve both semantic and syntactic processing. The sentence becomes semantically implausible as it is nonsensical that someone *grins* someone. Syntactically, the violation of the verb's subcategorization frame requires the involvement of syntactic repair.

The processes of identifying verb-arguments and assigning thematic roles to them in adequate time play a central role in the discussions on agrammatism (cf. Caplan & Futter, 1986; Caplan & Hildebrandt, 1986; Frisch, Saddy, & Friederici, 2000; Friederici & Gorrell, 1998; Grodzinsky, 1986; 1990; 2000). Here, we considered the possibility that the basal ganglia may be involved in the modulation of both syntactic and lexical-semantic processes as both processes are linked to controlled processing. In addition, we were interested in testing thematic role assignment in a more complex sentence structure, that is, in a passive verb-argument structure. For thematic role assignment to take place during online sentence processing, rapid construction of who does what to whom needs to occur. By using a passive construction, the thematic role assignment has to undergo transformation. Choosing this type of sentence structure allowed us to investigate whether potential disruption of thematic role assignment in more complex sentence structures results in a similar syntactic deficit as that seen in the previously tested, simpler syntactic structures (phrase structure and verb-agreement).

Two groups of patients were tested: patient with lesions of the BG and patients without BG lesions (mainly temporo-parietal lesions, see also Frisch et al., 2003). Correct sentences (*Im Institut wurde viel gestreikt und kritisiert*) and incorrect sentences formed by combining a subject NP with an intransitive verb made passive (* *Das Institut wurde viel gestreikt und kritisiert*) were presented auditorily and participants performed a sentence correctness judgement. Results revealed a double dissociation of the N400-P600 complex in the two patient groups. While pa-

tients with BG lesions showed the expected reduction of the P600 component preceded by a long-lasting negativity, patients with mainly temporo-parietal lesions showed no negativity, but positivity to verb-argument structure violations. We concluded that the data confirm the critical role of the basal ganglia in controlled syntactic processing and extended it to a possible contribution to controlled semantic processing (see Figure 5-5).

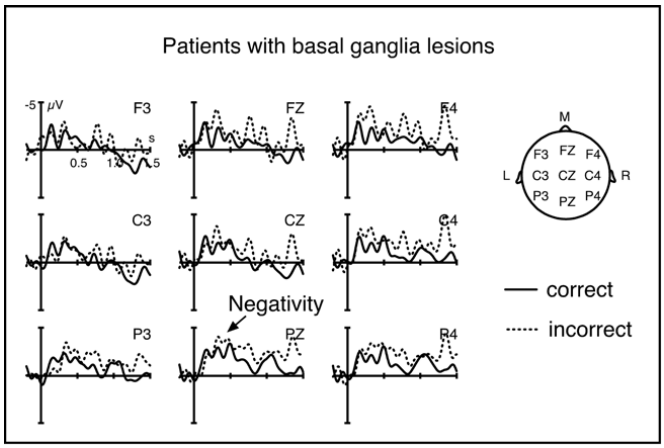

Figure 5-5. *Displayed are averaged brain responses in form of a late negativity to verb-argument structure violations (dotted line) and correct verb-argument structure (straight line) at a selected electrode sites for BG patients. The expected P600 as part of a bi-phasic N400/P600 brain response to verb-argument structure violations is not present in BG patients (adapted from Kotz et al., 2003a).*

Taking the combined results of Experiments 1-4, there is converging evidence that the basal ganglia are engaged in the modulation of controlled syntactic processes during receptive language processing. Interestingly, Experiment 4 also showed that patients with BG lesions show a modified N400 component. As verb-argument structure is often regarded as the intersection of syntactic and semantic processing, the delayed N400 component in the BG group may indicate that controlled semantic processes are also affected as a result of striatal lesions. However, the consequence appears less severe than for syntactic processes. Taken together, the studies by Friederici et al. (1999; 2003c), Frisch et al. (2003) and Kotz et al. (2003a) clearly point to a functional specification of the striatum in controlled syntactic processing of both simpler and more complex sentence structures and exclude the possibility that non-linguistic attentional mechanisms override controlled syntactic processes. The data also allow for the conclusion that the P3b oddball positivity and the P600 are not the same component, as patients with BG lesions indeed show a P3b, but only a strongly modulated or completely reduced P600.

5.2.5 Syntax – Ongoing experiments and outlook

As pointed out in the discussion above, several aspects remain to be investigated further. First of all, the complexity of non-linguistic and linguistic information needs to be equalized in order to fully reject the hypothesis that non-linguistic attentional processes are at the core of the basal ganglia syntactic processing deficit. In addition, the presentation rate in the P3 auditory oddball paradigm and the respective P600 paradigms was not consistent thus far. In an ongoing project, we are currently investigating stimulus complexity and varying temporal presentation rate in both non-linguistic and linguistic visual ERP paradigms, comparing BG lesion patients and patients with focal lesions of the premotor ventral cortex and their respective age-, gender-, and education-matched controls. These experiments allow us to address two open questions. First, by using more complex non-linguistic information (e.g. object sequences) in a visual serial prediction task (Schubotz, 1999) compared to a visual linguistic context (phrase structure violations as used in Experiment 1), we predict that the dissociation of the P300 and P600 will still occur under controlled contextual conditions. This will confirm the hypothesis that a pure attentional deficit is not at the core of the syntactic deficit. Second, by varying the temporal predictability of information in both the non-linguistic and linguistic context (random, isochronously, and chunked presentation), we are able to test the implications of "adequate" stimulus timing within a sequence and whether it is affected by BG lesions. Also, testing patients with premotor ventral as well as BG lesions clearly allows us to test the *forward model* of sequential information (e.g., Schubotz, Sakreida, Tittgemeyer & von Cramon, 2004) in two non-motor paradigms. As the basal ganglia are crucially involved in the timing of information processing (see Chapter 3.2.2.), varying the presentation time in both the non-linguistic and linguistic context should allow us to test whether controlled ERP components (in particular the P600) vary as a function of how information is sequenced in time. This is another important test to find out whether or not the basal ganglia are critically involved in language processing.

In addition, we are testing patients with anterior cortical lesions, lesions of the BG, and PD patients in a verb-participle production task. As all our evidence concerning the contribution of the basal ganglia to rule-based grammatical behaviour has been receptive, we want to ensure that modality (that is, production vs. perception) is not the critical factor contributing to the controversy in the literature.

5.3 BG and lexical-semantic processing

5.3.1 Experiment 5

As discussed in Chapter 3.1.2.2., there is extensive literature connecting not only syntactic but also lexical-semantic processing with the basal ganglia. In addition, there is dispute as to whether the basal ganglia alone, or the thalamus alone (in particular the pulvinar), or both structures are involved in lexical-semantic processing. Of importance, however, is to first specify the level of processing and modality investigated with a particular task. As was the case for syntactic processing, production and perception during lexical-semantic processing needs to be considered separately. Second, selection and/or categorization of lexical-semantic information needs to be distinguished.

There is evidence that patients with BG lesions suffer from semantic paraphasia implicating the lexicalisation stage during language production (Crosson, 1985; Damasio et al., 1982; Wallesch & Papagno, 1988). Very recent in vivo fibre tracking in patients during intraoperative language mapping (Henry, Berman, Nagarajan, Mukherjee & Berger, 2004) reports two cortico-subcortical connections related to speech arrest and anomia. The white matter connections associated with speech arrest, anomia, and mouth motor function are similar but distinct, including cortico-spinal, cortico-bulbar, and primary/supplementary motor association tracts as well as cortic-striatal connections. The authors speculate that the latter connections belong to the cortico-striatal motor loop going from the motor cortex to the putamen via the external capsula. In particular, the anterior and inferior putamen are thought to be connected to motor aspects of speech, while the superior and medial putamen are implied in lexical processes of anomia. Interestingly, the authors report work by Kotz et al. (2002) and Friederici et al. (2003 a) linking the two potentially functionally distinct putaminal areas reported for speech production to receptive fMRI language studies. Thus, language production and perception may both involve motor programmes.

However, lexical and/or semantic processing may occur at both the automatic and controlled levels of processing. Following the logic of automatic vs. controlled syntactic processing, parallels can be drawn for lexical- and/or semantic processing. If indeed the basal ganglia are more involved in controlled processes, it should be the selection or categorization of lexical- and/or semantic information that engage the basal ganglia. Longworth and colleagues (2005) discussed this option and postulated that the inhibition of semantic information could be impaired in BG patients.

In Experiment 5, Kotz and colleagues (2002) investigated auditory primed lexical decision in healthy participants using fMRI. Semantic priming was tested in an automatic processing situation (short inter-stimulus interval of 100ms between prime and target word) while participants judged whether the target word was a

German word or not. Furthermore, semantic prime-target pairs belong to two different semantic relation types: associative relations belonging or not belonging to the same category (e.g., *mouse-cat, mouse-cheese*) or semantic relations (*mouse-dog*) belonging to the same category. The lexical effect (direct contrast of words against pseudowords) revealed a cortico-striatal network involving the MTG bilaterally as well as the left putamen (anterior and posterior) and caudate. Looking at the semantic priming effect, bilateral fronto-temporal activation (BA 45, posterior STG) was found, but no subcortical activation. While activation of BA 45 activation has been linked to selection, the posterior STG activation has been interpreted as access to semantic information.

The data allow two conclusions in terms of the basal ganglia and their role in lexical-semantic processing. Lexical decision implies checking the word status of a stimulus by applying phonotactic rules and starting a lexical search. If a word or a pseudoword adheres to the phonotactic rules of a language, lexical search will be disrupted once a word is clearly identified and selection can occur. In turn, other word candidates are suppressed, and a lexical decision response takes place. Thus, selection of a word over a pseudoword occurs at the lexical level. This process seems to rely on a temporo-striatal network supporting the role of the striatum in lexical decision during auditory word processing. Interestingly, the lexical decision on pseudowords seems to be engaging the left anterior/middle rather than the left posterior superior temporal region, but not subcortical regions. This is supported by the fact that pseudowords compared to words activated the left anterior/middle STG, and patients with left lesions of the anterior temporal lobe showed no N400 lexicality effect, but an N400 priming effect in the auditory modality (see Kotz et al., 2002; Kotz & Friederici, 2003). Granted that both words and pseudowords elicit an N400, it appears that the neural underpinnings of the N400 and its relationship to lexical- and/or semantic information processing are far from being understood. However, the current results indeed show that the basal ganglia can be involved in the selection of words at the lexical level of processing.

Lexical Effect - Words versus Pseudowords

	Left hemisphere					Right hemisphere				
Location	*Z* score	*x*	*y*	*z*	BA	*Z* score	*x*	*y*	*z*	BA
					Words > pseudowords					
Anterior putamen	4.41	-23	13	1		-	-	-	-	
Posterior putamen	4.40	-32	6	9		-	-	-	-	
Caudate	4.27	-14	11	5		-	-	-	-	
Middle temporal gyrus	5.46	-44	-66	18	19	4.24	49	-49	9	21
Middle temporal gyrus	4.69	-53	-46	32	21	-	-	-	-	
Angular gyrus/tpTA	5.92	-36	-62	32	40	-	-	-	-	
					Pseudowords > words					
Inferior frontal sulcus	-3.30	-34	4	29	6/8	-3.70	28	6	26	6/8
Anterior superior temporal gyrus	-3.70	-56	2	0	22	-	-	-	-	
Middle superior temporal gyrus	-4.80	-56	-22	9	22	-	-	-	-	
Deep frontal operculum	-	-	-	-		-3.70	25	25	7	
Middle frontal gyrus	-	-	-	-		-4.50	40	26	19	46/45

Table 5-1. *Displayed are functional activations for contrasts between words and pseudowords (top) and pseudowords and words (bottom) in the lexical decision task. Z-scores indicate the magnitude of statistical significance. Localization is based on stereotactic coordinates (Talairach & Tournoux, 1988). The coordinates refer to the location of maximal activation thresholded at Z≥ 3.1 (uncorrected). Distances are relative to the intercommissural (AC-PC) line in the horizontal (x), anterior-posterior (y) and vertical (z) directions.*

What needs to be investigated further is why there was no apparent frontal activation in connection with the striatal activation for the lexicality effect. There are at least two options to be considered. The lack of frontal activation could simply be due to subject variance, i.e., some participants showed the effect, while others did not. On the other hand, it could be that the cortico-striatal loop involved in the access and selection of lexical and/or semantic information involves not only a fronto-striatal circuitry, but also a temporo-striatal circuitry for the auditory modality that is comparable to the visual temporo-striatal circuitry proposed by Middleton & Strick (2000). This circuitry could be envisioned as parallel circuitries that can shortcut selection in frontal areas when it is not competitive in nature (based on multiple candidates) but based on one-on-one selection as in lexical decision. Indirect evidence for this comes from the semantic priming effect in the current study. Here, we find activation in BA 45, which has been linked to selection between competing alternatives (Thompson-Shill, D'Esposito & Aguirre, 1997). But why is this activation not found in conjunction with basal ganglia activation? If indeed the suppression of competing alternatives is highly automatic, there should be no such activation. To test this option directly, a critical test would be to investigate semantic

selection with a working memory load. The possibility of an auditory temporo-striatal circuit will also be taken up in the final discussion in Chapter 6.

5.3.2 Experiments 1, 2, and 4

Taking up the hypothesis that the basal ganglia may be involved in the modulation of lexical-semantic processes, all studies with BG patients that involved semantic processing at the sentence level should be reconsidered. In both Experiments 1 and 2, semantic selection was tested by means of a semantic restriction selection criterion. That is, participants had to evaluate whether the verb phrase presented at the end of a sentence matched the previous context or not. In case of a semantic incongruency, integration of verb information should be hampered and elicit an N400 under controlled processing conditions. In Experiment 4, the integration of semantic and syntactic information offers a situation where selection of thematic roles can occur, but integration thereafter is violated due to the subcategorization violation of the verb.

Reconsidering the patient data of Experiments 1, 2, and 4, the following picture emerged. Patients with BG lesions (Experiment 1) did show an N400 effect elicited by semantic restriction violations, but the N400 effect was extended in latency and did not return to baseline (even after 1500 ms) as compared to controls. A similar picture emerged for the PD patients in Experiment 2. The N400 effect in Experiment 2 was statistically significant, but was absent at some electrode-sites and also showed an extended latency.

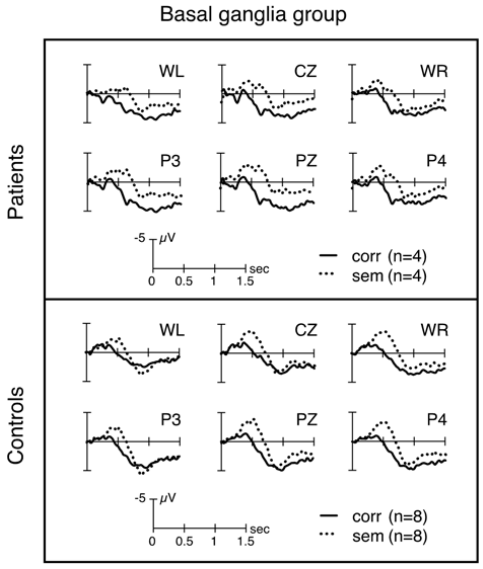

Figure 5-6. *Displayed are averaged controlled brain responses (N400) to semantic violations (dashed line) and correct semantics (straight line) at selected electrode sites for BG patients (top) and patient controls (bottom; adapted from Friederici et al., 1999).*

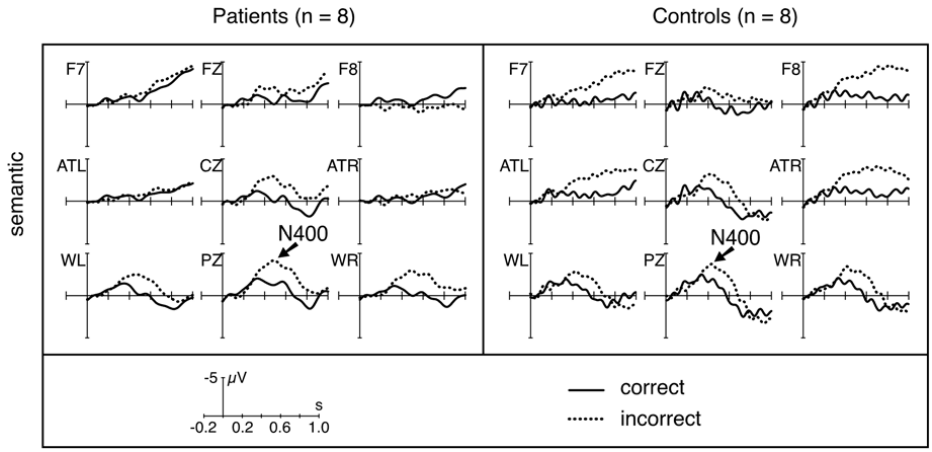

Figure 5-7. *Displayed are averaged controlled (N400) brain responses to semantic violations (dashed line) and correct semantics (straight line) at selected electrode sites for Parkinson patients (left) and controls (right; adapted from Friederici et al., 2003c).*

With regard to Experiment 4 (see Figure 5-5 above), there is an important post-hoc observation to be mentioned. Here, we discussed possible reasons why the modulation of the N400 in verb-argument structure violations is less severe than the modulation of the P600. From a functional standpoint, the N400 in the biphasic N400-P600 complex may not be the same N400 seen in lexical-semantic paradigms or in experiments involving semantic selection restrictions. If the N400 in combination with the P600 is more "syntactic" in nature, then the involvement of the striatum in the modulation of this biphasic ERP complex should be viewed as qualitatively different from that of a purely "semantic" N400. That is, the N400 elicited by violations of semantic selection restrictions should be modified differently than the N400 elicited by thematic role assignment after lesions or neurodegenerative change of the striatum. Clearly, this is not the case when comparing the extended latency of the N400 across the three patient experiments. While the extended latency in Experiments 1 and 2 have not been statistically confirmed, it is very likely that selection and final integration of semantic information was affected. However, the fact that the N400 and the P600, both elicited under controlled processing conditions, appear to be differentially affected after BG damage deserves further explanation.

While speculative, there is behavioural evidence that controlled semantic information processing is affected in PD patients (Copland, 2003; Longworth et al., 2005). However, on a critical note, patients are always medicated when they are tested. Thus, a direct comparison of the same patients in both medicated and unmedicated conditions should serve to determine if semantic deficit varies as a func-

tion of medication. Second, selection and integration of semantic and syntactic information could be qualitatively different. That is, while semantic violations are in principle local violations that can be detected online at the place of violation, the reanalysis of syntactic information involves detection, backtracking to the place of violation, and correction. Thus, syntactic reanalysis appears to engage the resequencing of information, which is not necessary in the case of semantic violations. Third, to test further if semantic selection restrictions and thematic role assignment engage the same N400, we are currently comparing the effects of verb-argument structure violations and semantic selectional restriction violations directly in the fMRI (Raettig, Kotz, Frisch & Friederici, 2005) and in a group of anterior cortical patients.

5.3.3 Lexical-semantics – Outlook and ongoing experiments

We have taken up the possibility that medication in PD patients distinctly affects semantic processing. In an ongoing project (Kotz, Schwarz, Winkler, Preul, von Cramon & Friederici, 2005) that investigates possible re-enervation of controlled syntactic processes in late stage PD after deep-stimulator placement (DSP) in both an on and off state, we also test the effects of L-Dopa and agonist medication on both semantic and syntactic controlled processes before DSP placement. Data is currently under statistical analyses. First evidence indicates that medication indeed affects controlled semantic and syntactic information processing differently. While PD patients show almost no N400 effect under medication, the N400 effect reappears under wash-out of L-Dopa and/or agonists. This is not the case for syntactic processing. Here, medication in late stage PD does not appear to affect syntactic processing. This is first evidence that L-Dopa treatment may affect semantic and syntactic processing qualitatively differently.

Furthermore, as mentioned above, we are following up the possible dissociation of the N400 elicited by semantic vs. thematic violations in an ongoing fMRI investigation (Raettig et al., 2005). Along the same lines, we have started to look at patients with anterior cortical lesions who seem to show dissociation between the two N400 types.

Last, we have tested the possibility that processing emotional semantics may also recruit the basal ganglia (Kotz, Paulmann & Raettig, 2005). Our primary interest in this investigation was to test the respective contribution of the right hemisphere in discriminating between emotional and neutral semantics. Comparable to the processing of emotional prosody, there has been discussion about the involvement of subcortical structures in the discrimination of emotional and neutral semantics. In order to test this hypothesis, the same participants were tested with two task instructions. In the implicit condition, subjects listened to prosodically neutral sen-

tences with three emotional semantic contents (positive, neutral, and negative) and decided on a three-point scale whether the second noun phrase of a sentence was of feminine, neutral, or masculine German grammatical gender. In the explicit condition, subjects had to categorize the same sentences (different randomisation) as positive, neutral, or negative on a three-point scale. Presentation of task instruction was counterbalanced across subjects. After correction of data in the implicit condition, each subject's rating of the emotional content (explicit task) was applied to the implicit condition to ensure maximal comparison of implicit and explicit emotional semantic processing.

Bilateral fronto-temporal activation was found for negative as compared to neutral semantics in the implicit task. In the explicit task, there was similar bilateral fronto-temporal activation as well as bilateral subcortical activation of the caudate, putamen (mid portion) and the thalamus (see Figure 5-8). Activation for the contrast between positive and neutral semantics did not pass statistical threshold, but did engage a similar network as the negative vs. neutral contrast under both task instructions. The current results clearly show that the basal ganglia system is involved when information (in this case, emotional semantics) is categorised and selected under controlled processing conditions. This further supports the notion that information processing under controlled conditions engages the basal ganglia system.

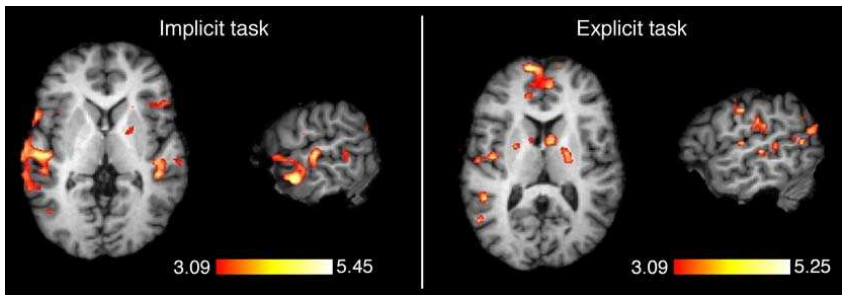

Figure 5-8. *Displayed are in an axial and left sagittal view the activation patterns for the direct contrast between negative (red) and neutral semantics in the implicit task (left) and the explicit task (right). Statistical threshold was set at Z≥3.09, uncorrected. Activated brain regions comprised of at least 163 mm^3 of connected neural tissue.*

5.4 BG and emotional prosodic processing

5.4.1 Experiment 6

Most discussion on emotional prosodic processing has centred on a cortical lateralisation hypothesis, or whether the right hemisphere plays a more enhanced role in emotional prosodic and perhaps in prosodic processing in general (Blumstein & Cooper, 1974; Heilman, Bowers, Speedie & Coslett, 1984; Starkstein et al., 1994).

However, some researchers have questioned a strong lateralisation of prosodic processing and proposed that prosodic processing engages a bilateral network (Bryan, 1989; Cancelliere & Kertesz, 1990; Dykstram Gandour & Stark, 1995; Pell & Baum, 1997; Van Lancker & Siditis, 1992) that may also include subcortical structures such as the basal ganglia (Brådvik et al., 1991; Blonder, Gur, Gur, Saykin & Hurtig, 1989; Cancelliere & Kertesz, 1990; Morris et al., 1999; Pell, 1998; Pell & Leonard, 2005).

In a first fMRI study (Kotz et al., 2003b), the neuronal network underlying emotional prosodic processing was investigated. In order to separate the effects of perception of pure emotional prosodic prosody and the interplay between emotional prosody and semantics, two conditions were created. For condition 1, a trained female speaker spoke semantically neutral sentences with either a happy, neutral, or angry prosody. For condition 2, the same sentences were filtered with the PURR-filter (for specifics, see Sonntag & Portele, 1998). This filter procedure eliminates the segmental and lexical information in an auditory sequence, but leaves suprasegmental information intact. Thus, both lexical emotional speech in condition 1 and purely prosodic speech in condition 2 displayed the same acoustic profile. Participants responded on a five-point scale whether the prosody they had heard was positive, neutral or negative.

It was predicted that a direct contrast between lexical and prosodic speech would point to brain areas that respond specifically to the interplay of prosodic and lexical information and to prosodic information only. If the basal ganglia modulate the perception of emotional prosodic processing, then there should be overall activation in the basal ganglia especially for the purely prosodic condition.

Results are displayed in Figure 5-9 and showed the following; 1) the lateralisation of purely prosodic effects was not mainly right lateralised but involved a bilateral fronto-striatal network; 2) the perception of combined lexical and emotional prosodic information also engaged a bilateral network, but here, temporo-striatal areas were activated. In summary, the contribution of the basal ganglia in both conditions supports the notion that the basal ganglia play a key role in emotional prosodic processing. However, there was a clear trade-off in terms of the cortico-striatal circuitry involved in the two conditions. In the purely prosodic condition, a classical, though bilateral, fronto-striatal network including the IFS/MFG, the frontal operculum, and the head of the caudate was activated. This could imply that when language content is eliminated, the categorisation of emotional prosody relies on a basal ganglia circuitry (in particular caudal) that is also linked to general cognitive processes (see Middleton & Strick, 2000). Thus, two questions remain: 1) Why was there no activation of the affective circuitry proposed for emotional evaluation? and 2) Is the activation reported here not specific to emotional prosodic processing but instead reflects the categorisation effort of the participants?

In contrast to pure prosody, the combined lexical and emotional prosodic condition showed that the temporo-striatal circuitry associated with the perception of emotional prosody in language context (as induced by the task) engages the secondary auditory cortex (anterior and posterior) as well as the basal ganglia (the anterior and middle portion of the putamen bilaterally). Here, as pointed out above (section 5.2.), additional evidence is provided for the existence of an auditory sensory circuitry between the basal ganglia and secondary auditory cortices, involving primarily the superior temporal gyri and also potentially the superior temporal sulci. This circuitry is comparable to the visual sensory circuitry proposed by Middleton and Strick (2000). This proposal will be taken up again in Chapter 6.

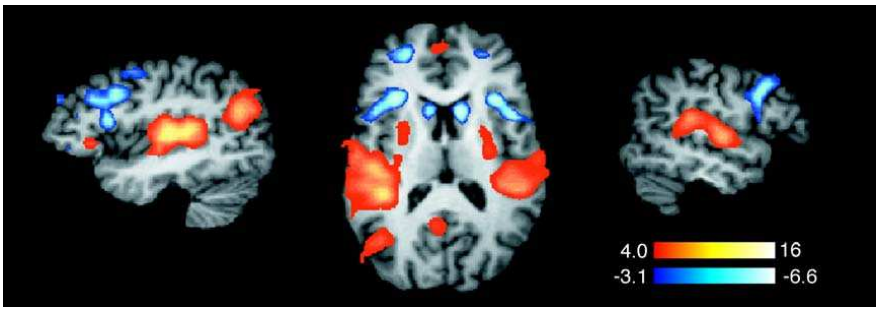

Figure 5-9. *Displayed are as a result of a direct contrast in left sagittal, axial, and right sagittal view the activation patterns for lexicalised (red) and delexicalised (blue) emotional speech. Functional activation was thresholded at Z≥4.0 for lexicalised speech and Z≥3.1 for delexicalised emotional speech.*

5.4.2 Emotional prosody – Outlook and ongoing experiments

Taking up the question whether the basal ganglia play a role in emotional prosodic processing, we retested the materials of Experiment 6 in a blocked presentation design (Kotz et al., in press). Previous results have shown enhanced bilateral, left-accentuated activation of both cortical and subcortical brain areas for emotional prosodic processing. The continuous categorisation of lexicalised and delexicalised emotional prosody may have forced participants to template matching of lexicalised and delexicalised emotional prosody. This in turn may have resulted in an increased effort to categorise emotional prosodic information. By presenting both lexicalised and delexicalised emotional prosody in separate blocks, but leaving the design event-related, we were able to retest the relative contribution of the basal ganglia to emotional prosodic processing. The results show that lexicalised emotional prosodic processing engages a bilateral temporo-striatal network, and delexicalised emotional prosodic processing activates a bilateral fronto-striato-thalamic network. In comparison to the activation patterns in Experiment 6, the lateralisation of activation was more right lateralised (see Figure 5-10.).

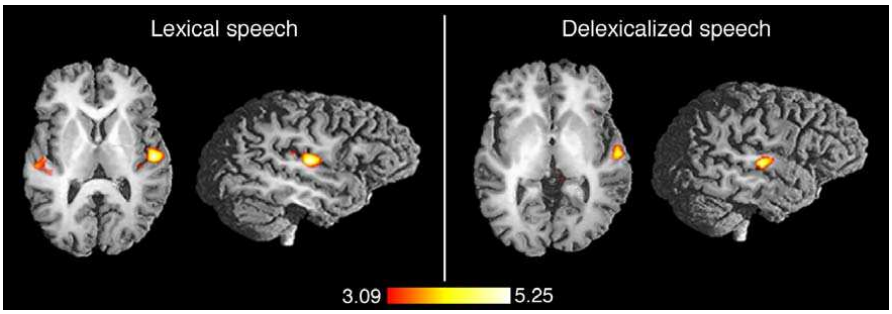

Figure 5-10. *Displayed are as a result of a direct contrast between emotional and neutral prosody in an axial and a right sagittal view the activation patterns for lexicalised and delexicalised emotional speech. Functional activation was thresholded at Z≥3.09 for both conditions. Results of a conjunction analysis reveal a common activation area in the right middle STG for both conditions.*

The data suggest that subcortical contribution to emotional prosodic processing does not vary as a function of template matching and increased effort while categorising emotional prosody. Additionally, activation of emotional prosodic processing was more right-hemisphere accentuated. At the moment we follow up two crucial questions: 1) Is the contribution of the basal ganglia to emotional prosodic processing task specific, that is, does explicit categorisation of emotional prosody rely on basal ganglia? 2) Does differentiation of emotional prosody (i.e. positive vs. negative emotional prosody) critically hinge on temporal cues?

As discussed in Chapter 5.3.3., categorisation and selection of lexical-semantic information may critically depend on the basal ganglia. If indeed the basal ganglia play a more general, domain non-specific role, then emotional prosodic processing may not depend on the basal ganglia when tested under implicit processing conditions. A recent fMRI experiment looks at this possibility in healthy participants. In addition, a series of ERP experiments has been started looking at implicit and explicit task effects as well as the temporal dynamics of basic emotions (happy, pleasant surprise, sad, angry, disgust, fear, and neutral) during emotional prosodic processing in both healthy, basal ganglia patients (Paulmann & Kotz, 2005), and Parkinson's patients.

5.5 General summary

To summarise, the current thesis set out to investigate the functional contribution of the basal ganglia to auditory language processing. In particular, the question was addressed whether this contribution is domain specific or not. To this end, both ERPs and fMRI were applied. Utilising ERPs, patients with BG damage (lesions or neurodegenerative change) and age-matched controls were tested in a number of

syntactic violation paradigms (phrase structure, verb-agreement, verb-argument structure) to test whether the basal ganglia play a role in rule-based automatic syntactic behaviour (Experiments 1 & 2). The results suggest that this is not the case as both BG and Parkinson's patients show a brain response to automatic syntactic processes comparable to age-matched controls. However, patients show a deficit for controlled syntactic processing. Experiments 3 & 4 explored whether this deficit is purely attention based and whether other controlled language-specific processes (i.e. lexical-semantic and/or thematic) are similarly affected as controlled syntactic processes. The data suggest that receptive syntactic processing deficits in BG patients cannot simply be explained as an epiphenomenona of an attention deficit as non-linguistic, attention-specific ERP components (P300) were comparable for patients and controls.

The role of the basal ganglia, or the basal ganglia in conjunction with the thalamus, in lexical-semantic processing is more complex. Generally, however, the present evidence points to the possibility that the BG system is engaged in the regulation of selection in lexical-semantic processing. In ERP studies (Experiments 1, 2, & 4) that used selectional restriction violations and verb-argument violations, both BG and Parkinson's patients displayed a delayed and reduced ERP response (N400) to incorrect semantic or thematic sentences. In an auditory fMRI experiment (Experiment 5) with healthy participants words activated the striatum of the left hemisphere during a lexical decision task. Both patient and fMRI data thus support the possibility that the basal ganglia play a role in selection.

Last, the basal ganglia seem to be actively involved in the perception of emotional prosodic cues. FMRI data acquired in two experiments with healthy participants (Experiment 6 & follow-up experiment) revealed bilateral striatal activation in explicit emotional prosodic categorisation tasks.

All of the current results render a picture of the basal ganglia in auditory language processing that could be domain-specific, but clearly deserves further investigation. In particular, non-linguistic (e.g., working memory, attention, and timing) and linguistic cognitive functions need to be compared directly with the same level of processing complexity and similar task demands in order to decide whether auditory language deficits in PD and BG lesion patients are in fact language-specific. Thus, whether the basal ganglia play a primary role in auditory language production and perception remains an open and challenging task to pursue in further research.

In the final chapter of this thesis I want to borrow from non-human primate research and sketch a model for a possible auditory temporo-stiatal loop as a basis for future research on auditory language processing in an extended functional network.

Chapter VI

Projections from and to the basal ganglia via the temporal lobe: Outlook on an auditory cortico-stratial loop

VI Projections from and to the basal ganglia via the temporal lobe: Outlook on an auditory cortico-striatal loop

Going back to evidence on cortical projections to and from the striatum, I would briefly like to refocus on the split circuitry model proposed by Joel & Weiner (2001). According to the authors a loop model that adheres to the direct/indirect pathway principles but includes both open and closed loops for information processing would allow transfer of information between cortical areas that 1) do not project to the striatum itself; and 2) support communication between closed circuitries and/or open and closed circuitries. This in turn could explain diverse functional deficits that have, for example, been reported in Parkinson patients. How could such a model be adapted to an auditory language-processing pathway that could be differentiated for language sub-processes and/or non-domain specific processes?

Auditory language processing relies on successful perception and integration of "meaningful units" evolving in time at several processing levels. Successful computation of such units is essential for successful auditory language comprehension. I would like to argue that in relation to functionally specific areas of the temporal lobe (see for a recent review Scott, 2005) and/or frontal brain regions, the basal ganglia might be a player in the successful computation and selection of auditory information during language processing.

In the non-linguistic domain the basal ganglia have been linked to the regulation of sequential processing (Brown, 1999), dopamine-dependent temporal discrimination (Rammsayer & Classen, 1997), the chunking of action sequencing (Graybiel, 1998), and temporal chunking (Schubotz & von Carmon, 2001) to name just a few. Sequencing and the correct timing of "meaningful units" in a sequence are also inherent to auditory language processing. However, language processing is highly automatised and only calls attention into action when expectancies or predictions are not fulfilled. Saint-Cyr (2003) proposed that the basal ganglia get engaged in attentional and preparatory function in the motor and action domain. Taking a big leap, one could speculate that the basal ganglia come into play when the computation of linguistic information is not occurring in appropriate time and in consequence affecting not only computation, but potentially also the re-sequencing, selection and response to auditory information. If true, a temporo-striato-temporal loop most likely in combination with a fronto-striatal loop (i.e. for selection and response functions) would have to be considered for auditory language processing. While the

nature of such a loop remains to be defined (open vs. closed or being part of a split ciruitry) I would like to take a first descriptive step in this direction.

Presented in Figure 6-1 is an attempt to adapt auditory non-human primate projection models to a potential auditory human projection model. This model describes input projections from temporal lobe areas to the basal ganglia as well as output projections from the thalamus to temporal lobe areas. While there is paucity of non-human primate research in terms of striato-thalamo-striatal projections (see LeDoux, Sakaguchi & Reis, 1984 for an exception in the rat model) as can be seen in the described model below, there is even less non-human primate or human research exploring potential connections between temporo-striato-temporal areas in the auditory domain (Yeterian & Pandya, 1998). However, evidence presented by Middleton & Strick (2000) provides an encouraging model for such connections in the visual domain.

In particular input projections from the superior temporal gyrus (STG; anterior and mid portions) to mainly anterior and mid portions of the putamen and caudate have been described in the squirrel monkey (Borgmann & Jürgens, 1999) and the rhesus monkey, respectively (Yeterian & Van Hoesen, 1978; Yeterian & Pandya, 1998). Furthermore, there are direct projections from the anterior portion of the STG as well as of the posterior STG and superior temporal sulcus (STS) to the amygdala as demonstrated in the macuaque monkey (Stefanacci & Ameral, 2000; 2002). As pointed out, clear ideas as to the nature of striato-thalamic projections are sparse. However, some auditory evidence describing outflow from posterior thalamic nuclei (i.e. medial pulvinar, medial geniculate nucleus) to anterior and posterior portions of the STG and STS (Hackett, Stepniewska & Kaas, 1998; Pandya & Rosene, 1993) in macaque and rhesus monkey models shows that connections (in some cases bi-directional) between the thalamus and the STG/STS exist. Romanski and colleagues (Romanski, Giguere, Bates & Goldman-Rakic, 1997) described projections from the medial pulvinar to the rostral STG/STS as crucial to auditory information processing. By further describing projections from the medial pulvinar to prefrontal cortex a first demonstration of parallel circuitry involving both temporal and frontal cortical brain regions connected to subcortical regions such as the striatum and the thalamus is given. While the current observations are by far conclusive in terms of a cortico-striatal auditory pathway model that could explain functionally differentiated auditory language processing, a closer exchange between animal modelling, functional neuroimaging, diffusion tensor imaging, and lesion studies is warranted in order to substantiate our understanding of a neural auditory pathway(s) supporting language processing.

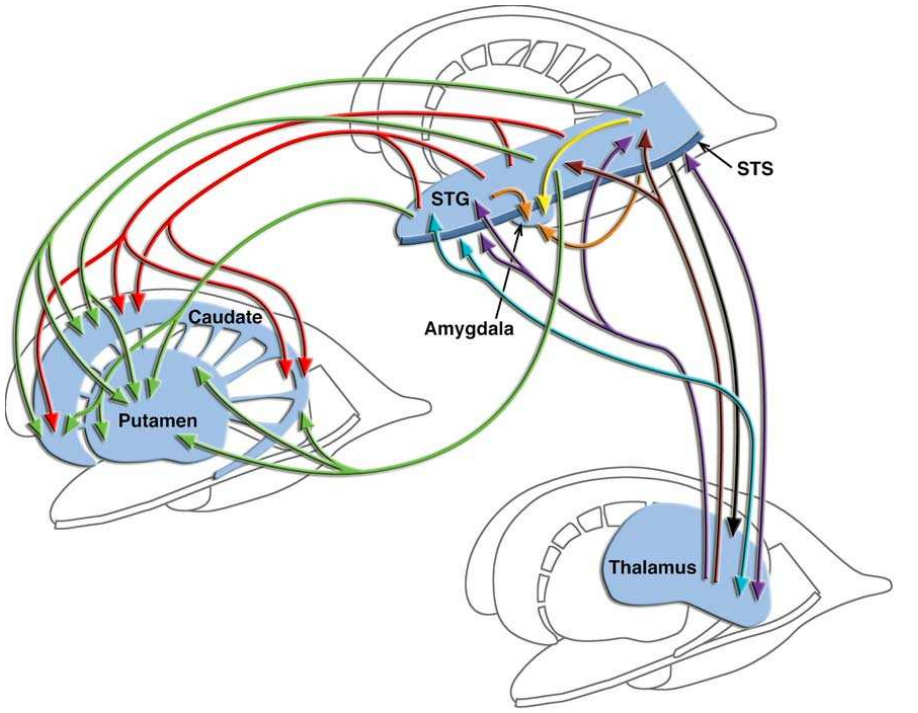

Figure 6-1. *Overlay on human brain structure of non-human primate studies revealing mainly anterior temporal input to the anterior and middle portions of the striatum and projections from the thalamus (here dominantly from the pulvinar and the medial geniculate nucleus) back to both anterior and posterior temporal areas in the superior temporal gyrus and the superior temporal sulcus. Colours reflect the specific tracer studies identified by author.*

Chapter VII

Deutschsprachige Kurzfassung

VII Deutschsprachige Kurzfassung

Die Rolle der Basalganglien bei der auditiven Sprachverarbeitung: Nachweise aus EKP-Läsionsstudien und funktionellen Kernspinstudien

Die vorliegende Arbeit untersucht den funktionellen Beitrag der Basalganglien in der auditiven Sprachverarbeitung. Eine zentrale Frage, die mit Hilfe der vorliegenden Untersuchungsreihe adressiert wurde, ist, ob die Basalganglien funktionsspezifisch zur auditiven Sprachverarbeitung beitragen oder nicht.

Versuchspersonen, die an Untersuchungen zur syntaktischen Verarbeitung teilnahmen, waren Patienten mit fokalen Läsionen der Basalganglien oder Parkinson Patienten, sowie Alterskontrollen. Experimente zur lexikalisch-semantischen Verarbeitung wurden sowohl mit den zuvor beschriebenen Patienten als auch mit jungen gesunden Personen durchgeführt, während Untersuchungen zur emotionalen Prosodieverarbeitung nur mit jungen Probanden stattfanden. Messmethodisch wurde sowohl die Elektroencephalographie (EEG) als auch die funktionelle Magnet-Resonanz Tomographie (fMRT) eingesetzt.

Untersuchungen spezifischer Gehirnläsionen ermöglichen Aussagen über die funktionelle Organisation der Sprache im Gehirn in Abhängigkeit von Plastizität und Reorganisation. Auch Untersuchungen der sprachlichen Funktionen bei hirngesunden Sprechern mit bildgebenden Verfahren, wie ereigniskorrelierten Hirnpotentialen (EKPs) und der funktionellen fMRT, haben dies zum Ziel. Diese Methoden geben weiteren Aufschluss darüber, wie die zeitliche Dynamik (EKPs) oder aber die Neurotopographie (fMRT) einzelner sprachlicher Funktionen aussehen. Das Lokalisieren und das zeitliche Differenzieren einzelner sprachlicher Funktionen liefert Daten, die ein *Mapping* der Organisation des neuronalen Systems für Sprache ermöglicht.

Im ersten Teil der vorliegenden Arbeit werden Patienten-EKP Studien vorgestellt, die sich mit der Verarbeitung syntaktischer Strukturen auseinandersetzen. Die Verwendung eines Verletzungsparadigmas akzentuiert dabei die Verarbeitung spezifischer regelgeleiteter syntaktischer Strukturen. Im Falle der Phrasenstrukturverletzung wird eine Wortkategorieerwartung verletzt. Das heißt, nach einer kasusmarkierten Präposition wird statt einem Nomen ein Verbpartizip präsentiert. Im Normalfall resultiert eine solche Verletzung in einer frühen anterioren Negativierung (E(L)AN), die mit der Identifikation von Wortkategorien einhergeht. Die-

ser früheren Negativierung folgt eine zentro-parietal auftretende Positivierung (P600), die mit Reanalyseprozessen korreliert wird.

Vorhergehende Arbeiten zum automatischen regelgeleiteten Verarbeiten syntaktischer Information (Ullman et al., 1997, Ullman et al., 2001) haben postuliert, dass regelgeleitetes syntaktisches Verarbeiten durch ein fronto-striatales Netzwerk unterstützt wird. Daraus ergeben sich folgende Hypothesen. Sowohl Patienten mit Läsionen links anteriorer Hirnstrukturen (z.b. dem Broca Areal) als auch Patienten mit Läsionen der Basalganglien sollten Ausfälle bei der Verarbeitung automatischen regelgeleiteten syntaktischen Wissens zeigen. Dies hätte zur Folge, dass beide Patientengruppen keine E(L)AN zeigen sollten, jedoch eine P600. Die Ergebnisse der Studie bestätigen den Ausfall automatischen Regelwissens bei Patienten mit links anterioren Läsionen, nicht aber bei Patienten mit fokalen Läsionen der Basalganglien (Friederici et al., 1999). Jedoch scheint es, dass Patienten mit Basalganglienläsionen eine reduzierte P600 Komponente aufweisen. Daraus lässt sich schließen, dass primär links anterior kortikale Areale bei der Umsetzung automatischen syntaktischen Regelwissens eine Rolle spielen.

Eine kritische Überlegung, die aus der vorliegenden Studie resultierte, war, inwiefern unterschiedliche klinische Ätiologien zu kontroversen Ergebnissen führen können. Ullman und Kollegen (1997) hatten in ihrer Studie Parkinsonpatienten untersucht. Diese neurodegenerative Erkrankung hat zur Folge, dass die neuronale Versorgung durch Dopamin auf Dauer nicht gewährleistet ist und zu sowohl motorischen als auch kognitiven Ausfallerscheinungen führt. Im Vergleich dazu führt eine Hirnläsion potentiell zu einer kompletten Unterbrechung eines neuronalen Informationstransfers.

In einer zweiten Studie wurden daher Parkinson Patienten in einem frühen Stadium der Erkrankung untersucht. Die Annahme war, dass Parkinson Patienten ein ähnliches Profil wie Patienten mit Läsionen der Basalganglien aufweisen sollten. Das heißt, eine E(L)AN als frühen Marker für Phrasenstrukturverletzung und eine reduzierte P600 als Reanalysereaktion. Parkinson Patienten zeigten ein äquivalentes Profil zu Patienten mit Läsionen der Basalganglien (Friederici, Kotz, et al., 2003). Es wurde geschlussfolgert, dass die Basalganglien bei der Verabreitung automatischen regelgeleiteten syntaktischen Wissens keine entscheidende Rolle spielen.

Im dritten Experiment zur syntaktischen Verarbeitung wurde untersucht, ob ein Ausfall oder eine Reduktion der P600 Komponente bei syntaktischer Reanalyse aufgrund eines allgemeinen Aufmerksamkeitsdefizits auftritt oder nicht. In der Lit-

eratur wurde bisweilen die P600 als eine zur P300 Familie gehörenden Komponente betrachtet, da beide Komponenten eine zentro-parietale Verteilung aufweisen, jedoch ihre Latenz aufgrund unterschiedlicher Stimuluskomplexität variieren kann (Gunter et al., 1997; Coulson et al., 1998a). Da die P600 im Kontext der syntaktischen Reanalyse unter Aufmerksamkeit ausgelöst wird, wurde in einem direkten Vergleich die P600 mit der P300 bei Patienten mit Basalganglienläsionen verglichen. Um die Komplexität der Verarbeitung ähnlich zu gestalten, wurden als syntaktische Verletzung, die Verletzung morphosyntaktischer Strukturen verwendet (Inflektionsverletzungen des Verbs) während die P300 durch einen Vergleich zwischen Standardtönen mit abweichenden Tönen evoziert wurde. Die Vorhersage war, dass die P600 keine P300 ist und daher Patienten mit Läsionen der Basalganglien eine reduzierte P600 und eine normale P300 zeigen sollten.

Diese Vorhersagen wurden durch die Ergebnisse bestätigt. Die Tatsache, dass eine klare Dissoziation zwischen den beiden Positivierungen auftrat erlaubt die Schlussfolgerung, dass die P600 keine P300 ist, und dass der Ausfall der P600 bei Patienten mit Basalganglienläsionen nicht aus einem generellen Aufmerksamkeitsdefizits resultiert (Frisch, Kotz et al., 2003).Wenn jedoch keine aufmerksamkeitsgeleitete syntaktische Reanalyse von Fehlern bei Patienten mit Läsionen der Basalganglien möglich ist, so stellt sich die Frage, ob andere sprachliche aufmerksamkeitsgeleitete Prozesse, wie die lexikalisch-semantische oder thematische Verarbeitung ähnlich betroffen sein sollte. Dazu bietet sich die Untersuchung von Verb-Argumentstrukturen an.

Eine Verletzung der Verbargumentstruktur löst bei hirngesunden Probanden einen bi-phasischen Komplex aus einer N400 und P600 aus (Frisch et al., 2004). Dieses Muster deutet an, dass Verbargumentstrukturen sowohl semantisch als auch syntaktisch verarbeitet werden. Des weiteren ist es dadurch möglich im direkten Vergleich zwei unter Aufmerksamkeitskontrolle stattfindende Prozesse zu vergleichen. Wenn also der Ausfall der P600-Komponente bei Patienten mit Basalganglienläsionen spezifisch mit syntaktischer Reanalyse korreliert ist, sollte die N400 bei Verbargument-Strukturverletzungen vergleichbar zu Kontrollen sein.

Experiment 4 testete Verbargumentstrukturen und ihre Verletzung bei Patienten mit Basalganglienläsionen im Vergleich zu Patienten mit links temporoparietalen Läsionen (Kotz et al., 2003). Interessanterweise gibt es in der Literatur zur Verarbeitung dieser Struktur Hinweise, dass eine zeitlich adäquate Zuweisung thematischer Rollen (d.h. wer macht was mit wem/was?) notwendig ist. Häufig wurde bereits dokumentiert, dass dies bei agrammatischen Patienten (d.h. meistens

Patienten mit links anterioren Hirnläsionen) nicht der Fall ist (z.b. Grodzinsky, 2000; Frisch et al., 2000).

Die Ergebnisse gestalteten sich wie folgt. Patienten mit Basalganglienläsionen zeigten keine P600. Die vorhergehende Negativierung war vorhanden, wies aber eine extrem lange Latenz auf. Im Vergleich dazu zeigten Patienten mit temporo-parietalen Läsionen ein P600, aber keine Negativierung. Daher bestätigen auch Daten aus der Testung komplexerer syntaktischer Strukturen, dass die Basalganglien eine entscheidende Rolle in der Modulation der P600 spielen. Funktionell lässt sich daraus schließen, dass strukturelle oder neurodegenerative Veränderungen der Basalganglien das Reanalysieren struktureller Information beeinträchtigt.

Zusammenfassend lässt sich sagen, dass die Ergebnisse der vier syntaktischen Experimente eine klare Rolle der Basalganglien bei der syntaktischen Verarbeitung belegen und zudem ausschließen, dass die Beeinträchtigung des syntaktische Reanalyseprozess rein aufmerksamkeitsbedingter Natur ist.

Die Tatsache, dass auch die mit der P600 kombinierte Negativierung, evoziert durch Verbargumentstrukturverletzungen, eine veränderte Latenz aufweist kann zwei Dinge bedeuten. Diese Negativierung ist funktionell nicht vergleichbar mit einer lexikalisch-semantisch evozierten N400, d.h. ist eher syntaktischer Natur. Das würde bedeuten, dass eine N400 bei semantischen Verletzungen unbeeinträchtigt sein sollte. Wenn jedoch semantische Verletzungen eine ähnliche Latenzverzögerung aufweisen wie die durch Verbargumentverletzungen evozierte Negativierung, dann spricht ein solches Ergebnis für eine zeitliche Veränderung der semantischen/thematischen Integration, die durch strukturelle/neurodegenerative Veränderungen in den Basalganglien erfolgt. Warum potentiell eine qualitativ unterschiedliche Beeinträchtigung lexikalisch-semantischer/thematischer und struktureller Prozesse auftritt bleibt eine offene Frage.

Die Patientenliteratur deutet darauf hin, dass sowohl die Basalganglien (Damasio, 1982; Wallesch & Papagno, 1988) als auch die Basalganglien im Verbund mit dem Thalamus (Crosson, 1985) eine Rolle bei lexikalisch-semantischer Verarbeitung spielen können. Neuere bildgebende Daten weisen zudem darauf hin, dass Faserbahnen zwischen kortiko-striatalen Gehirnarealen zum einen motorische Aspekte der Sprache regulieren, zum anderen lexikalische Prozesse (Henry et al., 2004). Um eine solche Hypothese zu überprüfen und zudem abzugrenzen, ob semantische und thematische Verletzungen in einer ähnliche Modulation der N400 resultieren, wurden Daten aus den Experimenten 1 und 2 reanalysiert.

Teil dieser Untersuchungen war neben den Phrasenstrukturverletzungen, auch eine Verletzung der semantischen Selektionsrestriktion. Im Falle einer nicht vorhanden semantischen Passung (z.b. “Der Honig wurde ermordet.” statt “Der Honig wurde gegessen.”) löst das nicht passende Wort eine N400 aus, die mit lexikalischer/semantischer Integration Hand in Hand geht. Eine genauere Betrachtung dieses Verletzungstyps ermöglichte zum einen die lexikalisch-semantische Integrationsfähigkeit bei Patienten mit Läsionen der Basalganglien und Parkinson Patienten zu überprüfen. Zum anderen konnten die Ergebnisse dieser beiden Experimente mit den Ergebnissen der thematischen Integration (Experiment 4) verglichen werden.

Trotz der Tatsache, dass ein solcher Vergleich zwischen Experimenten post-hoc ist, bestätigen die Ergebnisse, dass in beiden Patientengruppen die Latenz der Negativierung nach semantischen Selektionsverletzungen und thematischen Verletzungen ähnlich beeinträchtigt ist. Im Falle der Parkinson Patienten kam es sogar an manchen Elektroden zu ähnlich starken Ausfallerscheinungen wie für die P600.

Diese Ergebnisse belegen, dass auch semantische und thematische Integration bei strukturellen und neurodegenerativen Veränderungen der Basalganglien beeinträchtigt ist.

In einem weiteren Experiment (5; Kotz et al., 2002) wurde mit hirngesunden Probanden eine fMRT Studie durchgeführt. Mit Hilfe einer geprimten lexikalischen Entscheidungsaufgabe wurde überprüft, welche Gehirnareale bei lexikalischer Differenzierung zwischen Worten und Pseudoworten, aber auch beim erleichterten Zugriff auf semantisch relatierte Wortpaare aktiv sind. Während das Priming (d.h. erleichterter Zugriff auf relatierte semantische Information im Vergleich zu unrelatierter semantischer Information) ein fronto-temporales Netzwerk beanspruchte (BA 45 und posteriorer STG), wurde für die lexikalische Verarbeitung Aktivierung im MTG sowie dem anterioren und posterioren Striatum gefunden. Die Ergebnisse belegen, dass ein einfacher Zugriff auf Worte bei auditiver Verarbeitung neben klassischen semantischen Sprachareale auch durch die Basalganglien involviert.

Zusammenfassend ergibt sich aus der bereits beschriebenen Reihe von Patienten- und fMRT Experimenten folgendes Bild. In der auditiven Sprachverarbeitung sind die Basalganglien sowohl auf einfacher lexikalischer Ebene (Experiment 5) als auch bei der semantisch/thematischen Integration von semantischer Information (Experiment 1, 2, & 4) beteiligt. Das heißt, die Ebene der sprachliche Komplexität scheint auf beiden Verarbeitungsebenen (Wort/Satz) nicht den relativen Beitrag der Basalganglien zu regulieren. Offen bleibt dabei die Frage, ob eine

höhere Ebene der semantischen Komplexität, wie im Falle der semantischen Wort- oder Satzambiguität, bei Patienten mit Basalganglienläsionen ein deutlicheres Defizit auslösen würde, d.h. statt einer zeitlichen Verzögerung einen kompletten Ausfall der Negativierung.

Behaviorale Studien mit Parkinson Patienten bestätigen eine solche Möglichkeit (z.b. Copland, 2003). Jedoch muss in diesem Zusammenhang kritisch beachtet werden, dass die meisten semantischen Ambiguitätsstudien, die mit Parkinson Patienten durchgeführt wurden, Patienten im medizierten Zustand gemessen haben. Jedoch zeigten Parkinson Patienten auch bei einfacher semantischer Integration an selektiven Elektroden keine N400 Reaktion. Es wäre daher sinnvoll einen direkten Vergleich zwischen einfacher und komplexerer semantischer Verarbeitung bei Parkinson Patienten im medizierten und nicht-medizierten Zustand durchzuführen. Eine ähnliche Argumentation gilt demnach auch für Untersuchungen syntaktischer Natur. Jedoch bleibt hier zu bemerken, dass die Ausfallerscheinungen im Bezug auf syntaktische Renalayse (P600) bei Patienten mit Läsionen der Basalganglien und Parkinson Patienten nicht unterschiedlich war.

In den letzten beiden Experimenten, die die Untersuchungsreihe dieser Habilitationschrift beschließen, wurde ein weiterer Aspekt der auditven Sprachverarbeitung, emotionale Prosodie, untersucht. Obwohl bei Untersuchungen der emotionalen Prosodie primär die Frage im Vordergrund steht, ob ein rechtslatralisiertes korikales Netzwerk diesen Prozess unterstützt, gibt es einige Hinweise aus der klinischen Literatur, die auch den Basalganglien bei der Verarbeitung emotionaler Prosodie eine Rolle zuweisen. So weisen Studien mit Läsionspatienten und Parkinson Patienten darauf hin, dass sowohl die Identifikation, Erkennung sowie die Diskrimination emotionaler Prosodie gestört sein kann (Bradvik et al., 1991; Blonder et al., 1989; Cancelliere & Kertesz, 1990; Morris et al., 1999; Pell, 1998; Pell & Leonard, 2004).

In einer fMRT Untersuchung (Experiment 6) mit hirngesunden Probanden (Kotz et al., 2003) wurde die Erkennung und Zuordnung von emotional intonierten, semantisch neutralen Sätzen mit emotional intonierten gefilterten Sätzen verglichen. Um möglichst präzise Vorstellungen davon zu bekommen, welche Gehirnareale bei der Verarbeitung reiner Prosodie und kombinierter Prosodie und Semantik aktiv sind, wurden die semantisch neutralen Sätze mit unterschiedlichen emotionalen Prosodien (ärgerlich. neutral und glücklich) mit einem Spezialfilter bearbeitet (Sonntag & Portele, 1998), der segmentale und lexikalische Information eliminiert, jedoch die suprasegmentale Information aufrechterhält. Dies ermöglichte einen direkten Vergleich der suprasegmentalen Information in beiden Bedingungen.

Die Probanden führten mit Hilfe einer Fünf-Punktskala eine prosodische Kategorisierung der gehörten auditorischen Sequenzen durch. Wenn die Basalganglien in der Wahrnehmung und Kategorisierung emotionaler Marker eine Rolle spielen, so sollte insbesondere bei der Verarbeitung reiner prosodischer Stimuli Basalganglienaktivierung auftreten. In beiden Konditionen trat bilaterale Aktivierung der Basalganglien auf. Im direkten Vergleich wurde jedoch war bei der Verarbeitung lexikalisch-emotional-prosodischer Information ein temporo-putaminales Netzwerk aktiv, während in der reinen Prosodiebedingung ein fronto-caudales Netzwerk aktiviert wurde.

Die Tatsache, dass in beiden Bedingungen Basalganglienaktivierung auftrat, jedoch in differenzierten Arealen (Putamen vs. Caudatum) kann bedeuten, dass die Verarbeitung reiner Prosodie ohne sprachlichen Inhalt erschwert ist und dadurch einen Basalganglienkreislauf aktiviert, der auch bei genereller kognitiver Verarbeitung nachgewiesen wurde (Middleton & Strick, 2000). Die Frage entsteht, ob dieses Aktivierungsmuster emotional prosodische Verarbeitung reflektiert oder den Aufwand der Probanden emotional prosodische Information zu kategorisieren.

In einem ersten Schritt wurde daher in einem Folgeexperiment (Kotz et al., in press) die Präsentation gefilterter emotionaler Prosodie und lexikalischer emotionaler Prosodie getrennt, da die Annahme bestand, dass die Kategorisierung gefilterter emotionaler Prosodie durch einen nicht prädiktierbaren Wechsel zwischen den beiden sprachlichen Bedingungen erschwert worden sein kann.

Lexikalisierte und gefilterte emotionale Prosodie wurden in den drei zuvor verwendeten Kategorien (ärgerlich, neutral, glücklich) in Blöcken präsentiert. Die Blockabfolge wurde über die Probanden hinweg ausbalanciert. Die Ergebnisse aus diesem Experiment komplementieren die Ergebnisse aus Experiment 6. Während lexikalisierte emotionale Prosodie ein bilaterales temporo-striatales Netzwerk aktivierte, kam es bei Präsentation gefilterter emotionaler Prosodie wiederum zu einer bilateralen fronto-striato-thalamischen Aktivierung.

Diese Ergebnisse bestätigen, dass der Beitrag der Basalganglien zur emotional prosodischen Verarbeitung nicht nur von generellen kognitiven Faktoren abhängen kann. Jedoch untersuchen wir im Moment eine weitere wichtige Frage. Kann die Basalganglienaktivierung bei emotional prosodischer Verarbeitung von der Aufgabenstellung beeinflusst sein? Dazu haben wir ein weiteres fMRT Experiment mit den gleichen Stimuli wie in Experiment 6 durchgeführt. Statt einer Kategorisierungsaufgabe mussten die Probanden jedoch eine physikalische Qualität der

auditiven Stimuli beurteilen (Tonhöhe). Damit ist eine implizite Verarbeitung emotionaler Prosodie gewährleistet. Wenn unter diesen Verarbeitungsbedingungen dennoch Basalganglienaktivierung auftritt, kann diese Aktivierung nicht als allgemein kognitives Phänomen erklärt werden und bestätigt Vermutungen in der Literatur, dass die Basalganglien bei temporaler Sequenzzierung und Diskriminierung auditiver sprachlicher Stimuli eine Rolle spielen (siehe Pell & Leonard, 2004).

Die vorliegende Arbeit befasste sich mit einer Reihe von Untersuchungen, die es zum Ziel hatten, den funktionellen Beitrag der Basalganglien in der auditiven Sprachverarbeitung zu spezifizieren. Insbesondere stand die Frage im Vordergrund, ob dieser Beitrag sprachspezifisch sei oder nicht. Zur Untersuchung dieser Frage wurde sowohl das EKP und das fMRT eingesetzt. In den EKP-Studien wurden Patienten mit strukturellen und neurodegenerativen Veränderungen der Basalganglien, sowie klinische Kontrollen und Alterskontrollen mit verschiedenen syntaktischen Strukturen untersucht (Phrasenstruktur, Verbkohärenz, Verbargumentstruktur). Dabei konnte nachgewiesen werden, dass automatische regelgeleitete Syntaxverarbeitung bei subkortikalen Patienten intakt ist, während syntaktische Reanalyse betroffen ist. Dies wiederlegt zum einen die Hypothese, dass die Basalganglien eine entscheidende Rolle bei automatischem regelgeleitetem Wissen spielen (z.b. Ullman, 2001). Zum anderen bestätigen die Patientendaten, dass Reanalyseverhalten beeinträchtigt ist. Diese Beeinträchtigung tritt aber nicht als Folge einer primären Aufmerksamkeitsstörung oder komplexerer syntaktischer Verarbeitung auf.

Die Beteiligung der Basalganglien oder der Basalganglien im Zusammenhang mit dem Thalamus bei lexikalisch-semantischer Verarbeitung gestaltet sich komplexer. Jedoch deuten die Ergebnisse aus Patienten und fMRT – Untersuchungen an, dass die Basalganglien die Selektion lexikalisch-semantischer Information mitsteuern.

Die Basalganglien scheinen bei der Verarbeitung emotional prosodischer Information involviert zu sein, jedoch stehen hier noch entscheidende zu beantwortende Fragen im Raum, die klären müssen, ob die Beteiligung der Basalganglien prozessspezifisch oder eher aufgabenspezifisch ist.

Zusammengefasst bestätigen die vorliegenden Untersuchungen, dass die Basalganglien bei der auditiven Sprachverarbeitung eine sprachspezifische Rolle spielen können. Weitere Untersuchungen, die mit ähnlichen Aufgabenstellungen und ähnlicher Stimuluskomplexität sowohl sprachliche und nicht-sprachliche Verarbeitung direkt vergleichen stellen eine Herausforderung für weitere Untersuchungen sowohl mit Patienten als auch fMRT Untersuchungen in der nahen Zukunft dar.

References

Abdullaev, Y.G., Bechtereva, N.P. & Melnichuk, K.V. (1998). Neuronal activity of human caudate nucleus and prefrontal cortex in cognitive tasks. *Behavioural Brain Research, 97,* 159-177.

Abdullaev, Y.G. & Melnichuk, K.V. (1997). Cognitive operations in the human caudate nucleus. *Neuroscience Letters, 234,* 151-5.

Abutalebi, J., Miozzo, A. & Cappa, S.F. (2000). Do subcortical structures control 'language selection' in polyglots? Evidence from pathological language mixing. *Neurocase, 6,* 51-56.

Adolphs, R., Damasio, H. & Tranel, D. (2002). Neural systems for recognition of emotional prosody: A 3-D lesion study. *Emotion, 2,* 23-51.

Alexander, G.E. & Crutcher, M.D. (1990). Neural representations of the target (goal) of visually guided arm movements in three motor areas of the monkey. *Journal of Neurophysiology, 64,* 164-178.

Alexander, G.E., DeLong, M.R. & Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9,* 357-381.

Alexander, M.P. & LoVerme, S.R. Jr. (1980). Aphasia after left hemispheric intracerebral hemorrhage. *Neurology, 30,* 1193-202.

Allen, J.S., Damasio, H. & Grabowski, T.J. (2002). Normal neuroanatomical variation in the human brain: an MRI-volumetric study. *American Journal of Physical Anthropology, 118,* 341-358.

Allen, J.S., Damasio, H., Grabowski, T.J., Bruss, J. & Zhang, W. (2003). Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. *NeuroImage, 18,* 880-891.

Aron, A.R., Schlaghecken, F., Fletcher, P.C., Bullmore, E.T., Eimer, M., Barker, R., Sahakian, B.J. & Robbins, T.W. (2003). Inhibition of subliminally primed responses is mediated by the caudate and thalamus: evidence from functional MRI and Huntington's disease. *Brain, 126,* 713-723.

Baddeley, A., Ed. (1986). *Working memory.* New York, NY: Clarendon Press/Oxford University Press, pp. 289.

Bandettini, P.A. & Wong, E.C. (1998). A hypercapnia-based normalization method for improved spatial localization of human brain activation with fMRI. *NMR in Biomedicine, 10,* 197-203.

Bar-Gad, I. & Bergman, H. (2001). Stepping out of the box: Information processing in the neural networks of the basal ganglia. *Current Opinion in Neurobiology, 11,* 689-695.

Barrett, S.E. & Rugg, M.D. (1990). Event-related potentials and the semantic matching of pictures. *Brain & Cognition, 14,* 201-212.

Baum, S.R. & Pell, M.D. (1999). The neural bases of prosody: Insights from lesion studies and neuroimaging. *Aphasiology, 13,* 581-608.

Beiser, D.G. & Houk, J.C. (1998). Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. *Journal of Neurophysiology, 79,* 3168-88.

Belliveau, J.W., Kennedy, D.N., McKinstry, R.C., Buchbinder, B.R., Weisskoff, R.M., Cohen, M.S., Vevea, J.M., Brady, T.J. & Rosen, B.R. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. *Science, 254,* 716-718.

Bennett, K.M. & Castiello, U. (1996). Three-dimensional covert attentional functions in Parkinson's disease subjects. *Experimental Brain Research, 112,* 277-88.

Berns, G.S. & Sejnowksi, T.J. (1998). A computational model of how the basal ganglia produce sequences. J*ournal of Cognitive Neuroscience, 10,* 108-121.

Besson, M. & Faita, F. (1995). An event-related potential (ERP) study of musical expectancy: Comparison of musicians with nonmusicians. *Journal of Experimental Psychology: Human Perception & Performance, 2,* 1278-1296.

Besson, M. & Macar, F. (1987). An event-related potential analysis of incongruity in music and other non-linguistic contexts. *Psychophysiology, 24,* 14-25.

Binder, J.R., Frost, J.A., Hammeke, T.A., Cox, R.W., Rao, S.M. & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. The Journal of Neuroscience, 17, 353-362.

Blonder, L.X., Gur, R.E., Gur, R.C., Saykin, A.J. & Hurtig, H.I. (1989). Neuropsychological functioning in hemiparkinsonism. *Brain & Cognition, 9,* 244-257.

Blumstein, S. & Cooper, W.E. (1974). Hemispheric processing of intonation contours. *Cortex, 10,* 146-158.

Borgmann, S. & Jürgens, U. (1999). Lack of cortico-striatal projections from primary auditory cortex in the squirrel monkey. Brain Research, 836, 225-228.

Bornkessel, I. (2002). The Argument Dependency Model: A Neurocognitive Approach to Incremental Interpretation. In Max Planck Institute of Cognitive Neuroscience (Ed.), *MPI Series in Cognitive Neuroscience*, *28,* Leipzig.

Bornkessel, I., Schlesewsky, M. & Friederici, A.D. (2002). Beyond syntax: Language-related positivities reflect the revision of hierarchies. *NeuroReport, 13,* 361-364.

Bowman, E.M., Aigner, T.G. & Richmond, B.J. (1996). Neural signals in the monkey ventral striatum related to motivation for juice and cocaine rewards. *Journal of Neurophysiology, 75,* 1061-1073.

Brådvik, B., Dravins, C., Holtas, S., Rosen, I., Ryding, E. & Ingvar, D.H. (1991). Disturbances of speech prosody following right hemisphere infarcts. *Acta Neurologica Scandinavica, 84,* 114-126.

Breitenstein, C., Daum, I. & Ackermann, H. (1998). Emotional processing following cortical and subcortical brain damage: Contribution of the fronto-striatal circuitry. *Behavioural Neurology, 11,* 29-42.

Breitenstein, C., Van Lancker, D., Daum, I. & Waters, C.H. (2001). Impaired perception of vocal motions in Parkinson's disease: Influence of speech time processing and executive functioning. *Brain & Cognition, 45, 277-314.*

Brink, T.L., Yesavage, J.A., Lum, O., Heersema, P.A., Adey, M. & Rose, T.S. (1982). Screening tests for geriatric depression. *Clinical Gerontology, 1,* 37-43.

Broca, M.P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (Perte de la Parole). *Bulletins et Memoires de la Société Anatomique de Paris, 36,* 330-357.

Brown, R.G. (1999). The role of cortico-striatal circuits in learning sequential information. *Advances in Neurology, 80,* 31-39.

Brown, P., Corcos, D.M. & Rothwell, J.C. (1997). Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? *Brain, 120,* 401-408.

Brown, R.G., Jahanshahi, M. & Marsden, C.D. (1993). Response choice in Parkinson's disease. The effects of uncertainty and stimulus-response compatibility. *Brain,* 116, 869-885.

Brown, R.G. & Marsden, C.D. (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain, 114,* 215-231.

Brown, P. & Marsden, C.D. (1998). What do the basal ganglia do? *Lancet, 351,* 1801-1804.

Brown, R.G., Soliveri, P. & Jahanshahi, M. (1998). Executive processes in Parkinson's disease – Random number generation and response suppression. *Neuropsychologia, 36,* 1355-1362.

Brunner, R.J., Kornhuber, H.H., Seemüller, E., Suger, G. & Wallesch, C.W. (1982). Basal ganglia participation in language pathology. *Brain and Language, 16,* 281-99.

Bryan, K. (1989). Language prosody in the right hemisphere. *Aphasiology, 3,* 285-299.

Buchanan, T.W., Lutz, K., Mirzazade, S., Specht, K., Shah, N.J., Zilles, K. & Jancke, L. (2000). Recognition of emotional prosody and verbal components of spoken language: An fMRI study. *Cognitive Brain Research, 9,* 227-238.

Buxton, R.B., Ed. (2002). *An introduction to functional magnetic resonance imaging*. Cambridge: Cambridge University Press, pp. 536.

Cancelliere, A.E. & Kertesz, A. (1990). Lesion localization in acquired deficits of emotional expression and comprehension. *Brain & Cognition, 13,* 133-147.

Canter, G.J. (1963). Speech characteristics of patients with Parkinson's disease: I. Intensity, pitch, and duration. *Journal of Speech & Hearing Disorders, 28,* 221-229.

Canter, G.J. & Van Lancker, D.R. (1985). Disturbances of the temporal organization of speech following bilateral thalamic surgery in a patient with Parkinson's disease. *Journal of Communication Disorders, 18,* 329-349.

Canteras, N.S., Simerly, R.B. & Swanson, L.W. (1992). Projections of the ventral premammillary nucleus. *Journal of Coparative Neurology, 324,* 195-212.

Caplan, D. & Futter, C. (1986). Assignment of thematic roles to nouns in sentence comprehension by an agrammatic patient. *Brain and Language, 27,* 117-134.

Caplan, D. & Hildebrandt, N. (1986). Language deficits and the theory of syntax: A reply to Grodzinsky. *Brain and Language, 27,* 168-177.

Cappa, S.F. & Abutalebi, J. (1999). Aubcortical aphasia. In F. Fabro (Ed.), *The Concise Encyclopaedia of Language Pathology (pp. 319-327)*. Oxford: Pergamon Press.

Cappa, S. F., Cavalotti, G., Guidotti, M., Papagno, C. & Vignolo, L.A. (1983). Subcortical aphasia: Two clinical-CT scan correlation studies. *Cortex, 19,* 227-241.

Cappa, S.F. & Vignolo, L.A. (1979). "Transcortical" features of aphasia following left thalamic hemorrhage. *Cortex, 15,* 121-30.

Castaigne, P., Lhermitte, F., Signoret, J.L., Abelanet, R. (1980). [Description and scanographic study of Leborgne's brain. Broca's discovery] French. *Reviews in Neurology (Paris), 136,* 563-83.

Caviness, V.S. Jr., Kennedy, D.N., Bates, J. & Makris, N. (1996). The developing human brain: A morphometric profile. In R.W. Thatcher, G.R. Lyon, J. Rumsey & N. Krasnegor (Eds.), *Developmental Neuroimaging: Mapping the Development of Brain and Behavior* (pp. 3-14), New York: Academic Press.

Chwilla, D.J., Brown, C.M. & Hagoort, P. (1995). The N400 as a function of the level of processing. *Psychophysiology, 32,* 274-285.

Clarke, S., Bellmann, A., De Ribaupierre, F. & Assal, G. (1996). Non-verbal auditory recognition in normal subjects and brain-damaged patients: evidence for parallel processing. *Neuropsychologia, 34,* 587-603.

Cohen, M.S. & Bookheimer, S.Y. (1994). Localization of brain function using magnetic resonance imaging. *Trends in Neurosciences, 17,* 268-277.

Cohen, N.J. & Squire, L.R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science, 21,* 207-210.

Coles, M.G.H. & Rugg, M..D. (1995). Event-related brain potentials: An introduction. In M.D. Rugg & M.G.H. Coles (Eds.), *Electrophysiology of mind: Event-related brain potentials and cognition. Oxford psychology series, No. 25 (pp. 1-26),* London: Oxford University Press.

Contreras-Vidal, J.L. & Schultz, W. (1999). A predictive reinforcement model of dopamine neurons for learning approach behavior. *Journal of Computational Neuroscience, 6,* 191-214.

Cools, R., Clark, L., Owen, A.M. & Robbins, T.W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 22,* 4563-4567.

Coulson, S., King, J.W. & Kutas, M. (1998a). ERPs and domain specificity: Beating a straw horse. *Language & Cognitive Processes, 13,* 653-672.

Coulson, S., King, J.W. & Kutas, M. (1998b). Expect the unexpected: Event-related brain response to morphosyntactic violations. *Language & Cognitive Processes, 13,* 21-58.

Copland, D. (2003). The basal ganglia and semantic engagement: Potential insights from semantic priming in individuals with subcortical vascular lesions, Parkinson's disease, and cortical lesions. *Journal of the International Neuropsychological Society, 9,* 1041-1052.

Copland, D.A., Chenery, H.J. & Murdoch, B.E. (2000a). Processing lexical ambiguities in word triplets: Evidence of lexical-semantic deficits following dominant nonthalamic subcortical lesions. *Neuropsychology, 14,* 379-390.

Copland, D.A., Chenery, H.J. & Murdoch, B.E. (2000b). Understanding ambiguous words in biased sentences: Evidence of transient contextual effects in individuals with nonthalamic subcortical lesions and Parkinson's disease. *Cortex, 36,* 601-622.

Copland, D.A., Chenery, H.J. & Murdoch, B.E. (2001). Discourse priming of homophones in individuals with dominant nonthalamic subcortical lesions, cortical lesions and Parkinson's disease. *Journal of Clinical & Experimental Neuropsychology, 23,* 538-556.

Crosson, B. (1985). Subcortical functions in language: A working model. *Brain and Language, 25,* 257-292.

Crosson, B. (1999). Subcortical mechanisms in language: Lexical-semantic mechanisms and the thalamus. *Brain & Cognition, 40,* 414-438.

Crosson, B., Rao, S.M., Woodley, S.J., Rosen, A.C., Bobholz, J.A., Mayer, A., Cunningham, J.M., Hammeke, T.A., Fuller, S.A., Binder, J.R., Cox, R.W. & Stein, E.A. (1999). Mapping of semantic, phonological, and orthographic verbal working memory in normal adults with functional magnetic resonance imaging. *Neuropsychology, 13,* 171-187.

Damasio, A.R. (1983). Language and the basal ganglia. *Trends in Neurosciences, 6,* 442-444.

Damasio, A.R. (1985). Prosopagnosia. *Trends in Neurosciences, 8,* 132-135.

Damasio, A.R. & Damasio, H. (1997). Commentary: Advances in cognitive neuroscience. In D. Magnusson (Ed.), *The lifespan development of individuals: Behavioral, neurobiological, and psychosocial perspectives: A synthesis* (pp. 265-273)., New York, NY: Cambridge University Press.

Damasio, A.R., Damasio, H., Rizzo, M., Varney, N. & Gersh, F. (1982). Aphasia with nonhemorrhagic lesions in the basal ganglia and internal capsule. *Archives of Neurology, 39,* 15-24.

Damasio, A.R., Damasio, H. & Van Hoesen, G.W. (1982). Prosopagnosia: anatomic basis and behavioral mechanisms. *Neurology, 32,* 331-341.

Deacon, D., Hewitt, S., Yang, C.-M. & Nagata, M. (2000). Event-related potential indices of semantic priming using masked and unmasked words: Evidence that the N400 does not reflect a post-lexical process. *Cognitive Brain Research, 9,* 137-146.

Deichmann, R., Gottfried, J.A., Hutton, C. & Turner, R. (2003). Optimized EPI for fMRI studies of the orbitofrontal cortex. *NeuroImage, 19,* 430-41.

Demonet, J.-F., Price, C., Wise, R. & Frackowiak, R.S.J. (1994). A PET study of cognitive strategies in normal subjects during language tasks: Influence of phonetic ambiguity and sequence processing on phoneme monitoring. *Brain, 117,* 671-682.

Deutsch, A. & Bentin, S. (2001). Syntactic and semantic factors in processing gender agreement in Hebrew: Evidence from ERPs and eye movements. *Journal of Memory & Language, 45,* 200-224.

Dominey, P., Arbib, M. & Joseph, J.-P. (1995a). A model of corticostriatal plasticity for learning oculomotor associations and sequences. *Journal of Cognitive Neuroscience, 7,* 311-336.

Dominey, P.F. & Jeannerod, M. (1997). Contribution of frontostriatal function to sequence learning in Parkinson's disease: Evidence for dissociable systems. *NeuroReport, 8,* iii-ix.

Dominey, P.F., Ventre-Dominey, J., Broussolle, E. & Jeannerod, M. (1995b). Analogical transfer in sequence learning. Human and neural-network models of frontostriatal function. *Annals of the New York Academy of Sciences, 769,* 369-373.

Donchin, E., Gratton, G., Dupree, D. & Coles, M. (1988). After a rash action: Latency and amplitude of the P300 following fast guesses. In G.C. Galbraith, M.L. Kietzman & E. Donchin (Eds.), *Neurophysiology and psychophysiology: Experimental and clinical applications (pp. 173-188).* Hillsdale, NJ, England: Lawrence Erlbaum Associates.

Donchin, E., Ritter, W. & McCallum, W.C. (1978). Cognitive psychophysiology: The endogenous components of the ERP. In E. Callaway, P. Tueting & S.H. Koslow (Eds.), *Event related brain potentials in man (pp. 349-411)*. New York: Academic Press.

Downes, J.J., Roberts, A.C., Sahakian, B.J., Evenden, J.L., Morris, R.G. & Robbins, T.W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia, 27,* 1329-1343.

Dykstra, K., Gandour, J. & Stark, R.E. (1995). Disruption of prosody after frontal lobe seizures in the non-dominant hemisphere. *Aphasiology, 9,* 453-476.

Faglioni, P., Botti, C., Scarpa, M., Ferrari, V. & Saetti, M.C. (1997). Learning and forgetting processes in Parkinson's disease: A model-based approach to disentangling storage, retention and retrieval contributions. *Neuropsychologia, 35,* 767-779.

Fiebach, C.J., Friederici A.D., Müller, K. & von Cramon, D.Y. (2002). fMRI evidence for dual routes to the mental lexicon in visual word recognition. *Journal of Cognitive Neuroscience, 14,* 11-23.

Fraïle, V. & Cohen, H. (1999). Temporal control of voicing in Parkinson's disease and tardive dyskinesia speech. *Brain & Cognition, 40,* 118-122.

Frazier, L. (1987). Theories of sentence processing. In J.L. Garfield (Ed.), *Modularity in knowledge representation and natural-language understanding* (pp. 291-307), Cambridge, MA: The MIT Press.

Friederici, A.D. (1995). The time course of syntactic activation during language processing: A model based on neuropsychological and neurophysiological data. *Brain and Language, 50,* 259-281.

Friederici, A.D. (1998). The neurobiology of language comprehension, In A.D. Friederici (Ed.), *Language Comprehension: A Biological Perspective (pp. 263-301).* Heidelberg: Springer.

Friederici, A.D. (2002). Towards a neural basis of auditory sentence processing. *Trends in Cognitive Sciences, 6,* 78-84.

Friederici, A.D. & Frisch, S. (2000). Verb-argument structure processing: The role of verb-specific and argument-specific information. *Journal of Memory and Language, 43,* 476-507.

Friederici, A.D. & Gorrell, P. (1998). Structural prominence and agrammatic theta-role assignment: A reconsideration of linear stragies. *Brain and Language, 65*, 253-275.

Friederici, A.D., Gunter, T.C., Hahne, A. & Mauth, K. (2004). The relative timing of syntactic and semantic processes in sentence comprehension. *NeuroReport, 15,* 165-169.

Friederici, A.D., Hahne, A. & Mecklinger, A. (1996). The temporal structure of syntactic parsing: Early and late event-related brain potential effects elicited by syntactic anomalies. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 22*, 1219-1248.

Friederici, A.D., Hahne, A. & Saddy, D. (2002). Distinct neurophysiological patterns reflecting aspects of syntactic complexity and syntactic repair. *Journal of Psycholinguistic Research, 31,* 45-63.

Friederici, A.D., Hahne, A. & von Cramon, D.Y. (1998). First-pass versus second-pass parsing processes in a Wernicke's and a Broca's aphasic: Electro-physiological evidence for a double dissociation. *Brain and Language, 62*, 311-341.

Friederici, A.D. & Kotz, S.A. (2003). The brain basis of syntactic processes: Functional imaging and lesion studies. *NeuroImage, 20,* S8-S17.

Friederici, A.D., Kotz, S.A., Werheid, K., Hein, G. & von Cramon, D.Y. (2003c). Syntactic comprehension in Parkinson's disease: Investigating early automatic and late integrational processes using event-related brain potentials. *Neuropsychology, 17,* 133-142.

Friederici, A.D. & Mecklinger, A. (1996). Syntactic parsing as revealed by brain responses: First-pass and second-pass parsing processes. *Journal of Psycholinguistic Research, 25,* 157-176.

Friederici, A.D., Mecklinger, A., Spencer, K.M., Steinhauer, K. & Donchin, E. (2001). Syntactic parsing preferences and their on-line revisions: A spatio-temporal analysis of event-related brain potentials. *Cognitive Brain Research, 11,* 305-323.

Friederici, A.D., Pfeifer, E. & Hahne, A. (1993). Event-related brain potentials during natural speech processing: Effects of semantic, morphological and syntactic violations. *Cognitive Brain Research, 1*, 183-192.

Friederici, A.D., von Cramon, D.Y. & Kotz, S.A. (1999). Language related brain potentials in patients with cortical and subcortical left hemisphere lesions. *Brain, 122*, 1033-1047.

Friederici, A.D., Rüschemeyer, S.-A., Hahne, A. & Fiebach, C.J. (2003a). The role of left inferior frontal and superior temporal cortex in sentence comprehension: Localizing syntactic and semantic processes. *Cerebral Cortex*, *13*, 170-177.

Friederici, A.D., Schlesewsky, M. & Fiebach, C.J. (2003b). Wh-movement vs. scrambling: the brain makes a difference. In S. Karimi (Ed.), *Word Order and Scrambling (pp. 325-367)* Boston: Blackwell.

Frisch, S. & Friederici, A. D. (1998): Die Verarbeitung von Verb-Argument-Struktur-Information beim Satzverstehen: Evidenz aus Studien mit ereigniskorrelierten Hirnpotentialen. In H. Lachnit, A. Jacobs & F. Rösler (Eds.), *Experimentelle Psychologie. Abstracts der 40. TeaP* (p. 84), Lengerich: Pabst, 84.

Frisch, S. & Friederici, A. D. (1999): Einfluß der Wortstellung auf Verb-Argument-Struktur-Verletzungen: Evidenz aus zwei EKP-Studien. In E. Schröger, A. Mecklinger & A. Widmann (Eds.), *Experimentelle Psychologie*. *Abstracts der 41. TeaP* (pp. 134-135), Lengerich: Pabst.

Frisch, S., Hahne, A. & Friederici, A.D. (2004). Word category and verb-argument structure information in the dynamics of parsing. *Cognition, 91,* 191-219.

Frisch, S., Kotz, S.A., von Cramon D.Y. & Friederici, A.D. (2003). Why the P600 is not just a P300: The role of the basal ganglia. *Clinical Neurophysiology, 114,* 336-340.

Frisch, S., Saddy, D. & Friederici, A.D. (2000). Cutting a long story (too) short. *Behavioral and Brain Sciences, 23,* 34-35.

Frisch, S. & Schlesewsky, M. (2001). The N400 reflects problems of thematic hierarchizing. *NeuroReport, 12,* 3391-3394.

Friston, K.J., Frith, C.D., Liddle, P.F. & Frackowiak, R.S. (1993). Functional connectivity: the principal-component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow Metabolism, 13,* 5-14.

Gabrieli, J.D.E. (1998). Cognitive neuroscience of human memory. *Annual Review of Psychology, 49,* 87-115.

Gabrieli, J.D.E., Singh, J., Stebbins, G.T. & Goetz, C.G. (1996). Reduced working memory span in Parkinson's disease: Evidence for the role of frontostriatal system in working and strategic memory. *Neuropsychology, 10,* 321-332.

Ganis, G., Kutas, M. & Sereno, M.I. (1996). The search for "common sense": An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8,* 89-106.

George, M.S., Parekh, P.I., Rosinsky, N., Ketter, T.A., Kimbell, T.A., Heilmann, K.M., Herscovitch, M.D. & Post, R.M. (1996). Understanding emotional prosody activates right hemisphere regions. *Archives of Neurology, 53,* 665-670.

Gerfen, C.R. (1988). Synaptic organization of the striatum. *Journal of Electron Microscopy*
Technique, 10, 265-281.

Gerfen, C.R. (1992). Substance P (neurokinin-1) receptor mRNA is selectively expressed in cholinergic neurons in the striatum and basal forebrain. *Brain Research, 556,* 165-70.

Gibbon, J., Malapani, C., Dale, C.L. & Gallistel, C.R. (1997). Toward a neurobiology of temporal cognition: Advances and challenges. *Current Opinion in Neurobiology, 7,* 170-184.

Goldman-Rakic, P.S. (1992). Neuronal development and plasticity of association cortex in primates. *Neurosciences Research Program Bulletin, 20,* 520-532.

Gomez Gonzalez, C.M., Clark, V.P., Fan, S., Luck, S.J. & Hillyard, S.A. (1994). Sources of attention-sensitive visual event-related potentials. *Brain Topography, 7,* 41-51.

Goodglass, H. & Kaplan, E., Eds. (1972). The assessment of aphasia and related disorders. Philadelphia: Lea & Febiger.

Goulet, S., Dore, F.Y. & Murray, E.A. (1998). Aspiration lesions of the amygdala disrupt the rhinal corticothalamic projection system in rhesus monkey. *Experimental Brain Research, 119,* 131-140.

Gräber, S., Hertrich, I., Daum, I., Spieker, S. & Ackermann, H. (2002). Speech perception deficits in Parkinson's disease: Underestimation of time intervals compromises identification of durational phonetic contrasts. *Brain and Language, 82,* 65-74.

Graybiel, A.M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. *Trends in Neurosciences, 13,* 244-54.

Graybiel, A.M. (1995). The basal ganglia. *Trends in Neurosciences, 18,* 60-2.

Graybiel, A.M. (1997). The basal ganglia and cognitive pattern generators. *Schizophrenia Bulletin, 23,* 459-469.

Graybiel, A.M. (1998). The basal ganglia and chunking of action repertoires. *Neurobiology of Learning & Memory, 70,* 119-136.

Graybiel, A.M. (2000). The basal ganglia. *Current Biology, 10,* R509-11.

Graybiel, A.M., Aosaki, T., Flaherty, A.W. & Kimura, M. (1994). The basal ganglia and adaptive motor control. *Science, 265,* 1826-1831.

Graybiel, A.M. & Kimura, M. (1995). Adaptive neural networks in the basal ganglia. In J.C. Houk, J.L. Davis & D.G. Beiser (Eds.), *Models of information processing in the basal ganglia. Computational neuroscience* (pp. 103-116), Cambridge, MA: The MIT Press.

Grodzinsky, Y. (1986). Language deficits and the theory of syntax. *Brain and Language, 27,* 135-159.

Grodzinsky, Y., Ed. (1990). *Theoretical perspectives on language deficits*. Cambridge, MA: The MIT Press, pp. 192.

Grodzinsky, Y. (2000). The neurology of syntax: Language use without Broca's area. *Behavioral & Brain Sciences, 23,* 1-71.

Grossman, M., Carvell, S., Gollomp, S., Stern, M.B., Vernon, G. & Hurtig, H.I. (1991). Sentence comprehension and praxis deficits in Parkinson's disease. *Neurology, 41,* 1620-1626.

Grossman, M., Carvell, S., Gollomp, S., Stern, M.B., Reivich, M., Morrison, D., Alavi, A. & Hurtig, H. (1993). Cognitive and physiological substrates of impaired sentence processing in Parkinson's disease. *Journal of Cognitive Neuroscience, 5,* 480-498.

Grossman, M., Carvell, S., Stern, M.B., Gollomp, S. & Hurtig, H.I. (1992). Sentence comprehension in Parkinson's disease: The role of attention and memory. *Brain and Language, 42,* 347-384.

Grossman, M., Kalmanson, J., Bernhardt, N., Morris, J., Stern, M.B. & Hurtig, H.I. (2000). Cognitive resource limitations during sentence comprehension in Parkinson's disease. *Brain and Language, 73,* 1-16.

Grossman, M., Kenny, J.V., Lee, V., Chambers-Evans, J., Goding, M. & McHarg, L. (1999). Emotional distress in critically-injured patients three months after a potentially life-threatening accident. *Journal of Neuroscience Nursing, 31,* 159-73.

Grossman, M., Zurif, E., Lee, C., Prather, P., Kalmanson, J., Stern, M.B. & Hurtig, H.I. (2002). Information processing speed and sentence comprehension in Parkinson's disease. *Neuropsychology, 16,* 174-181.

Gunter, T.C., Friederici, A.D. & Schriefers, H. (2000). Syntactic gender and semantic expectancy: ERPs reveal early autonomy and late interaction. *Journal of Cognitive Neuroscience, 12,* 556-568.

Gunter, T.C., Stowe, L.A. & Mulder, G. (1997). When syntax meets semantics. *Psychophysiology, 34,* 660-676.

Gurd, J.M. & Oliveira, R.M. (1996). Competitive inhibition models of lexical-semantic processing: Experimental evidence. *Brain and Language, 54,* 414-433.

Haaland, K.Y., Harrington, D.L., O'Brien, S. & Hermanowicz, N. (1997). Cognitive-motor learning in Parkinson's disease. *Neuropsychology, 11,* 180-186.

Haber, S.N. (2003). The primate basal ganglia: parallel and integrative networks. *Journal of Chemical Neuroanatomy, 26,* 317-330.

Hackett, T.A., Stepniewska, I. & Kaas, J.H. (1998). Thalamocortical connections of the parabelt auditory cortex in macaque monkeys. *The Journal of Comparative Neurology, 400,* 271-286.

Hagoort, P. (1993). Impairments of lexical semantic processing in aphasia: Evidence from the processing of lexical ambiguities. *Brain and Language, 45,* 189-232.

Hahne, A. & Friederici, A.D. (1999). Electrophysiological evidence for two steps in syntactic analysis: Early automatic and late controlled processes. *Journal of Cognitive Neuroscience, 11*, 194-205.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Liegeois, C., Chauvel, P. & Musolino, A. (1995a). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography & Clinical Neurophysiology, 94,* 191-220.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J.P. & Biraben, A. (1995b). Intracerebral potentials to rare target and distractor auditory and visual stimuli: II. Medial, lateral and posterior temporal lobe. *Electroencephalography & Clinical Neurophysiology, 94,* 229-250.

Halgren, E., Dhond, R.P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J.D. & Dale, A.M. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *NeuroImage, 17,* 1101-1116.

Harrington, D.L. & Haaland, K.Y. (1999). Neural underpinnings of temporal processing: a review of focal lesion, pharmacological, and functional imaging research. *Review in the Neurosciences, 10,* 91-116.

Harrington, D.L., Haaland, K.Y. & Hermanowicz, N. (1998). Temporal processing in the basal ganglia. *Neuropsychology, 12,* 3-12.

Hayes, A.E., Davidson, M.C., Keele, S.W. & Rafal, R.D. (1998). Toward a functional analysis of the basal ganglia. *Journal of Cognitive Neuroscience, 10,* 178-198.

Heilman, K.M., Bowers, D., Speedie, L. & Coslett, H.B. (1984). Comprehension of affective and nonaffective prosody. *Neurology, 34,* 917-921.

Heinze, H.J., Luck, S.J.., Mangun, G.R. & Hillyard, S.A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays: I. Evidence for early selection. *Electroencephalography & Clinical Neurophysiology, 75,* 511-527.

Heit, G., Smith, M.E. & Halgren, E. (1990). Neuronal activity in the human medial temporal lobe during recognition memory. *Brain, 113,* 1093-1112.

Henry, R.G., Berman, J.L., Nagarajan, S.S., Mukherjee, P. & Berger, M.S. (2004). Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. *NeuroImage, 21,* 616-622.

Hier, D.B., Davis, K.R., Richardson, E.P. & Mohr, J.P. (1977). Hypertensive putaminal hemorrhage. *Annals of Neurology, 1,* 152-9.

Hikosaka, O., Nakahara, H., Rand, M.K., Sakai, K., Lu, X., Nakamura, K., Miyachi, S. & Doya, K. (1999). Parallel neural networks for learning sequential procedures. *Trends in Neurosciences, 22,* 464-471.

Hillyard, S.A. & Picton, T.W. (1987). Electrophysiology of cognition. In V.B. Mountcastle, F. Plum & S.R. Geiger (Eds.), *Handbook of Physiology. Section 1, Vol. 5, Pt. 2* (pp. 519-584), Bethesda: American Physiological Society.

Hsieh, S., Hwang, W.J., Tsai, J.J. & Tsai, C.Y. (1996). Precued shifting of attention between cognitive sets in Parkinson patients. *Psychological Reports, 78,* 815-823.

Hoehn, M.M. & Jahr, M.D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology, 17,* 424-442.

Holcomb, P.J. (1988). Automatic and attentional processing: An event-related brain potential analysis of semantic priming. *Brain and Language, 35,* 66-85.

Holcomb, P.J. (1993). Semantic priming and stimulus degradation: Implications for the role of the N400 in language processing. *Psychophysiology, 30,* 47-61.

Holcomb, P.J. & McPherson, W.B. (1994). Event-related brain potentials reflect semantic priming in an object decision task. *Brain and Cognition, 24,* 259-276.

Holcomb, P.J. & Neville, H.J (1990). Auditory and visual semantic priming in lexical decision: A comparison using event-related brain potentials. *Language & Cognitive Processes, 5,* 281-312.

Houk, J.C. (1995). Information processing in modular circuits linking basal ganglia and cerebral cortex. In J.C. Houk, J.L. Davis & D.G. Beiser (Eds.), *Models of Information Processing in the Basal Ganglia (pp. 3-10)*. Cambridge, MA: The MIT Press.

Husain, M.M., McDonald, W.M., Doraiswamy, P.M., Figiel, G.S., Na, C., Escalona, P.R., Boyko, O.B., Nemeroff, C.B. & Krishnan, K.R. (1992). A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Research, 40,* 95-99.

Indefrey, P., Brown, C.M., Hellwig, F., Amunts, K., Herzog, H., Seitz, R.J. & Hagoort, P. (2001). A neural correlate of syntactic encoding during speech production. Proceedings of the National Academy of Sciences of the USA, 8, 5933-5936.

Inglis, W.L. & Winn, P. (1995). The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. *Progress in Neurobiology, 47,* 1-29.

Inui, T., Otsu, Y., Tanaka, S., Okada, T., Nishizawa, S. & Konishi, J.(1998). A functional MRI analysis of comprehension processes of Japanese sentences. *NeuroReport, 9,* 3325-3328.

Jezzard, P., Matthews, P.M. & Smith, S.M., Eds. (2001). *Functional MRI: an introduction to methods.* Oxford: Oxford University Press.

Joel, D. & Weiner, I. (1994). The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. *Neuroscience, 63,* 363-379.

Joel, D. & Weiner, I. (1997). The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. *Brain Research Reviews, 23,* 62-78.

Joel, D. & Weiner, I. (1999). Striatal contention scheduling and the split circuit scheme of basal ganglia-thalamocortical circuitry: From anatomy to behaviour. In R. Miller & J.R. Wickens (Eds.), *Conceptual Advances in Brain Research: Brain Dynamics and the Striatal Complex* (pp. 209-236). Amsterdam: Harwood Academic Publishers.

Joel, D. & Weiner, I. (2001). The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience, 93,* 451-474.

Jueptner, M. & Weiller, C. (1998). A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain, 121,* 1437-1449.

Just, M.A., Carpenter, P.A. & Keller, T.A. (1998). The capacity theory of comprehension: new frontiers of evidence and arguments. *Psychological Review, 103,* 773-780.

Kaan, E., Harris, A., Gibson, E. & Holcomb, P. (2000). The P600 as an index of syntactic integration difficulty. *Language & Cognitive Processes, 15,* 159-201.

Kaan, E. & Swaab, T.Y. (2002). The brain circuitry of syntactic comprehension. *Trends in Cognitive Sciences, 6,* 350-356.

Kemp, J.M & Powell, T.P. (1970). The cortico-striate projection in the monkey. *Brain, 93,* 525-546.

Kiefer, M. & Spitzer, M. (2001). The limits of a distributed account of conceptual knowledge. *Trends in Cognitive Neurosciences, 5,* 469-471.

Knösche, T., Maess, B. & Friederici, A.D. (1999). Processing of syntactic information monitored by brain surface current density mapping based on MEG. *Brain Topography, 12,* 75-87.

Koelsch, S., Kasper, E., Gunter, T.C. & Friederici, A.D. (2004). Music, language, and meaning: Brain signatures of semantic processing. *Nature Neuroscience, 7,* 302-307.

Kotz, S.A., Cappa, S. F., von Cramon, D.Y. & Friederici, A.D. (2002). Modulation of the lexical-semantic network by auditory semantic priming: an event-related functional MRI study. *NeuroImage, 17,* 1761-1772.

Kotz, S.A. & Friederici, A.D. (2003). Electrophysiology of normal and pathological language processing. *Journal of Neurolinguistics, 16*, 43-58.

Kotz, S.A., Frisch, S., von Cramon D.Y. & Friederici, A.D. (2003a). Syntactic language processing: ERP lesion data on the role of the basal ganglia. *Journal of the International Neuropsychological Society, 9,* 1053-1060.

Kotz, S.A., Meyer, M., Alter, K., Besson, M., von Cramon D.Y. & Friederici, A.D. (2003b). On the lateralization of emotional prosody: An event-related functional MR investigation. *Brain and Language, 86,* 366-376.

Kotz, S.A., Meyer, M. & Paulmann, S. (in press). Lateralization of emotional prosody in the brain: An overview and synopsis on the impact of study design. *Progress in Brain Research.*

Kotz, S.A., Paulmann, S. & Raettig, T. (2005). Varying task demands during the perception of emotional content: EfMRI evidence. *Journal of Cognitive Neuroscience, Supplement,* 63.

Kotz, S.A., Schwarz, J., Winkler, D. Preul, C., von Cramon, D.Y. & Friederici, A.D. (2005). recovery of syntactic function during auditory language processing following subthalamic nucleus stimulation in Parkinson's disease. Proceedings of the Plasticity in Speech Perception Conference, London, June 2005.

Kraut, M.A., Calhoun, V., Pitcock, J.A., Cusick, C. & Hart, J. Jr. (2003). Neural hybrid model of semantic object memory: Implications from event-related timing using fMRI. *Journal of the International Neuropsychological Society, 9,* 1031-1040.

Kraut, M.A., Kremen, S., Moo, L.R., Segal, J.B., Calhoun, V. & Hart, J. Jr. (2002). Object activation in semantic memory from visual multimodal feature input. *Journal of Cognitive Neuroscience, 14,* 37-47.

Kuperberg, G.R., McGuire, P.K., Bullmore, E.T., Brammer, M.J., Rabe-Hesketh, S., Wright, I.C., Lythgoe, D.J., Williams, S.C.R. & David, A.S. (2000). Common and distinct neural substrates for pragmatic, semantic, and syntactic processing of spoken sentences: An fMRI study. *Journal of Cognitive Neuroscience, 12,* 321-341.

Kutas, M. & Federmeier, K. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences, 4,* 463-470.

Kutas, M. & Hillyard, S.A. (1980a). Event-related brain potentials to semantically inappropriate and surprisingly large words. *Biological Psychology, 11,* 99-116.

Kutas, M. & Hillyard, S.A. (1980b). Reading between the lines: Event-related brain potentials during natural sentence processing. *Brain and Language, 11,* 354-373.

Kutas, M. & Hillyard, S.A. (1983). Event-related brain potentials to grammatical errors and semantic anomalies. *Memory & Cognition, 11,* 539-550.

Kutas, M. & Hillyard, S.A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature, 307,* 161-163.

Kutas, M., McCarthy, G. & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science, 197,* 792-795.

Lange, J.J., Wijers, A.A., Mulder, L.J. & Mulder, G. (1998). Color selection and location selection in ERPs: Differences, similarities and "neural specificity". *Biological Psychology, 48,* 153-182.

Larsson, J., Gulyas, B. & Roland, P.E. (1996). Cortical representation of self-paced finger movement. *NeuroReport, 7,* 463-468.

Lawrence, A.D., Sahakian, B.J. & Robbins, T.W. (1998). Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends in Cognitive Sciences, 2, 10,* 379-388.

LeDoux, J.E., Sakaguchi, A. & Reis, D.J. (1994). Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. *Journal of Neuroscience, 4,* 683-698.

Levin, H.S., High, W.M. Jr., Williams, D.H., Eisenberg, H.M., Amparo, E.G., Quinto, F.C. & Evert, J. (1989). Dichotic listening and manual performance in relation to magnetic resonance imaging after closed head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 1162-1169.

Lewis, P.A. & Miall, R.C. (2002). Brain activity during non-automatic motor production of discrete multi-second intervals. *NeuroReport, 13,* 1731-1735.

Lichtheim, O. (1884). On aphasia. *Brain, 7*, 443-484.

Lieberman, P. (2001). Human language and our reptilian brain. The subcortical bases of speech, syntax, and thought. *Perspectives in Biology and Medicine, 44,* 32-51.

Lieberman, P., Friedman, J. & Feldman, L.S. (1990). Syntax comprehension deficits in Parkinson's disease. *Journal of Nervous and Mental Diseases, 178,* 360-365.

Lieberman, P., Kako, E., Friedman, J., Taichman, G., Feldman, L.S. & Jiminez, E.B. (1992). Speech production, syntax comprehension, and cognitive deficits in Parkinson's disease. B*rain and Language, 43,* 169-189.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412,* 150-157.

Longworth, C.E., Keenan, S.E., Barker, R.A., Marslen-Wilson, W.D. & Tyler, L.K. (2005). The basal ganglia and rule-governed language use: evidence from vascular and degenerative conditions. *Brain, 128,* 584-596.

Luck, S.J. & Hillyard, S.A. (1994). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology, 31,* 291-308.

Luck, S.J., Hillyard, S.A., Mouloua, M., Woldorff, M.G., Clark, V.P. & Hawkins, H.L. (1994). Effects of spatial cuing on luminance detectability: Psychophysical and electrophysiological evidence for early selection. *Journal of Experimental Psychology: Human Perception & Performance, 20,* 887-904.

MacLean, P. (1990). *The Triune Brain in Evolution*. New York: Plenum Press, pp. 543.

Maess, B., Friederici, A.D., Damian, M., Meyer, A. S. & Levelt, W. J. M. (2002). Semantic category interference in overt picture naming: Sharpening current density localization by PCA. *Journal of Cognitive Neuroscience, 14,* 455-462.

Malapani, C., Dubois, B., Rancurel, G. & Gibbon, J. (1998) Cerebellar dysfunctions of temporal processing in the seconds range in humans. *NeuroReport, 9,* 3907-3912.

Mangels, J.A., Ivry, R.B. & Shimizu, N. (1998). Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. *Cognitive Brain Research, 7,* 15-39.

Mangun, G.R. & Hillyard, S.A. (1990). Allocation of visual attention to spatial locations: Tradeoff functions for event-related brain potentials and detection performance. *Perception & Psychophysics, 47,* 532-550.

Martin, K.E., Phillips, J.G., Iansek, R. & Bradshaw, J.L. (1994). Inaccuracy and instability of sequential movements in Parkinson's disease. *Experimental Brain Research, 102,* 131-140.

Matsumoto, D., Kasri, F. & Kooken, K. (1999). American-Japanese cultural differences in judgements of expression intensity and subjective experience. *Cognition & Emotion, 13,* 201-218.

McCarthy, G. & Wood, C.C. (1985). Scalp distributions of event-related potentials: an ambiguity associated with analysis of variance models. *Electroencephalography & Clinical Neurophysiology, 62,* 203-208.

McDonald, C., Brown, G.G. & Gorrell, J.M (1996). Impaired set-shifting in Parkinson's disease: new evidence from a lexical decision task. *Journal of Clinical and Experimental Neuropsychology, 18,* 793-809.

McNamara, P., Krueger, M., O'Quin, K., Clark, J. & Durso, R. (1996). Grammaticality judgments and sentence comprehension in Parkinson's disease: A comparison with Broca's aphasia. *International Journal of Neuroscience, 86,* 151-166.

Meck, W.H. (1983). Selective adjustment of the speed of internal clock and memory processes. *Journal of Experimental Psychology: Animal Behavior Processes, 9,* 171-201.

Meck, W.H. (1996). Neuropharmacology of timing and time perception. *Cognitive Brain Research, 3,* 227-242.

Meck, W.H. & Benson, A.M. (2002). Dissecting the brain's internal clock: How frontal-striatal circuitry keeps time and shifts attention. *Brain & Cognition, 48,* 195-211.

Mecklinger, A., Schriefers, H., Steinhauer, K. & Friederici, A.D. (1995). Processing relative clauses varying on syntactic and semantic dimensions: An analysis with event-related potentials. *Memory and Cognition, 23,* 477-494.

Middleton, F.A. & Strick, P.L. (1996). The temporal lobe is a target of output from the basal ganglia. *Proceedings of the National Academy of Sciences of the USA, 93,* 8683-8687.

Middleton, F.A. & Strick, P.L. (2000). Basal ganglia output and cognition: Evidence from anatomical, behavioral, and clinical studies. *Brain & Cognition, 42,* 183-200.

Middleton, F.A. & Strick, P.L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *Journal of Neuroscience, 21,* 700-12.

Mink, J.W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. Progress in Neurobiology, 500, 381-425.

Mishkin, M., Malamut, B. & Bachevalier, J. (1984). Memories and habits: Two neural systems. In G. Lynch, J.L. McGaugh & N.M. Weinberger (Eds.), *Neurobiology of Learning and Memory (pp. 65-77)*. New York: Guilford Press.

Miyachi, S., Hikosaka, O., Miyashita, K., Karadi, Z. & Rand, M.K. (1997). Differential roles of monkey stratum in learning of sequential hand movements. *Experimental Brain Research, 115,* 1-5.

Morgenstern, R., Gold, R. & Oelssner, W. (1983). Locomotor activity and the nucleus accumbens. *Biomedica Biochimica Acta, 42,* 947-53.s

Moro, A., Tettamanti, M., Perani, D., Donati, C., Cappa, S.F. & Fazio, F. (2001). Syntax and the brain: disentangling grammar by selective anomalies. *NeuroImage, 13,* 110-118.

Morris, J.S., Scott, S.K. & Dolan, R.J (1999). Saying it with feeling: neural responses to emotional vocalizations. *Neuropsychologia, 37*, 1155-1163.

Mummery, C.J., Patterson, K., Hodges, J.R. & Price, C.J. (1998). Functional neuroanatomy of the semantic system: Divisible by what? *Journal of Cognitive Neuroscience, 10,* 766-777.

Murray, L.L. (2000). Spoken language production in Huntington's and Parkinson's diseases. *Journal of Speech, Language, and Hearing Research, 43,* 1350-1366.

Naeser, M.A., Alexander, M.P., Helm-Estabrooks, N., Levine, H.L., Laughlin, S.A. & Geschwind, N. (1982). Aphasia with predominantly subcortical lesion sites: description of three capsular/putaminal aphasia syndromes. *Archives of Neurology, 39,* 2-14.

Nadeau, S.E. & Crosson, B. (1997). Subcortical aphasia. *Brain and Language, 58,* 355-402

Näätänen, R., Ed. (1992) *Attention and brain function*. Hillsdale, NJ: Lawrence Erlbaum Associates, pp. 494.

Näätänen, R. & Picton, T.W. (1987). The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology, 24,* 375-425.

Natsopoulos, D., Grouios, G., Bostantzopoulou, S., Mentenopoulos, G., Katsarou, Z. & Logothetis, J. (1993). Algorithmic and heuristic strategies in comprehension of complement clauses by patients with Parkinson's disease. *Neuropsychologia, 31,* 951-964.

Natsopoulos, D., Katsarou, Z., Bostantzopoulou, S., Grouios, G., Mentenopoulos, G. & Logothetis, J. (1991). Strategies in comprehension of relative clauses by parkinsonian patients. *Cortex, 27,* 255-268.

Neumann, J., Lohmann, G., Zysset, S. & von Cramon, D.Y. (2003). Within-subject variability of BOLD response dynamics. *NeuroImage, 19,* 784-796.

Neville, H.J., Nicol, J.L., Barss, A., Forster, K.I. & Garrett, M.F. (1991). Syntactically based sentence processing classes: Evidence from event-related brain potentials. *Journal of Cognitive Neuroscience, 3,* 151-165.

Ni, W., Constable, R.T., Mencl, W.E., Pugh, K.R., Fulbright, R.K., Shaywitz, S.E., Shaywitz, B.A., Gore, J.C. & Shankweiler, D. (2000). An event-related neuroimaging study distinguishing form and content in sentence processing. *Journal of Cognitive Neuroscience, 12,* 120-133.

Nigam, A., Hoffman, J.E. & Simons, R.F. (1992). N400 to semantically anomalous pictures and words. *Journal of Cognitive Neuroscience, 4,* 15-22.

Nobre, A.C. & McCarthy, G. (1995). Language-related field potentials in the anterior-medial temporal lobe: II. Effects of word type and semantic priming. *Journal of Neuroscience, 15,* 1090-1099.

Norris, D.G., Zysset, S., Mildner, T. & Wiggins, C.J. (2001). An investigation of the value of spin-echo-based fMRI using a Stroop color-word matching task and EPI at 3 T. *NeuroImage, 15,* 719-726.

Nunez, P.L, Ed. (1981). *Electric fields of the brain: The Neurophysics of EEG.* New York: Oxford University Press, pp. 484.

Nunez, P., Ed. (1995). *Neocortical dynamics and human EEG rhythms.* New York: Oxford University Press, pp. 722.

Ogawa, S. & Lee, T.M. (1990). Magnetic resonance imaging of blood vessels at high fields: In vivo and in vitro measurements and image simulation. *Magnetic Resonance in Medicine, 16,* 9-18.

Olmstead, M.C., Munn, E.M., Franklin, K.B.J. & Wise, R.A. (1998). Effects of pedunculopontine tegmental nucleus lesions on responding for intravenous heroin under different schedules of reinforcement. *Journal of Neuroscience, 18,* 5035-5044.

Osterhout, L. & Holcomb, P.J. (1992). Event-related brain potentials elicited by syntactic anomaly. *Journal of Memory & Language, 31,* 785-806.

Osterhout, L. & Holcomb, P.J. (1993). Event-related potentials and syntactic anomaly: Evidence of anomaly detection during the perception of continuous speech. *Language & Cognitive Processes, 8,* 413-437.

Osterhout, L. & Holcomb, P.J. & Swinney, D.A. (1994). Brain potentials elicited by garden-path sentences: Evidence of the application of verb information during parsing. *Journal of Experimental Psychology: Learning, Memory, & Cognition, 20,* 786-803.

Owen, A.M. (1997). Cognitive planning in humans: neuropsychological, neuroanatomical and neuropharmacological perspectives. *Progress in Neurobiology, 53,* 431-450.

Owen, A.M., James, M., Leight, P.N., Summers, B.A., Marsden, C.D., Quinn, N.P., Lange, K.W. & Robbins, T.W. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 115,* 1727-1751.

Paller, K.A., McCarthy, G. & Wood, C.C. (1992). Event-related potentials elicited by deviant endings to melodies. *Psychophysiology, 29,* 202-206.

Pandya, D.N. & Rosene, D.L. (1993). Laminar termination patterns of thalamic, callosal, and association afferents in the primary auditory area of the rhesus monkey. *Experimental Neurology, 119*, 220-234.

Pascual-Leone, A., Grafman, J. & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science, 263,* 1287-1289.

Parent, A., Ed. (1986). *Comparative Neurobiology of the Basal Ganglia*. New York: Wiley.

Parent, A. & Hazrati, L.N. (1995a). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Research Reviews, 20,* 91-127.

Parent, A. & Hazrati, L.N. (1995b). Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Research Reviews, 20,* 128-154.

Parsons, L.M. (2001) Integrating cognitive psychology, neurology and neuroimaging. *Acta Psychologica, 107,* 155-181.

Patriot, A., Grafman, J., Sadato, N., Wachs, J. & Hallett, M. (1995). Brain activation during the generation of non-emotional and emotional plans. *NeuroReport, 6,* 1397-1400.

Patriot, A., Verin, M., Pillon, B., Teixeira-Ferreira, C., Agid, Y. & Dubois, B. (1996). Delayed response tasks in basal ganglia lesions in man: Further evidence for a striato-frontal cooperation in behavioural adaptation. *Neuropsychologia, 34,* 709-721.

Paulmann, S. & Kotz, S.A. (2005). When emotional prosody and semantics interact in time: ERP evidence. *Journal of Cognitive Neuroscience, Supplement*, 63.

Pell, M.D. (1998). Recognition of prosody following unilateral brain lesion: Influence of functional and structural attributes of prosodic contours. *Neuropsychologia, 36,* 701-715.

Pell, M.D. & Baum, S.R. (1997). The ability to perceive and comprehend intonation in linguistic and affective contexts by brain-damaged adults. *Brain and Language, 57,* 80-99.

Pell, M.D. & Leonard, C.L. (2003). Processing emotional tone from speech in Parkinson's disease: a role for the basal ganglia. *Cognitive Affective Behavioral Neuroscience, 3,* 275-288.

Pell, M.D. & Leonard, C.L. (2005). Facial expression decoding in early Parkinson's disease. *Cognitive Brain Research, 23,* 327-340.

Penke, M., Weyerts, H., Gross, M., Zander, E., Münte, T.F. & Clahsen, H. (1997). How the brain processes complex words: An event-related potential study of German verb inflections. *Cognitive Brain Research, 6,* 37-52.

Petrides, M. (1994). Functional specialization within the dorsolateral frontal cortex. *Revue de Neuropsychologie, 4,* 305-325.

Pickett, E.R., Kuniholm, E., Protopapas, A., Friedman, J. & Lieberman, P. (1998). Selective speech motor, syntax and cognitive deficits associated with bilateral damage to the putamen and the head of the caudate nucleus: A case study. *Neuropsychologia, 36,* 173-188.

Pilgrim, L.K., Fadili, J., Fletcher, P. & Tyler, L.K. (2002). Overcoming confounds of stimulus blocking: an event-related fMRI design of semantic processing. *NeuroImage, 16,* 713-723.

Pinker, S. & Ullman, M.T. (2002). The past and future of the past tense. *Trends in Cognitive Sciences, 6,* 456-463.

Price, C. J., Moore, C. J., Humphreys, G. W. & Wise, R. J. S. (1997). Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience, 9,* 727-733.

Raettig,T., Kotz, S.A., Frisch, S. & Friederici, A.D. (2005). Neural correlates of verb-argument structure and semantic processing: An efMRI study. *Journal of Cognitive Neuroscience, Suppl*., 77.

Rammsayer, T.H. (1993). On dopaminergic modulation of temporal information processing. *Biological Psychology, 36,* 209-222.

Rammsayer, T.H. (1999). Neuropharmacological evidence for different timing mechanisms in humans. *Quarterly Journal of Experimental Psychology: Comparative & Physiological Psychology, 52B,* 273-286.

Rammsayer, T. & Classen, W. (1997). Impaired temporal discrimination in Parkinson's disease: temporal processing of brief durations as an indicator of degeneration of dopaminergic neurons in the basal ganglia. *International Journal of Neuroscience, 91,* 45-55.

Rammsayer, T.H. & Lima, S.D. (1992). Duration discrimination of filled and empty auditory intervals: Cognitive and perceptual factors. *Perception & Psychophysics, 50,* 565-574.

Raymer, A.M., Moberg, P. Crosson, B., Nadeau, S. & Rothi, L.J. (1997). Lexical-semantic deficits in two patients with dominant thalamic infarction. *Neuropsychologia, 35,* 211-219.

Raz, N., Torres, I.J. & Acker, J.D. (1995). Age, gender, and hemispheric differences in human striatum: A quantitative review and new data form in vivo MRI morphometry. *Neurobiology of Learning & Memory, 63,* 133-142.

Reber, P.J. & Squire, L.R. (1999). Intact learning of artificial grammars and intact category learning by patients with Parkinson's disease. *Behavioral Neuroscience, 113,* 235-242.

Ritter, W., Simson, R. & Vaughan, H.G. Jr. (1983). Event-related potential correlates of two stages of information processing in physical and semantic discrimination tasks. *Psychophysiology, 20,* 168-179.

Rolls, E.T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex, 10,* 284-294.

Rolls, E.T., Baylis, G.C. & Hasselmo, M.E. (1984). The responses of neurons in the cortex in the superior temporal sulcus of the monkey to band-pass spatial frequency filtered faces. *Vision Research, 27,* 311-326.

Rolls, E.T., Critchley, H.D. & Treves, A. (1996). Representation of olfactory information in the primate orbitofrontal cortex. *Journal of Neurophysiology, 75,* 1982-1986.

Romanski, L.M., Giguere, M., Bates, J.F. & Goldman-Rakic, P.S. (1997). Topographic organization of medial pulvinar connections with the prefrontal cortex in the rhesus monkeys. *Journal of Comparative Neurology, 379*, 313-332.

Rossell, S.L., Bullmore, E.T., Williams, S.C.R. & David, A.S. (2001). Brain activation during automatic and controlled processing of semantic relations: A priming experiment using lexical-decision. *Neuropsychologia, 39,* 1167-1176.

Rossell, S.L., Price, C.J. & Nobre, A.C. (2003). The anatomy and time course of semantic priming investigated by fMRI and ERPs. *Neuropsychologia, 41,* 550-564.

Ruchkin, D.S., Johnson, R. Jr., Canoune, H.L., Ritter, W. & Hammer, M. (1990). Multiple sources of P3b associated with different types of information. *Psychophysiology, 27,* 157-176.

Sagar, H.J., Sullivan, E.V., Gabrieli, J.D., Corkin, S. & Growdon, J.H. (1988). Temporal ordering and short-term memory deficits in Parkinson's disease. *Brain, 111,* 525-539.

Saint-Cyr, J.A. (2003). Frontal-striatal circuit functions: Context, sequence, and consequence. *Journal of the International Neuropsychological Society, 9,* 103-127.

Saint-Cyr, J.A., Taylor, A.E. & Lang, A.E. (1988). Procedural learning and neostriatal dysfunction in man. *Brain, 111,* 941-951.

Saint-Cyr, J.A., Taylor, A.E., Trépanier, L.L. & Lang, A.E. (1992). The caudate nucleus: Head ganglion of the habit system. In G. Valler, S.F. Cappa & C.W. Wallesch (Eds.), *Neuropsychological Disorders Associated with Subcortical Lesions* (pp. 204- 226). Oxford, Oxford Science Publications.

Schirmer, A. (2004). Timing speech: A review of lesion and neuroimaging findings. *Cognitive Brain Research, 21,* 269-287.

Schirmer, A., Kotz, S.A. & Friederici, A.D. (2002). Sex differentiates the role of emotional prosody during word processing. *Cognitive Brain Research, 14,* 228-233.

Schubotz, R.I. (1999). Instruction differentiates the processing of temporal and spatial sequential patterns: Evidence from slow wave activity in humans. *Neuroscience Letters*, *265*, 1-4.

Schubotz, R.I., Sakreida, K., Tittgemeyer, M. & von Cramon, D.Y. (2004). Motor areas beyond motor performance: Deficits in serial prediction following ventrolateral premotor lesions. *Neuropsychology, 18,* 638-645.

Schubotz, R.I. & von Cramon, D.Y. (2001). Interval and ordinal properties of sequences are associated with distinct premotor areas. *Cerebral Cortex, 11,* 210-222.

Schupp, H.T., Lutzenberger, W., Birbaumer, N., Miltner, W. & Braun, C. (1994). Neurophysiological differences between perception and imagery. *Cognitive Brain Research, 2,* 77-86.

Scott, S.K. (2005). Auditory processing – speech, space and auditory objects. Current Opinion in *Neurobiology, 15,* 197-201.

Smid, H.G.O.M., Jakob, A. & Heinze, H.-J. (1999). An event-related brain potential study of visual selective attention to conjunctions of color and shape. *Psychophysiology, 36 1999,* 264-279.

Smith, E.E. & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283,* 1657-1661.

Solanti, M. & Knight, R.T. (2000). Neural origins of the P300. Critical Reviews in *Neurobiology, 14,* 199-224.

Sonntag, G.P. & Portele, T. (1998). PURR – A method for prosody evaluation and investigation. *Journal of Computer Speech and Language, 12,* 437-451.

Squire, L.R., Knowlton, B. & Musen, G. (1993). The structure and organization of memory. *Annual Review of Psychology, 44,* 453-495.

Stefanacci., L. & Amaral, D. (2000). Topographic organization of cortical inputs to the lateral nucleus of the macaque monkey amygdala: A retrograde tracing study. *Journal of Comparative Neurology, 421*, 52-79.

Stefanacci., L. & Ameral, D. (2002). Some observations on the cortical inputs to the macaque monkey amygdala: An antrograde tracing study. *Journal of Comparative Neurology, 451*, 301-323.

Starkstein, S.E., Federoff, J.P., Price, T.R., Leiguarda, R.C. & Robinson, R.G. (1994). Neuropsychological and neuroradiologic correlates of emotional prosody comprehension. *Neurology, 44,* 515-522.

Strick, P.L., Dum, R.P. & Picard, N. (1995). Motor areas on the medial wall of the hemisphere. *Novartis Foundation Symposium, 218,* 64-75.

Stromswold, K., Caplan, D., Alpert, N. & Rauch, S. (1996). Localization of syntactic comprehension by positron emission tomography. *Brain and Language, 52,* 452-473.

Swaab, T., Brown, C. & Hagoort, P. (1997). Understanding ambiguous words in sentence contexts: Electrophysiological evidence for delayed contextual selection in Broca's aphasia. *Neuropsychologia, 36,* 737-761.

Swaab, T., Brown, C. & Hagoort, P (1998). Understanding ambiguous words in sentence contexts: electrophysiological evidence for delayed contextual selection in Broca's aphasia. *Neuropsychologia, 36,* 737-61.

Swennilson, E., Torvika, A., Lowe, R. & Leksell, L. (1960). Treatment of parkinsonism by stereotatic thermolesions in the pallidal region. A clinical evaluation of 81 cases. *Acta Psychiatrica et Neurological Scandinavia, 35,* 358-377.

Talairach, J., Tournoux, P., Eds. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.

Taylor, A.E., Saint-Cyr, J.A. & Lang, A.E. (1986). Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain, 109,* 845-883.

Taylor, A.E., Saint-Cyr, J.A. & Lang, A.E. (1990). Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". *Brain and Cognition, 13,* 211-232.

Thompson-Schill, S.L., D'Esposito, M. & Aguirre, G.K. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proceedings of the National Academy of Sciences of the USA, 94*, 14792-14797.

Tremblay, L. & Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. *Nature, 398,* 704-708.

Tyler, L.K., de Mornay-Davies, P., Anokhina, R., Longworth, C., Randall, B. % Marslen-Wilson, W.D. (2002). Dissociations in processing past tense morphology: neuropathology and behavioral studies. *Journal of Cognitive Neuroscience, 14*, 79-94.

Ullman, M.T. (2001). A neurocognitive perspective on language: the declarative/procedural model. *Nature Reviews Neuroscience, 2,* 717-726.

Ullman, M.T., Corkin, S., Coppola, M., Hickok, G., Growdon, J.H., Koroshetz, W.J. & Pinker, S. (1997). A neural dissociation within language: Evidence that the mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. *Journal of Cognitive Neuroscience, 9,* 266-276.

Vakil, E. & Herishanu-Naaman, S. (1998). Declarative and procedural learning in Parkinson's disease patients having tremor or bradykinesia as the predominant symptom. *Cortex, 34,* 611-620.

Vallar, G., Perani, D., Cappa, S.F., Messa, C., Lenzi, G.L. & Fazio, F. (1988). Recovery from aphasia and neglect after subcortical stroke: neuropsychological and cerebral perfusion study. *Journal of Neurology, Neurosurgery, and Psychiatry, 51,* 1269-1276.

Van Berkum, J.J.A., Hagoort, P. & Brown, C.M. (1999). Semantic integration in sentences and discourse: Evidence from the N400. *Journal of Cognitive Neuroscience, 11,* 657-671.

Van Buren, J.M. & Ojemann, G.M. (1966). The fronto-striatal arrest response in man. *Electroencephalography and Clinical Neurophysiology, 21*, 114-130.

Van Hoesen, G.W., Yeterian, E.H. & Lavizzo-Mourey, R. (1981). Widespread corticostriate projections from temporal cortex of the rhesus monkey. Journal of Comparative Neurology, 199, 20-219.

Van Lancker, D. & Sidtis, J.J. (1992). The identification of affective-prosodic stimuli by left- and right-hemisphere-damaged subjects: All errors are not created equal. *Journal of Speech & Hearing Research, 35,* 963-970.

Van Petten, C. & Kutas, M. (1990). Interactions between sentence context and word frequency in event-related brain potentials. *Memory & Cognition, 18,* 380-393.

Vriezen, E.R. & Moscovitch, M. (1990). Memory for temporal order and conditional associative-learning in patients with Parkinson's disease. *Neuropsychologia, 28,* 1283-1293.

Wallesch, C.W. (1985).Two syndromes of aphasia occurring with ischemic lesions involving the left basal ganglia. *Brain and Language, 25,* 357-361.

Wallesch, C.W. (2003). Sprache. In H.-O. Karnath & P. Thier (Eds.), Neuropsychologie (pp. 551-555). Stuttgart: Springer.

Wallesch, C.W. & Blanken, G. (2000). Recurring utterances-how, where, and why are they generated? *Brain and Language, 71,* 255-257.

Wallesch, C.W. & Papagno, C. (1988). Subcortical aphasia. In F.C. Rose, R. Whurr & M.A. Wyke (Eds.), *Aphasia (pp. 256-287)*. London: Whurr Publishers.

Watters, P.A. & Patel, M. (2002). Competition, inhibition, and semantic judgment errors in Parkinson's disease. *Brain and Language, 80,* 328-339.

Wedell, D.H. (1994). Contextual contrast in evaluative judgments: A test of pre- versus postintegration models of contrast. *Journal of Personality & Social Psychology, 66,* 1007-1019.

Weiller, C., Willmes, K., Reiche, W., Thron, A., Isensee, C., Buell, U. & Ringelstein, E.B. (1993). The case of aphasia or neglect after striatocapsular infarction. *Brain, 116,* 1509-1525.

Wernicke, C., Ed. (1874). *Der aphasische Symptomenkomplex*. Breslau: Cohn and Weigert.

Westwater, H., McDowall, J., Siegert, R., Mossman, S. & Abernethy, D. (1998). Implicit learning in Parkinson's disease: Evidence from a verbal version of the serial reaction time task. *Journal of Clinical & Experimental Neuropsychology, 20,* 413-418.

Wichmann, T. & DeLong, M.R. (1996). Functional and pathophysiological models of the basal ganglia. Current Opinion in Neurobiology, 6, 751-758.

Wildgruber, D., Hertrich, I., Riecker, A., Erb, M., Anders, S., Grodd, W. & Ackermann, H. (2004). Distinct Frontal Regions Subserve Evaluation of Linguistic and Emotional Aspects of Speech Intonation. *Cerebral Cortex, 14,* 1384-1389.

Wildgruber, D., Pihan, H., Ackermann, H., Erb, M. & Grodd, W. (2002). Dynamic brain activation during processing of emotional intonation: influence of acoustic parameters, emotional valence, and sex. NeuroImage, 15, 856-869.

Wise, S.P., Murray, E.A. & Gerfen, C.R. (1996). The frontal cortex-basal ganglia system in primates. *Critical Reviews in Neurobiology, 10,* 317-356.

Yamaguchi, S. & Knight, R.T. (1991). P300 generation by novel somatosensory stimuli. *Electroencephalography & Clinical Neurophysiology, 78,* 50-55.

Yesavage, J.A., Brink, T.L., Lum, O., Huang, V., Adey, M. & Leiter, V.O. (1983). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research, 17,* 37-49.

Yeterian, E.H. & Pandya, D.N. (1998). Corticostriatal connections of the superior temporal region in rhesus monkeys. *Journal of Comparative Neurology, 399,* 384-402.

Yeterian, E.H. & Van Hoesen, G.W. (1978). Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. *Brain Research, 139,* 43-63.

Zhu, X.L., Hamel, W., Schrader, B., Weinert, D., Hedderich, J., Herzog, J., Volkmann, J., Deuschl, G., Müller, D. & Mehdom, H.M. (2002). Magnetic resonance imaging-based morphometry and landmark correlation of basal ganglia nuclei. *Acta Neurochirurg (Wien), 144,* 959-969.

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Hiermit erkläre ich, dass ich die vorliegende Habilitationsschrift selbständig verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie die wörtlich oder inhaltlich übernommenen Stellen als solche gekennzeichnet habe.

Leipzig, den 27.04.2005 Sonja A. Kotz

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