On the Causal Mechanisms of Stuttering

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Stuttering and the basal ganglia circuits:
a critical review of possible relations

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Stuttering and the basal ganglia circuits: a critical review of possible relations

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Abstract

The possible relation between stuttering and the basal ganglia is discussed. Important clues to the pathophysiology of stuttering are given by conditions known to alleviate dysfluency, like the rhythm effect, chorus speech, and singing. Information regarding pharmacologic trials, lesion studies, brain imaging, genetics, and developmental changes of the nervous system is reviewed. The symptoms of stuttering are compared with basal ganglia motor disorders like Parkinson's disease and dystonia. It is proposed that the basal ganglia-thalamocortical motor circuits through the putamen are likely to play a key role in stuttering. The core dysfunction in stuttering is suggested to be impaired ability of the basal ganglia to produce timing cues for the initiation of the next motor segment in speech. Similarities between stuttering and dystonia are indicated, and possible relations to the dopamine system are discussed, as well as the interaction between the cerebral cortex and the basal ganglia. Behavioral and pharmacologic information suggests the existence of subtypes of stuttering.
Learning outcomes: As a result of this activity, the reader will (1) become familiar with the research regarding the basal ganglia system relating to speech motor control; (2) become familiar with the research on stuttering with indications of basal ganglia involvement; and (3) be able to discuss basal ganglia mechanisms with relevance for theory of stuttering.

Keywords: Stuttering; Basal ganglia; Dopamine; Dystonia; Cluttering

1. Introduction

Research concerning the nature of stuttering has produced an extensive amount of data during the past century, but the mechanisms behind the speech disruptions and the speech

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initiation problems are still not clear. An intriguing aspect of stuttering is the various conditions which can temporarily alleviate dysfluency in most cases: the rhythm effect (speaking to the pace of a metronome), singing, chorus speech, and altered auditory feedback (Wingate, 2002). The often dramatic improvements in fluency caused by these conditions indicate that stuttering is not the result of some general speech motor instability, instead there seem to be specific causal mechanisms leading to the speech problems.

In this article, possible relationships between stuttering and the functions of the basal ganglia (BG) circuits are reviewed and discussed. This review leads to the proposal that the circuits through the basal ganglia play a key role in the mechanisms of stuttering.

The BG are the largest subcortical structures in the human forebrain, and they are placed in a key position to influence motor behavior, emotions, and cognition (Graybiel, 2000). The idea that stuttering may be related to the BG is not new. As early as 1934, Seeman suggested that stuttering is the result of disturbed BG function (as cited in Van Riper, 1982). More recent suggestions for BG involvement in stuttering come from Rosenberger (1980), Caruso (1991), Wu et al. (1995), Lebrun (1998), and Victor and Ropper (2001), and others.

First an overview of the basal ganglia anatomy and functions will be presented. Thereafter several aspects of basal ganglia functions and disorders will be discussed in relation to stuttering: motor control and timing, lesions, brain imaging, dopamine, emotional influences, developmental changes of the BG, and similarities between stuttering and disorders like Parkinson's disease and dystonia. The BG operate in a close relation with the cerebral cortex, and therefore some important findings about the cortex and stuttering will also be discussed, from the perspective of the basal ganglia functions. Lastly tentative conclusions will be presented. Among the suggested conclusions can be mentioned that the core dysfunction in stuttering is proposed to be impaired ability of the basal ganglia to produce timing cues, that developmental changes of dopamine receptor density in the putamen might explain the frequent pattern of early childhood onset and recovery of stuttering, and that stuttering is likely to be a heterogeneous disorder with subtypes showing different responses to different types of dopaminergic medication.

2. Overview of the basal ganglia anatomy and functions

Even though the understanding of the BG circuits still must be considered as highly incomplete, knowledge has grown rapidly during the last decades. The model presented here is simplified, mainly limited to the aspects most relevant to the discussion. (For more thorough reviews, see for example Mink, 1996, and Victor & Ropper, 2001.)

The basal ganglia consist of a set of interconnected subcortical nuclei. The main input nucleus is the *striatum*, which receives topographical excitatory projections from almost the entire cerebral cortex, especially from the sensorimotor and frontal cortex (Parent, 1996). The striatum and the downstream structures in the basal ganglia are organized in topographically and functionally segregated pathways. The cortical inputs to the striatum are convergent, for example in such a way that sensory and motor cortex areas converge into single striatal zones (Flaherty & Graybiel, 1991).

The striatum is located close to the *globus pallidus*, which is divided into an external (GPe) and an internal part (GPi) (DeLong, 2000). The GPi is one of the main output nuclei[1] of the BG, and it projects, via various nuclei in the *thalamus*, to most cortical areas of the frontal lobe (Alexander, Crutcher, & DeLong, 1990). This architecture means that the BG is part of extensive loops, *basal ganglia-thalamocortical circuits*, which link almost the entire cortex to the cortex of the frontal lobe. The GPi also has descending output to the brain stem. Through this pathway the BG can influence brain stem functions like inhibition of auditory input (Swerdlow & Geyer, 1999). In summary, the BG modulate the activity of the frontal cortex and the activity of parts of the brain stem.

The striatum can be divided into three main parts: (a) the *putamen*, (b) the *caudate nucleus*, and (c) the *ventral striatum*. This division roughly corresponds to a functional division of the basal ganglia-thalamocortical circuits: (a) (*sensori*)*motor circuits* of the putamen, with output to the *primary motor cortex*, the *supplementary motor area* (SMA), and the *premotor cortex*; (b) *associative circuits* of the caudate nucleus, with output to the *prefrontal cortex*; and (c) *limbic circuits* of the ventral striatum, with output to the *anterior cingulate cortex* and *medial prefrontal cortex* (DeLong, 2000; Parent, 1996). The ventral (limbic) striatum also receives input from limbic structures, such as the amygdala and hippocampus (Joel & Weiner, 2000).

The striatum projects to the GPi by two pathways, the *direct* and the *indirect* (see Fig. 1). The indirect pathway also includes the *subthalamic nucleus* (STN). All projections from the striatum, the GPe, and the GPi are inhibitory, while the projections from the cortex, the STN and the thalamus are excitatory. The GPi is tonically active, thereby suppressing thalamic activity. Activation of the direct pathway inhibits neurons in the GPi, which in turn disinhibits thalamic neurons, finally resulting in excitation of cortical neurons. Activation of the indirect pathway has the opposite effect, activating the GPi and thereby inhibiting the cortex (DeLong, 2000). In this way the two pathways balance each other, modulating cortical activity.

Mink and Thach (1993) suggested a model where the indirect pathway provides a diffuse background inhibition of behavioral impulses, while the direct pathway gives a focused activation of the desired behavioral program. In this model, the basal ganglia play an important role in inhibiting potentially competing motor programs. This may be a general mechanism for action selection where ''the winner takes all,'' by facilitation of the strongest cortical signal and suppression of the rest (Kropotov & Etlinger, 1999). In other words, a mechanism for increasing the signal-to-noise ratio in both the motor and the cognitive system.

A key role in the basal ganglia is played by the dopamine projections from the *substantia nigra pars compacta* (SNc) to the striatum, modulating the activity of striatal neurons in a complex way. According to a simplified model, the striatal neurons forming the direct pathway mainly have *excitatory* D1-receptors, while the striatal neurons in the

[1] The output structures of the basal ganglia are the GPi and the *substantia nigra pars reticulata*(SNr), which have similar neurons and similar connections. In monkey it has been shown that the bulk of the output from the putamen passes through GPi, while the most of the pathways from the caudate nucleus pass through the SNr (Mink, 1996). In order to simplify the discussion will both GPi and SNr be referred to as *GPi*.

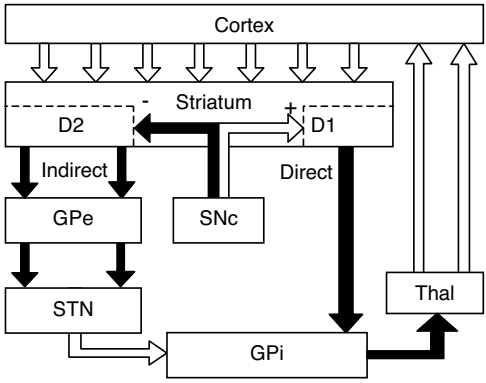

Fig. 1. Simplified diagram of basal ganglia-thalamocortical circuitry (motor circuit). White arrows are excitatory, black are inhibitory. GPe = external segment of globus pallidus; GPi = internal segment of globus pallidus; STN = subthalamic nucleus; SNc = substantia nigra pars compacta; Thal = thalamus. The striatum projects to the GPi by a direct and an indirect pathway. The activity in these pathways is modulated by dopamine from the SNc: D1-receptors activate the striatal neurons forming the direct pathway while D2-receptors inhibit the striatal neurons in the indirect pathway. Adapted from Mink and Thach (1993), Graybiel (2000), and DeLong (2000).

indirect pathway mainly have *inhibitory* D2-receptors. This means that increased release of dopamine would facilitate behavioral activation through the direct pathway. At the same time the increased release of dopamine inhibit the striatal neurons forming the indirect pathway, resulting in loss of background inhibition of behavioral activity. In brief, an excessive release of dopamine would lead to general disinhibition of motor and other behavioral impulses. On the other hand, insufficient release of dopamine would lead to a general inhibition of movements and impulses. A well-regulated level of dopamine is therefore essential for the proper functioning of the basal ganglia circuits.

Dopamine also seems to be involved in basal ganglia learning processes, by strengthening or weakening the efficacy of corticostriatal synapses (Mink, 1996; Reynolds, Hyland, & Wickens, 2001). In this way the striatum may learn to respond in certain ways to certain patterns of cortical activation.

3. The rhythm effect, motor control, and timing

3.1. The rhythm effect

Execution of a complex motor sequence requires control of two main aspects: the spatial pattern of muscular activation and the exact timing of each submovement. One of the most effective ways for persons who stutter to instantly create fluency is to speak to the pace of a metronome, the so-called *rhythm effect*. This effect is reported to be independent of speech rate, with marked reduction of stuttering even at high speeds like 184 beats per minute (Van Riper, 1982). The rhythmic stimuli provide *external cues* for

the timing of each syllable. This phenomenon has a direct parallel in persons with Parkinson's disease, a disorder of basal ganglia functions due to reduced release of dopamine. In Parkinson's disease the ability to perform movement sequences is greatly improved by auditory or visual cues (Georgiou et al., 1993; Glickstein & Stein, 1991).

3.2. Internally versus externally cued movements

The difference between *externally* and *internally cued* movements is an important theme in motor control research (see, e.g. Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). Several studies indicate a dominant role of the SMA in internally cued movements, while the lateral premotor cortex (preMC) seems to play a key role in externally cued movements (Cunnington, Bradshaw, & Iansek, 1996). These two motor areas receive their main subcortical input from different sources: the SMA from the basal ganglia, and the preMC from the cerebellum (Strick, 1985). In Parkinson's disease, the basal ganglia-SMA system is dysfunctional, while the cerebellar-preMC system seems to be preserved (Haslinger et al., 2001). Additional support for this location of functions comes from experimental lesions in monkeys. Impaired ability for self-initiated movements but preserved ability for externally cued movements have been observed after bilateral lesions of the putamen (Nixon & Passingham, 1998), the medial SMA, or the anterior cingulate cortex (Thaler, Chen, Nixon, Stern, & Passingham, 1995). Lesions of the preMC did not result in this type of impairment (Thaler et al., 1995). Investigation of externally cued movements in Parkinson's disease suggests that the external cues facilitate movements through the cerebellar-preMC system (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999), thereby bypassing the dysfunctional basal ganglia (Glickstein & Stein, 1991) and the SMA (Cunnington, Iansek, Bradshaw, & Phillips, 1995). This is supported by a study of Penhune, Zattore, and Evans (1998) indicating that the cerebellum plays an important role in extracting temporal information from sensory stimuli.

Cunnington et al. (1996) suggested that the SMA is especially involved in self-initiated, well-learned, complex, and sequential movements, and that the functions of the SMA are more closely related to the timing of movements than to the spatial programming. These types of function suggest an important role for the SMA in speech. Furthermore, Cunnington et al. proposed that the basal ganglia, via the SMA, provide *internal timing cues* to facilitate the initiation of the submovements in a well-learned motor sequence. This model presents a possible mechanism for the rhythm effect in stuttering: that external timing cues compensate for deficient internal cues from the basal ganglia to the SMA. The idea that stuttering is a disorder of motor timing is not new. It was the core in the reasoning of Van Riper (1982), and this line has been continued by Kent (1984), Caruso (1991), and others.

3.3. Chorus speech

Most persons who stutter show no dysfluencies when reading in unison with somebody else (Van Riper, 1982). It seems likely that the mechanism behind this effect is similar to

the rhythm effect. In chorus reading, the voice of the other person provides external timing cues, a timing pattern that is possible to follow.

3.4. Song

Also singing creates instant fluency in most stuttering persons (Van Riper, 1982). Singing is the production of musical tones by means of the voice (Encyclopædia Britannica, 2003b). Music consists of several elements, but the one indispensable element in all music is rhythm; melody can not exist without rhythm (Encyclopædia Britannica, 2003a). Rhythm, in music, is the placement of sounds in time (Encyclopædia Britannica, 2003a). A conclusion is that during singing, the brain got to have an internal representation of the intended timing of each sound. This is a difference between speech and song: rhythm is not an indispensable element in speech. As discussed above, when a distinct rhythm is applied to speech, stuttering usually disappears (the rhythm effect). It seems reasonable to suppose that during singing, the internal representation of rhythm provides internal timing cues for the initiation of each syllable in a similar way as a metronome provides external timing cues. If this assumption is correct, the dramatic effect of singing to eliminate stuttering in most persons who stutter can be viewed as an indication of dysfunctional timing cues in stuttered speech.

That the mechanisms of cerebral control of singing differ from the control of speech has been shown by Jeffries, Fritz, and Braun (2003). Using PET brain imaging these authors compared the pattern of activation during speech with the pattern during song with words. Speech resulted mainly in left hemisphere activation, while singing was accompanied by widespread right hemisphere activation. An interesting finding was that speech resulted in increased activity in the left dorsal putamen (the basal ganglia motor circuit) while singing did not result in such activation of either left or right putamen. This result is well in line with the suggestion discussed above, that normal speech requires timing cues from (the left) basal ganglia system, while singing is based on a different strategy for timing of syllables, mainly involving right hemisphere structures.

A further indication for a common mechanism behind the effects of chorus reading and singing comes from the description of ‘‘psychogenic stuttering’’ by Deal (1982). It was reported that neither chorus speech nor singing had any effect on the stuttering in this case. These observations suggest the existence of stuttering-like syndromes with different causal mechanisms.

3.5. The effect of increased attention

Persons with stuttering are often able to speak fluently for a while if they change to a non-automatic way of speaking, like imitating a foreign accent or acting in a role (Bloodstein, 1995). In a similar way, persons with Parkinson’s disease can achieve improved motor ability without external cues, merely by being instructed to consciously attend to a particular aspect of the movement (Cunnington, Iansek, & Bradshaw, 1999). An interpretation of these observations is that structures outside the basal ganglia system, for example the preMC, have the ability to provide internal timing cues for movement sequences, but only during de-automatization of the movements.

3.6. Basal ganglia timing cues

3.6.1. Timing cues from the GP to the SMA

Studies of monkeys have shown that neurons in different parts of the globus pallidus (GP) signal just before the end of a submovement in a well-learned and predictable motor sequence. It has been proposed that this signal is an internal cue that is generated by the basal ganglia to mark the end of a component in a movement sequence. This signal would be appropriate to serve as a trigger for the SMA to switch to the next movement in the sequence (Brotchie, Iansek, & Horne, 1991; Mushiake & Strick, 1995). According to this model is the first segment of a movement sequence initiated by structures outside the basal ganglia (e.g. by the motor cortex). Then the basal ganglia provide cues for the initiation of the following segments in the sequence (Mink, 1996).

One may speculate whether this model can explain one of the main symptoms of stuttering, namely repetitions of the first sound or syllable of a word. In this case, the first component of the phrase would be initiated by structures outside the basal ganglia, but then the basal ganglia fails, for some reason, to produce a cue that marks the end of the first component. The result would be that the sequence breaks and the first component is repeated.

Marsden and Obeso (1994) proposed a model of motor cueing in which some neurons in the GPi increase their activity in order to suppress unwanted motor activity in the SMA, while other GPi neurons reduce their activity to release the wanted motor action. This model suggests a mechanism for the way in which impaired generation of timing cues might at the same time lead to the release of dysfunctional motor activity and the absence of the desired motor activation. This combination of simultaneous releasing and inhibiting cues can be generated as a result of the focused versus diffuse projections of the direct and the indirect pathways, as discussed in Section 2.

3.6.2. Cueing and signal-to-noise ratio in the direct and indirect pathways

A prerequisite for a proper function of the suggested shift-cues from the basal ganglia to the SMA is that there is sufficient contrast between the releasing cue and the surrounding inhibition, both from a spatial and a temporal viewpoint. The spatial aspect is related to the contrast between the focal activation from the direct pathway and the background inhibition from the indirect pathway. The temporal aspect refers to the contrast between the amplitude of the cue and the baseline level of activation in the direct pathway, before and after the cue. These contrasts can also be viewed as signal-to-noise ratios.

It is likely that there are a large number of ways in which these signal-to-noise ratios may be compromised, for example by floor- or ceiling-effects, both in the spatial and temporal aspects. It may be speculated that all types of reduced signal-to-noise ratio in these circuits might lead to disturbed function of the shift-cues, but probably with some differences in symptomatology. Reduced signal-to-noise ratio due to a ceiling-effect might be expected to result in a general disinhibition of motor impulses, while a floor-effect might result in shift-problems without accessory involuntary movements. The underlying pathology may be of various types, from lesions to imbalance in basal ganglia receptor systems.

3.6.3. Cueing and the TANs

It seems likely that these learned movement cues from the basal ganglia are dependent on the functions of certain interneurons in the striatum, "*Tonically active neurons*" (TANs). The TANs are thought to be cholinergic interneurons, with the ability to modulate both projection neurons and interneurons in the striatum (Blazquez, Fujii, Kojima, & Graybiel, 2002). They differ from other neurons in the striatum by having a high (tonic) firing rate at rest. What make the TANs especially interesting is that they show signals related to the learning of behavioral responses, and that these signals are very widely dispersed and temporally coordinated through the striatum (Graybiel, Aosaki, Flaherty, & Kimura, 1994). This puts them in a position to serve an integrative and synchronizing function, important for the timing of movements.

This integrative function is important since the motor circuits through the putamen are somatotopically organized in parallel, and mainly segregated (Alexander et al., 1990; Jaeger, Kita, & Wilson, 1994). To coordinate the activity in different muscles these segregated circuits must be synchronized. It has been suggested that the TANs are involved in this type of motor binding (Blazquez et al., 2002; Graybiel et al., 1994). Another type of neurons that may be involved in striatal synchronization is a small population of GABAergic interneurons which are connected by electrotonic synapses and have the ability to block a large number of projection neurons simultaneously (Koos & Tepper, 1999).

3.6.4. Cueing as an effect of practice

The responses in the TANs and in the GP neurons grow stronger and more well-defined after practice of a certain behavior (Brotchie et al., 1991; Graybiel et al., 1994). If stuttering is related to impaired cueing from these neurons, stuttering would be expected to decrease after practice of a certain speech sequence. Indeed, this seems to be the case: firstly, the so-called *adaptation effect* shows that the frequency of stuttering tends to decrease if the same text is read several times (Wingate, 1986). Secondly, the more frequently a word occurs in the language, the smaller is the probability of stuttering (Bloodstein, 1995; Dayalu, Kalinowski, Stuart, Holbert, & Rastatter, 2002). Increased practice of a certain sequence may lead to stronger cues from the basal ganglia and reduction of the stuttering.

4. "Neurogenic" stuttering

4.1. The relation between "neurogenic" and "developmental" stuttering

One way to get information about which structures that may be involved in stuttering is to analyze the rare cases of stuttering with adult onset after brain lesions, called *neurogenic* or *acquired* stuttering. Neurogenic stuttering shows both similarities and differences compared with developmental stuttering (Ringo & Dietrich, 1995). Some cases of neurogenic stuttering seem to be indistinguishable from developmental stuttering (Lebrun, Leleux, Rousseau, & Devreux, 1983; Van Borsel & Taillieu, 2001).

The published reports indicate that the dominant feature of neurogenic stuttering is repetitions of sounds or syllables, sometimes in conjunction with prolongations of sounds.

Blocks are less frequently reported. Nevertheless, Heuer, Sataloff, Mandel, and Travers (1996) reported one case of stuttering after lesion in the left putamen, showing blocks, frequent use of filler sounds (e.g. ''uh''), aversion of eye gaze, and eye closing during speech blocks. Andy and Bhatnagar (1992) described cases of neurogenic stuttering with spasmodic blocks at word initial position, but without any accessory behaviors such as facial grimaces or limb movements. In summary, blocks with struggle seem to be less common in neurogenic stuttering, but there appears to be no sharp divide between developmental and neurogenic stuttering. Neurogenic stuttering might be more or less similar to developmental stuttering depending on the location of the lesion.

Also childhood stuttering can be caused by cerebral lesions. In a group of 313 persons with known lesions during childhood but with normal intelligence, Bohme (1968) found that 24% stuttered.

4.2. Localization of lesions in neurogenic stuttering

4.2.1. Problems of localization

Neurogenic stuttering has been reported after lesions to almost all parts of the brain, except the occipital lobe (Van Borsel, Van Der Made, & Santens, 2003). The exact location of the lesions in neurogenic stuttering has often been uncertain, especially in older reports and in cases with diffuse lesions. At the same time, it is almost impossible to exclude the existence of small undetected lesions. This means that single cases which are reported to have lesions in structures seemingly unrelated to theories of neural functions in stuttering have little explanatory value. Another problem is that lesions in one structure may disrupt functions of other structures.

4.2.2. Lesions of the basal ganglia-thalamocortical circuit?

Do the published cases of neurogenic stuttering indicate involvement of the basal ganglia-thalamocortical motor circuit? This circuit consists of the putamen (striatum), globus pallidus, ventrolateral (VL) thalamus (Parent, 1996), and cortical motor areas like the SMA. Indeed, a large proportion of the best documented cases had lesions of these structures. Ludlow et al. (1987) investigated 10 cases of neurogenic stuttering caused by missile wounds to the brain in wartime. The sites of lesions in this group were compared with the sites of lesions in a group of persons with missile wounds to the brain, but without speech problems. The only gray matter structures that were significantly more frequently affected in the stuttering group were the striatum and the globus pallidus. In 10 persons with stuttering, 8 had lesions of these structures. The left putamen was lesioned in the case reported by Kono, Hirano, Ueda, and Nakajima (1998), in one of three cases reported by Heuer et al. (1996), and in two of three cases reported by Ciabarra, Elkind, Roberts, and Marshall (2000). Cases of neurogenic stuttering with lesion of the left thalamus have been reported by Van Borsel et al. (2003) (the VL nucleus), and by Heuer et al. (1996). Further, stuttering after lesions in the SMA was described by Van Borsel, Van Lierde, Van Cauwenberge, Guldemont, and Van Orshoven (1998), Ackermann, Hertrich, Ziegler, and Bitzer (1996), and by Nagafuchi and Takahashi (1989, as cited in Abe, Yokoyama, & Yorifuji, 1993). Further support for involvement of the basal ganglia-thalamocortical motor circuit comes from studies of stimulation of brain regions

during surgery with awake patients. Ojemann and Ward (1971) studied the effect of stimulation of the left VL thalamus during surgery. The authors report that stimulation of some points in the VL nucleus resulted in repetition of the first syllable of words. In a similar way Penfield and Welch (1951) investigated the responses from stimulation of the SMA. They found places in the SMA where stimulation elicited repetition of the first syllable of words.

In summary, it seems clear that lesions of the basal ganglia-thalamocortical motor circuit are a frequent cause of neurogenic stuttering. It is, however, very difficult to estimate the portion of the cases with neurogenic stuttering that is related to basal ganglia dysfunction.

4.2.3. Lateralization of lesions

Most cases of neurogenic stuttering are reported after lesions to the left hemisphere, only a few reports of neurogenic stuttering after right side lesions have been published, for example by Lebrun, Leleux, and Retif (1987) and by Ludlow, Rosenberg, Salazar, Grafman, and Smutok (1987). Furthermore, some of these cases might have had undetected left hemisphere lesions causing the stuttering. In summary, left hemisphere lesions constitute the bulk of the published cases of neurogenic stuttering, but it seems that also right side lesions may have this effect.

4.3. The putamen is influenced by the CM nucleus in the thalamus

As discussed in Section 3.6.3, the TANs in the putamen may play a key role in the generation of movement related cues from the basal ganglia. It has been found that the learned responses of the TANs in the putamen are almost abolished after inactivation of the *centremedian nucleus* (CM) in the thalamus (Matsumoto, Minamimoto, Graybiel, & Kimura, 2001). The CM nucleus is among the largest thalamic nuclei in humans. Its main projections innervate the entire sensorimotor parts of the striatum (approximately covering the putamen) (Parent, 1996). An interesting coincidence is that the CM nucleus has been reported to be involved in some cases of stuttering.

Andy and Bhatnagar (1992) reported four patients with neurogenic stuttering who were treated with stimulation of the left CM nucleus for relief of chronic pain. The treatment resulted in almost total relief of the stuttering. What could be the mechanism behind this effect? All cases showed pathologic electrical discharges in the left thalamus (not seen in the scalp EEG). The authors suggested that the discharges emanated from low-threshold neurons, which were inactivated by the low-level stimulation. Their hypothesis was supported by the observation that mechanical perturbation of the CM nucleus during surgery of a non-stuttering person elicited electrical discharges and stuttering, consisting of repetitions of the first syllable (Andy & Bhatnagar, 1991). One of the cases with acquired stuttering was tested for chorus reading, which made the speech normal. This suggests that the stuttering was related to defective internal cues, so that the speech was normalized by external timing cues from the voice of another person. Further, these cases showed no adaptation effect, which indicates that the cueing function was not improved by practice. Interestingly, none of them developed concomitant symptoms like facial grimaces, limb movements, or anxiety related to stuttering. All four cases had repetitions of sounds, syllables, or words, and hesitations. Two of them exhibited prolongations of sounds.

The stuttering occurred predominantly at word initial position. In summary, these data are in accord with a model where the neurogenic stuttering was caused by pathologic signals from the CM nucleus to the putamen, resulting in a disturbing effect on the TANs and the internal cueing process.

Abe et al. (1993) described a related case, with onset of stuttering after infarction involving the left CM nucleus. The stuttering consisted of repetitions of the first syllable in words. A possible interpretation is that the destruction of the CM nucleus resulted in inactivation of the TANs in the putamen, as described by Matsumoto et al. (2001), with disturbance of the cueing function.

4.4. Summary

The lesion research suggests that the basal ganglia circuits through the putamen may play an important role in many cases of neurogenic stuttering. Lesions causing stuttering are usually located in the left hemispheres.

5. Imaging of brain activation in stuttering

In relation to the theme of this paper two main questions may be asked regarding imaging of cerebral activation: Do brain imaging data indicate (a) abnormalities in the basal ganglia in persons who stutter, and (b) activation that might compensate for basal ganglia dysfunctions? Another aspect is that brain imaging in stuttering has often been related to the hypothesis that stuttering is caused by anomalous cerebral lateralization (the *cerebral dominance theory*, Travis, 1978), and that right hemisphere activity may disrupt left hemisphere control of speech.

5.1. Abnormalities in the basal ganglia?

Wu et al. (1995) reported low striatal metabolism in a PET study of four persons who stuttered. This reduction of metabolism has not, however, been found in other PET studies. A possible cause of different results in different studies might be that the stuttering population consists of subtypes, which could exert a strong influence on the results of studies with a small number of participants. In another PET study, Fox et al. (1996) found increased activation in the left globus pallidus during reading with stuttering, compared with fluent reading in controls. The interpretation of PET-activation in the basal ganglia is, however, quite difficult. The intrinsic circuits of the basal ganglia are very complex, and so is the relation between metabolism and signaling in the basal ganglia structures (Jueptner & Weiller, 1995; Lauritzen, 2001; Waldvogel et al., 2000).

5.2. Activation compensating for deficient speech automaticity?

If stuttering is related to a dysfunction of automatization of speech it may be expected that persons who stutter will show increased cerebral activation due to compensatory

strategies, like increased conscious control of speech initiation. Which pattern of brain activation is related to non-automatic self-initiated movements? Jenkins et al. (2000) used brain imaging (PET) to investigate activation elicited by self-initiated and irregularly paced movements with the right index finger, in normal persons. Compared to rest, the results showed widespread bilateral activation (e.g. in the lateral premotor cortex, SMA, and the anterior cingulate cortex) with slight right hemisphere dominance in most regions, even though it was the *right* index finger that was moved. Increased right hemisphere activation is a very frequent finding in research on stuttering (De Nil, 1999).

Two of the areas with right hemisphere dominance that were activated by finger movements in Jenkins et al. (2000) were the insula and the supramarginal gyrus (BA 40). In a PET study of stuttering Braun et al. (1997) calculated correlations between individual variations of speech fluency (based on 2-s periods) and brain activation. It was found that the activation of these structures (the right insula and the right supramarginal gyrus) correlated with increased fluency ($r = 0.7$ and 0.52, respectively). De Nil, Kroll, Kapur, and Houle (2000) reported increased activation of these two regions, with right side dominance, during oral reading compared with silent reading, in persons who stutter. This increased activation during reading with stuttering suggests that the correlations between increased fluency and activation in these regions (Braun et al.) were not an effect of *de-activation* during stuttering, but rather an effect of *activation* during fluent periods of speech. Activation of the insula was also found by Fox et al. (1996), but in this study the activation was bilateral. In summary, the reviewed results support the suggestion that the right insula and the right supramarginal gyrus were activated as parts of a non-automatic compensatory system that decreased stuttering. This interpretation was also suggested by Braun et al. (1997). Other cortical areas correlating with increased fluency in the study by Braun et al. were the right frontal operculum (BA 45 and 47) and the right inferior somatosensory cortex (BA 1, 2, 3, and 43).

In the discussion of the rhythm effect (see Section 3.2), it was suggested that the lateral premotor cortex and the cerebellum form a system that compensates for dysfunctions in the basal ganglia-SMA system. For example, that external cues facilitate movements in Parkinson's disease through this cerebellar-preMC system (Hanakawa et al., 1999). Fox et al. (1996) found strong bilateral activation of the cerebellum in a PET-study of persons who stutter, both during stuttering and fluent chorus speech. The finding of increased cerebellar activity during stuttering is supported by Braun et al. (1997) (bilateral activation), and De Nil et al. (2000) (right side activation). Fox et al. also found strong activation of the right superior lateral preMC, and De Nil et al., similarly, reported right hemisphere activation of lateral preMC regions (BA 6 and 44). It seems quite possible that this cerebellar and preMC activation reflects attempts to compensate for dysfunctions in the basal ganglia system.

Another finding that may be an expression of compensatory activity is the strong increased SMA activation, with right side dominance, during stuttered speech, reported by Fox et al. (1996) and Ingham, Fox, Costello, and Zamarripa (2000). If the core problem in stuttering is that the basal ganglia fail to provide sufficient timing cues to the SMA, then it might be the case that the SMA gets increased activation as a consequence of the need for compensatory processing.

5.3. Lateralization and stuttering

A conclusion from the review above is that observations of increased right hemisphere activation during speech in persons who stutter are likely to reflect, at least partly, compensatory neural activity. This explanation does not, however, apply to results indicating anomalous lateralization of other functions in persons who stutter, such as perception of language. Examples of this are studies with dichotic listening (Curry & Gregory, 1969) and tachistoscopic viewing (Hand & Haynes, 1983; Moore, 1976). Nevertheless, it is still possible that these observations represents an epiphenomenon: If stuttering often is related to subtle non-specific left hemisphere dysfunctions, the stuttering population would tend, on average, to show reduced left side dominance for all functions which normally have left side lateralization, such as perception of language.

Another problem with the cerebral dominance theory of stuttering is, as pointed out by Ingham (2001), that females tend to show less left hemisphere dominance than males, but stuttering is clearly more common in males. In summary, the arguments for the cerebral dominance theory of stuttering do not seem convincing.

6. Stuttering and dopamine

6.1. Dopaminergic drugs and stuttering

Beginning in the 1950s, dopaminergic drugs were tested for the treatment of stuttering, mostly using dopamine blockers but also stimulants. The rationale for trying dopamine blockers was that they were considered as tranquilizers (Kent, 1963).

6.1.1. Stuttering and D2-receptor blockade

The drug that has been most thoroughly tested for treatment of stuttering is the D2-blocker haloperidol. Gattuso and Leocata (1962) claimed very favorable results in children. Since then at least nine controlled studies have been made with haloperidol and stuttering (see Brady, 1991, for a review), with generally positive results in some of the subjects. The drug seems to exert its main effect on the severity of stuttering behavior and not so much on the frequency of stuttering. In a few cases, the improvement was reported to have been dramatic (Healy, 1974), but in most cases the experience of side effects or merely slight improvement led to termination of treatment. Brady (1991) suggested that haloperidol is more effective in the treatment of stuttering than most other neuroleptics due to its high specificity for D2-receptors.

The model of basal ganglia function presented in the introduction above suggests a possible mechanism of action: D2-receptors are mostly located on the striatal neurons forming the indirect pathway. Blockade of these inhibitory receptors will lead to increased activity of the indirect pathway, thereby strengthening the diffuse inhibition of motor activity. This explanation is in accordance with the observation that haloperidol exerts its main effect in reducing superfluous motor activation during stuttering, not in reducing the number of disruptions. This also means that D2 blockade might lead to improvement even if the superfluous motor activity is caused by some other factor than D2 hyperactivity.

6.1.2. Stuttering and stimulants—the possibility of subgroups

Also stimulant drugs, stimulating dopamine and norepinephrine, have been found to reduce stuttering in some cases. Fish and Bowling (1962) reported a case of dramatic reduction of stuttering while taking amphetamine for weight reduction, the improvement persisting also after medication was discontinued. They conducted a double blind trial with amphetamine in 22 persons with stuttering and mental retardation. In the treatment group, 5 out of 11 persons improved, while only 1 out of 11 in the placebo group improved. In three of the improved cases the improvement was claimed to be so great that their whole course in life was changed, and that the improvement obtained by 3 months of treatment was maintained, with only occasional medication for one patient.

Later Fish and Bowling (1965) investigated if persons with stuttering and mental retardation, who did not improve on amphetamine, instead would improve on a D2-receptor blocker. Of 28 persons with stuttering, 14 improved on amphetamine while two deteriorated. The D2-blocker led to improvement in 8 out of 12 persons who did not improve on amphetamine. Only 4 out of 26 did not improve on any of the medications (and they were not improved by a combination of the drugs).

A similar study was reported by Langova and Moravek (1964), using a single dose of the stimulant phenmetrazine (proprietary name Preludin, which has effects similar to amphetamine) and long-term administration of the D2-blocker chlorpromazine. The participators were divided into ''stuttering'' ($N = 17$ for the stimulant trial and $N = 12$ for the D2-blocker trial), ''cluttering'' ($N = 8$ and 13), and ''stuttering-cluttering'' groups ($N = 11$). In summary, 88% of the persons with ''stuttering'' were regarded as improved by the stimulant, none getting worse. On the other hand, 67% got worse on the D2-blocker and none got better. In contrast, the persons with stuttering-cluttering or cluttering showed the opposite tendencies: 79% got worse on the stimulant and none got better, while 79% got better on the D2-blocker and only 4% got worse. The reported subjective feelings also differed between the groups. The persons with cluttering tended to feel tense and uneasy on the stimulant and more tranquil on the D2-blocker. The ''stuttering'' persons tended to report the reverse, namely unpleasant feelings while being treated with the D2-blocker and pleasant and more harmonious feelings with the stimulant.

The results of this study suggest the existence of two neurochemically different subgroups of stuttering, ''stimulant responsive'' and ''D2-blocker responsive,'' relating to the suggested dichotomy between ''stuttering'' and ''stuttering-cluttering.'' Unfortunately, this type of study has not been replicated. However, the figures in Fish and Bowling (1965) and Langova and Moravek (1964) are similar if the stuttering and stuttering-cluttering groups are merged: about half of the persons with stuttering were improved on stimulants and about one third were improved by D2-blockers.

One problem with the study by Langova and Moravek (1964) is that the concept of ''stuttering-cluttering'' seems to be unsubstantiated by published research, and that the criteria for this diagnosis are not clear. Daly (1996) described stuttering-cluttering as a disorder with significant characteristics of both stuttering and cluttering, pertaining not only to speech but also to symptoms of behavior, motor functions, and language. Daly lists for example the following traits as frequent among persons with cluttering: language delay, misarticulation, motor problems, attention deficits, impatient listening, impulsivity,

and carelessness. Persons with stuttering without cluttering are reported to have for example the following typical traits: tense pauses in speech, being fearful and anxious about speech, using starter sounds and word substitutions, showing more stuttering under pressure, and having fluent episodes. Daly's description seems to roughly fit Van Riper's (1982) characterization of developmental tracks in stuttering: tracks I and III corresponding to ''stuttering'' and track II corresponding to ''stuttering-cluttering.'' According to Daly about 40% of the persons who stutter may be classified into the stuttering-cluttering group. In contrast, a study of 2628 stuttering school children, based on reports from speech-language pathologists, found cluttering in only 0.7% of the children (Blood, Ridenour, Qualls, & Hammer, 2003). It seems clear that different criteria for the diagnosis of cluttering have been used. There is an obvious need for further research to clarify these aspects, and to investigate the possibility of two pharmacologically distinct subgroups.

In interviews with three adults who stutter the author of this paper has obtained personal reports of the effects of various drugs on stuttering, supporting the importance of complex neurochemical factors as well as supporting the heterogeneity in responses. In all these cases the drugs were used for recreational purposes, for short periods of time. The first case claimed that his stuttering made him almost mute when using marijuana, which at the same time improved his creativity. On the other hand, alcohol was said to make his speech almost normal, with deterioration afterwards. He noticed no difference in his speech when trying amphetamine. The second case reported clearly reduced stuttering during use of amphetamine. The third case, with severe stuttering, told how when trying ecstasy (MDMA) twice he spoke fluently for some hours, also according to his friends. Amphetamine did not affect his speech.

The claim of the effect of ecstasy on stuttering is especially interesting in the context of basal ganglia functions, since a case of remarkable improvement of motor symptoms in Parkinson's disease has been reported in the media (BBC Horizon, 2001). This anti-parkinsonian effect of ecstasy has been confirmed in studies of primates (Iravani, Jackson, Kuoppamaki, Smith, & Jenner, 2003). Investigations of this effect of ecstasy points to a serotonergic mechanism, indirectly modulating the dopamine system. The exact mechanism is still not known, but an agonist effect on serotonin receptor subtype 5-HT1a or 1b is suggested (Iravani et al.). It is interesting to note that the anti-parkinsonian effect in primates was fully blocked by the selective serotonin reuptake inhibitor (SSRI) fluvoxamine (Iravani et al.).

Ecstasy is not suitable for the treatment of stuttering, because of a suspected risk that it might induce Parkinson's disease (Kuniyoshi & Jankovic, 2003) and because of the risk of misuse and addiction. However, the possibility of influencing dopamine functions and basal ganglia motor symptoms through serotonergic mechanisms is interesting. Effects of other serotonergic drugs have been reported in stuttering, especially for the SSRI paroxetine (see, e.g. Boldrini, Rossi, & Placidi, 2003; Costa & Kroll, 2000; Schreiber & Pick, 1997). The author of this paper has interviewed a stuttering man who experienced long-lasting and clear improvement of speech on paroxetine, after about 3 weeks. When he stopped and restarted medication the stuttering changed accordingly. He claimed that another SSRI, citalopram, did not improve speech. There are indications of subtle differences in pharmacological effects between different SSRIs, and that paroxetine shows

similarities with agonists for the 5-HT1a receptor (Sokolowski & Seiden, 1999). As discussed above, an agonist effect on the 5-HT1a receptor has also been suggested for ecstasy (Iravani et al., 2003). It is possible that paroxetine and ecstasy affect stuttering through the same pathway.

In this context it should be mentioned that severe psychiatric withdrawal symptoms, with hypomania, irritability, and intrusive thoughts, has been reported for two stuttering men after discontinuing high-dose (50 mg) paroxetine treatment (Bloch, Stager, Braun, & Rubinow, 1995). This risk should be considered if trying paroxetine. If withdrawal symptoms occur the dose should be tapered slowly. The studies reporting an effect of paroxetine on stuttering used a lower dose, usually 20 mg.

6.1.3. Drug-induced stuttering

Some cases of drug-induced stuttering can be found in the literature. Burd and Kerbeshian (1991) reported a case of a 3-year-old girl who was treated for hyperactivity. Stimulants resulted in stuttering that disappeared on discontinuation of the drugs. Interestingly, the medications had no effect on the hyperactivity. Also D2-blockers have been reported to induce stuttering (Brady, 1998). This is in line with the results reported above, that both stimulants and D2-blockers can make stuttering worse, but in different subgroups.

6.2. Stuttering and FDOPA-PET

One of the most remarkable reports in the research on stuttering comes from a brain imaging study using FDOPA-PET, by Wu et al. (1997). FDOPA is a precursor of dopamine, intended to measure the rate of dopamine synthesis in the brain (Barrio, Huang, & Phelps, 1997). The persons who stuttered showed about three times higher uptake of FDOPA in many parts of the brain, compared with the controls. The study is limited by the small number of participants, three persons who stuttered, but even so the result was statistically significant.

How can this result be interpreted? If the measurements are correct they imply that at least a substantial subgroup of persons who stutter have a deviant dopamine system. The results of the treatment trial by Langova and Moravek (1964), discussed above, suggests the existence of biochemically different subgroups. It may well be the case that the result of this study of FDOPA represents only one of these subgroups.

6.3. Temperament and motor activity

6.3.1. Temperamental and gross motor effects of dopamine

If stuttering is related to deviations in dopamine functions, are there any indications of this in gross motor activity or in temperament? Motor effects of dopamine have been demonstrated in mice lacking the gene for the dopamine reuptake transporter. These mice have a raised level of dopamine in the synaptic cleft and are very hyperactive (Giros, Jaber, Jones, Wightman, & Caron, 1996). Cocaine acts in the same way, blocking the reuptake of dopamine. At moderate doses some of the effects of cocaine are motor excitement, talkativeness, mood amplification (both euphoria and dysphoria), and heightened energy.

Higher doses may result in motor stereotypes, irritability or anxiety (Feldman, Meyer, & Quenzer, 1997). In research on personality differences high dopamine activation is mainly related to traits like behavioral activation and impulsive sensation seeking (Depue & Collins, 1999; Pickering & Gray, 1999), but a relation to increased anxiety and neuroticism has also been suggested (Derryberry & Reed, 1999).

In summary, dopamine seems to have an activating effect, both motor and temperamental, but might also, at higher levels, increase anxiety. This is in accord with the model of basal ganglia function presented in the introduction: dopamine facilitates motor, cognitive and limbic impulses. It is possible that high dopamine activation can lead to increased responsiveness to both rewarding and threatening stimuli.

6.3.2. Temperamental and gross motor tendencies in stuttering

Comings et al. (1996) investigated the effects of different variants of dopamine-related genes in persons with Tourette syndrome, their relatives, and in controls. A variant of the D2-receptor gene was significantly related to increased frequency of stuttering, mania, ADHD, tics, and obsessive-compulsive disorder. The relationships were weak, although statistically significant.

Embrechts, Ebben, Franke, and van de Poel (2000) studied the temperament of 38 stuttering and 38 non-stuttering children aged 3–7 years. Temperament was evaluated by a questionnaire to the caregivers. The result showed that the stuttering group had a significantly higher level of gross motor activity and of impulsivity, and significantly lower attentional focusing, inhibitory control (capacity to suppress inappropriate approach responses), and perceptual sensitivity (detection of low intensity stimuli). It is also interesting to note that the stuttering group had *lower* scores in shyness, fear and sadness, though not significantly lower. The largest group difference was in gross motor activity level.

Oyler (1994) investigated the personality of 25 stuttering and 25 non-stuttering children aged 7–12 years. She reported higher ''sensitivity'' in the stuttering group. Other significant differences were higher frequency of problems of learning, language, attention and motor coordination, and higher frequency of family history of problems with language, attention, and hyperactivity.

In summary, the results above repeatedly suggest increased behavioral activation in persons with stuttering, both motor and temperamental. This is in line with the effects of high dopamine activation but other causes are quite possible. The results also show the main symptoms of attentional deficit hyperactivity disorder (ADHD) (Schachar & Tannock, 2002). As discussed above, traits like motor hyperactivity, attention deficits, and impulsivity seem to be typical of persons with ''stuttering-cluttering'' but not of persons with ''pure stuttering'': the traits of ADHD might be limited to this stuttering-cluttering subgroup. This points to the importance of considering subgroups and not only looking at the overall mean.

6.4. Stuttering and ADHD

Is stuttering frequent in persons with ADHD? Biederman et al. (1993) reported 13% lifetime incidence of stuttering in a group of 120 adults with ADHD, compared with 2% in

controls. A group of 140 children with ADHD (mean age 10.5 years) had only a 3.6% incidence of stuttering. The result of this study suggests that stuttering and ADHD do not have a strong relation in childhood, and that ADHD combined with stuttering tends to be more persistent than ADHD in general, resulting in a higher lifetime incidence of stuttering in adults with ADHD.

There are some indications that ADHD with stuttering may be neurochemically different from most cases of ADHD. About 74% of adults with ADHD tend to improve on stimulants (Faraone et al., 2000), while Langova and Moravek (1964) found that 79% of persons with stuttering-cluttering or cluttering (who often seem to have traits of ADHD) got worse on a stimulant, and none got better. Burd and Kerbeshian (1991) described a hyperactive child who got transient stuttering as a side-effect of stimulants, but no improvement in the hyperactivity. However, this pattern may not be consistent, since anecdotal information suggests that some cases with ADHD and stuttering are treated successfully with stimulants.

Another question is if the increased behavioral activation shown by some cases of stuttering should be regarded as a type of ADHD or a type of ''hypomania.'' Brody (2001) suggests that ADHD and mania (or hypomania) are confounded in most existing research. Brody considers impairment of executive functions to be a characteristic of ADHD, but not of mania.

6.5. Is stuttering a motor stereotypy?

Stereotypy (repetitive behavior patterns) is a feature of many neurologic and psychiatric disorders. It can range from repetition of single movements to complex behaviors or cognitive stereotypes like in obsessive-compulsive disorder. The basal ganglia are suggested to be central for the expression of stereotypes, and motor stereotypes can be induced by dopamine stimulating drugs (Canales & Graybiel, 2000).

An important objection may be raised against a suggestion of stuttering as a stereotypy: Stereotypic repetitions seem to be, at least partly, based on some type of drive to execute the behavior (Graybiel, Canales, & Capper-Loup, 2000). In stuttering there is hardly any ground for suspecting that the repetitions are based on a drive to repeat that specific segment. Instead it is more reasonable to suppose that the repetitions are merely the result of an inability to continue to the next segment in the sequence. An observation supporting this contention is that persons with stuttering normally do not repeat the final segment of a phrase (Bloodstein, 1995; Rosenbek, Messert, Collins, & Wertz, 1978).

Nevertheless, there may be a subgroup of persons with ''stuttering'' who really do show a stereotypic speech disorder. These are the rare cases which Van Riper (1982) refers to as stuttering *track IV.* Van Riper described their stuttering as highly stereotyped, almost deliberate. A characteristic feature is lengthy repetitions of words already spoken normally. Few signs of avoidance or fear are shown. The speech repetitions are often accompanied by other symptoms like stereotyped postures, grunting, biting, or tongue protrusion. The diagnosis Tourette syndrome with palilalia (Bruun, Cohen, & Leckman, 1984; Graybiel & Canales, 2001) seems to fit well with the characteristics of this group. Tourette syndrome is a neuropsychiatric syndrome characterized by complex

tics. The pathophysiology most likely involves the caudate nucleus in the basal ganglia (Wolf et al., 1996).

6.6. Stuttering, emotions, and learning

6.6.1. Emotions and basal ganglia disorders

It is a common clinical experience that stuttering is influenced by emotional reactions and stress. This aspect is well compatible with the model of stuttering as a basal ganglia disorder. Victor and Ropper (2001) write in a textbook of neurology that ''Stress and nervous tension characteristically worsen both the motor deficiency and the abnormal movements in all extrapyramidal [basal ganglia] syndromes, just as relaxation improves them'' (p. 75).

6.6.2. Emotional variations in dopamine release?

The dopamine neurons in the substantia nigra pars compacta (SNc) project to the striatum, providing a dense dopaminergic input. Normally these neurons have a tonic firing rate, providing a low, well-regulated, extracellular level of dopamine (Schultz, 1998). An interesting aspect is that the dopamine neurons have been found to show rapid variations of their firing rate according to the situation. Increased release of dopamine in the striatum has been shown to strengthen active synapses between cortical and striatal neurons, and to facilitate learning of behaviors (Reynolds et al., 2001). However, the pattern and functional consequences of these ''phasic'' variations of dopamine are still a matter of debate.

The *reward prediction error model* (Schultz, 1998) states that the dopamine neurons vary their firing rate in relation to *prediction of rewards*. Events that are more rewarding than predicted will increase the release of dopamine, while omission of a predicted reward will lead to reduction of dopamine release (Schultz & Dickinson, 2000). These error-related responses of the dopamine neurons would make them suited to constitute a teaching signal for learning of behavioral responses (Waelti, Dickinson, & Schultz, 2001), with strengthening of behaviors that were more rewarding than predicted and weakening of behaviors that failed to produce the predicted reward. This model of dopamine variation might be relevant for automatization of speech motor patterns, since (a) reward-related variation in the dopamine release has been found in the putamen (Schultz, 2000), which is the sensorimotor region of the striatum, and (b) simulation of a neural network indicates that the reward-related changes of dopamine release constitute an excellent teaching signal for learning of sequential movements (Suri & Schultz, 1998).

Such a mechanism would be of interest in relation to the development and treatment of stuttering. A negative emotional experience of stuttering could be described as an event that was less rewarding than predicted, thereby reducing dopamine release and weakening the motor program for the intended speech sequence that failed. This mechanism might result in a ''vicious circle,'' where negative experiences of stuttering lead to increased stuttering, etc. On the other hand, positive emotional experiences of a functional speech pattern would tend to strengthen the automaticity of this pattern.

The validity of this reward-prediction model has, however, been questioned, partly because it has been shown that also aversive and neutral stimuli may trigger phasic

dopamine release. An alternative model of dopamine functioning was described by Horvitz (2002). This model states that phasic increase of dopamine reflects salient unexpected events, regardless of whether they are rewarding, neutral, or aversive. Horvitz did not, however, rule out the possibility that future research may show that the reward-model suggested by Schultz is correct, since there are some indications that the nature of dopamine responses to rewards differs from dopamine responses to non-reward stimuli. Such a difference might result in different effects on the synapses in the striatum.

6.6.3. Emotional states, dopamine, and stuttering

It has been reported that some persons who stutter temporarily became ''almost magically fluent speakers'' when they fell in love, and that ''loving'' a vocation or a situation facilitates speech fluency (Starkweather, 1996). On the other hand, Mowrer (1998) reported the appearance and disappearance of stuttering in a 2.5-year-old boy in accordance with the appearance and disappearance of fearful events. Onset of stuttering in relation to emotional stress has been reported both in children (Sermas & Cox, 1982) and adults (Roth, Aronson, & Davis, 1989).

It might be speculated that this emotional influence is partly related to emotionally induced variations in the release of dopamine. It may be noteworthy that the learned responses in the TANs in the striatum have been found to be abolished after dopamine depletion, but are restored by a dopamine receptor agonist (apomorphine) (Aosaki, Graybiel, & Kimura, 1994). If some cases of stuttering are related to a sub-optimal level of synaptic dopamine, emotional events that affect the release of dopamine may have a direct effect on the severity of stuttering.

This suggestion is supported by a recent brain imaging study using a dopamine receptor ligand (Goerendt et al., 2003). The study indicated that release of dopamine in the striatum is involved in the execution of pre-learned movement sequences. The authors suggest that it is increased *tonic* release of dopamine, and not *phasic* release, that is important for facilitation of initiation and sequencing of movements. It seems possible that emotionally related suppression of dopamine release might impair the execution of automated sequential movements, like speech.

7. Stuttering and dystonia

7.1. Introduction

Similarities between stuttering and *dystonia* have been suggested by Kiziltan and Akalin (1996). The term dystonia signifies motor symptoms characterized by involuntary muscular contractions, often in the form of co-contractions where the agonist and the antagonist muscles are activated simultaneously, with spreading of contraction to adjacent muscles. Dystonia can affect a specific part of the body, like a hand or an eyelid (*focal dystonia*), or it can affect most parts of the body (Friedman & Standaert, 2001). In a similar way, many cases of stuttering also show excessive muscular tension in various parts of the body. For example, there are reports of co-contraction and inappropriate

tension in laryngeal adductor and abductor muscles in some cases of stuttering (Freeman, 1979; Freeman & Ushijima, 1978; Shapiro, 1980).

7.2. Dystonia and the basal ganglia

7.2.1. Dystonia and basal ganglia lesions

There are strong indications for a relationship between dystonia and basal ganglia dysfunction (Friedman & Standaert, 2001). Bhatia and Marsden (1994) studied the consequences of small isolated lesions of the putamen. In 15 out of 20 cases the main symptom was dystonia. Using magnetic resonance imaging (MRI) Rondot, Bathien, Tempier, and Fredy (2001) investigated the localization in 40 cases of dystonia with observable cerebral lesions. In 21 cases the location was the striatum, in 6 the globus pallidus, in 7 the thalamus, and in 6 the midbrain. All these locations are related to the basal ganglia circuits. In a study with transcranial ultrasound Naumann, Becker, Toyka, Supprian, and Reiners (1996) found that 44 out of 57 persons with idiopathic dystonia (cervical or generalized dystonia, or writer's cramp), showed increased signal in focal points in the putamen or in globus pallidus, contralateral to the affected muscles.

7.2.2. Dystonia and reduced inhibition of the cortex

Increased cortical, spinal and brain stem excitability has been reported in dystonia, and has been suggested to be consequences of basal ganglia disturbances (Chen, Wassermann, Canos, & Hallett, 1997). These results are in line with findings of reduced output from the globus pallidus pars interna (GPi) in dystonia (Vitek et al., 1999) which would result in reduced inhibition of the target structures. Reduced output from the GPi could, in turn, be the result of lesions of the putamen, according to the model presented in Fig. 1. Focal lesions of the putamen would result in loss of neurons in both the direct and indirect pathways, with loss of the background inhibition provided by the indirect pathway (reflected in reduced GPi output) and loss of the focal cues provided by the direct pathway. This may lead to a combination of difficulties to initiate segments in a movement sequence (due to loss of the direct pathway) and impaired inhibition of involuntary muscular contractions.

7.3. Dystonia and dopamine

Some cases of dystonia are related to the dopamine system, and, in parallel to the findings about stuttering discussed in Section 6.1.2, also dystonia seems to be a neurochemically heterogeneous disorder. Some cases are improved by L-dopa, increasing dopamine synthesis, and dystonia can also be an early symptom of Parkinson's disease (Perlmutter, Tempel, Black, Parkinson, & Todd, 1997). Other cases show amelioration by a dopamine-depleting and dopamine-receptor-blocking drug, tetrabenazine (Jankovic & Beach, 1997). Furthermore, both D2-blockers and L-dopa can cause acute dystonia as a side-effect (Victor & Ropper, 2001).

Another link between dystonia, dopamine and stuttering comes from genetic research on *torsion dystonia*. Early-onset torsion dystonia is a disorder characterized by dystonic movements and postures, which in most cases are caused by a single gene. About 30–40% of the carriers of the gene develop the disorder (Augood et al., 1998). Fletcher, Harding,

and Marsden (1991) reported that 8 out of 71 persons with torsion dystonia had a family history of stuttering, compared with only 1 person in the control group. The gene that causes torsion dystonia is mostly expressed in the substantia nigra pars compacta (Augood et al., 1998), which provides the dopaminergic innervation to the putamen. This implies a disturbance of dopamine function in the etiology of torsion dystonia. The high incidence of a family history of stuttering suggests that this dopaminergic dysfunction also increases the risk of stuttering.

7.4. Task-specificity

An interesting aspect of focal dystonia is that it often is task-specific, being present for example when a person is walking forward but not when walking backward or when dancing. Some types of dystonia have been called "occupational cramps," affecting highly automated sequential motor tasks like writing with a pen (*writer's cramp*), typing, playing a certain musical instrument, or using a telegraph. Victor and Ropper (2001) describe these disorders: "In each case a delicate motor skill, perfected by years of practice and performed almost automatically, suddenly comes to require a conscious and labored effort for its execution. Discrete movements are impaired by a spreading innervation of unneeded muscles . . ." (p. 116). This task-specificity, together with the observation that dystonia often gets worse under stress, has sometimes led to the incorrect conclusion that task-specific dystonia is psychogenic (Sheehy & Marsden, 1982). Also, stuttering tends to be highly task-specific: The apparent motor problems are limited to speech, and the symptoms are often reduced if changing to a non-automatic way of speaking, like using a foreign accent (Bloodstein, 1995).

7.5. Fast sequential movements—expansion of cortical maps and increased gain

7.5.1. Expansion of cortical maps

Task-specific dystonia especially affects certain types of behavior, like writing, typing, or playing the piano. The highest incidence, 14%, has been reported in telegraphists (Sheehy & Marsden, 1982). The affected behaviors tend to be sequential, fast, and well-learned. A reason why this type of behaviors tends to be affected by dystonia may be *cortical plasticity.* Byl, Merzenich, and Jenkins (1996) studied the effect of repeated stereotyped rapid hand movements (opening and closing of the hand) in two monkeys. During the test period (several months) both monkeys developed a movement control disorder. Electrophysiologic mapping of the primary sensory cortex showed *dedifferentiation* of cortical representations of the skin of the hands—the receptive fields were 10 to 20 times larger than normal. Many receptive fields extended across two or more digits.

This effect could be explained by integrative plasticity in the primary sensory cortex, so that somatosensory inputs which are repeatedly activated simultaneously (within a time period of about 10–100 ms) will become integrated into one receptive field (Byl et al., 1996). If the hand is opened and closed very fast, the muscular afferents from the flexor and the extensor muscles may become summarized in the sensory cortex. The normal somatosensory map is degraded and the ability to control individual muscles becomes impaired. This model might explain why telegraphists have the highest incidence of

dystonia: they make about nine muscular contractions per second, more than twice as many as a typist (Sheehy & Marsden, 1982). Faster repetitions and highly stereotyped movements increase the risk of sensory integration of different muscles. Another prerequisite for development of sensory degradation is that the behavior is consciously attended to. Behaviors performed automatically do not give significant sensory plasticity (Byl et al., 1996).

Also the motor cortex can develop expanded representations as a result of motor practice. It has been found that the degree of motor cortex plasticity is strongly dependent on the level of GABA-based inhibition of the cortex (Butefisch et al., 2000; Ziemann, Muellbacher, Hallett, & Cohen, 2001). Ziemann et al. (2001) demonstrated that a decrease of GABAergic inhibition of the cortex in combination with motor practice resulted in a dramatic increase of indications of expanded representation in the motor cortex. The increase was paralleled by an increase in peak movement acceleration.

7.5.2. Increased gain in sensorimotor loops

Sanger and Merzenich (2000) have proposed a computational model of task-specific focal dystonia. Their suggestion is that writer's cramp and similar disorders are the manifestation of a sensorimotor loop with a gain >1. The gain of a loop is >1 if the output of the loop is stronger than the input. If so, the signal will be amplified so that it gets out of control (similar to the effect of putting a microphone too close to a connected loudspeaker). The authors suggest that this increase in gain may result from expansion of the cortex area representing a limb, either in the sensory or motor cortex. This model is in accord with several aspects of dystonia: (a) increased motor cortex excitability; (b) the prevalence of basal ganglia disturbances which are likely to result in disinhibition of the cortex; (c) behaviors likely to result in cortical plasticity are especially affected by dystonia; and (d) blockade of sensory feedback often relieves the problem (see next section).

7.6. Sensory effects in dystonia and stuttering

Another parallel between stuttering and dystonia is that both disorders often are much improved by blocking or altering the sensory feedback (''sensory'' here also includes auditory feedback). Blockade of muscle afferents by lidocaine injection has been shown to abolish co-contractions in writer's cramp (Kaji et al., 1995). A similar effect is demonstrated by the ''sensory trick'' in dystonia: tactile sensory stimulation of the affected body part often dramatically reduces the muscular contractions (Kaji, 2001). In stuttering there are reports of cases where anesthetization of the larynx has led to marked reduction of the speech problems (Dworkin, Culatta, Abkarian, & Meleca, 2002; Webster & Gould, 1975, as cited in Bloodstein, 1995). Furthermore, masking of auditory feedback (MAF) has been shown to alleviate stuttering (Burke, 1969; MacCulloch, Eaton, & Long, 1970), as well as frequency shift of the auditory feedback (FAF) (Hargrave, Kalinowski, Stuart, Armson, & Jones, 1994), or delaying the auditory feedback (DAF) (Van Riper, 1982).

An interesting observation was made by Dewar, Dewar, and Anthony (1976): ''ex-stammerers'' exhibiting fluent speech still showed abnormal contractions of face muscles, which were abolished by masking of the auditory feedback. This finding indicates that stuttering might be related to ''dystonic'' activity in facial muscles also during fluent speech, and that this activity may be normalized by blockade of the auditory feedback.

If stuttering is reduced by masking noise, is there a relation between stuttering and impairment of hearing? Van Riper (1982) reported that he had authenticated a case where an adult male, with severe stuttering since childhood, ''immediately stopped stuttering completely after an accident in which he became completely deafened'' (pp. 383–384). Further, an old investigation among 14,458 deaf children in oral speaking schools reported only 8 cases (0.05%) of stuttering (Harms & Malone, 1939). However, the ability of masking noise to improve stuttering does not seem to be dependent on a total masking of the auditory feedback, since reduction of stuttering also has been shown when only one ear is exposed to noise (Yairi, 1976).

A curious observation was reported by Baron, Legent, Nedelec, and Venisse (1969). A 17-year-old male had stuttered since early childhood, and had also had chronic otitis in the left ear, starting at age 2 or 3. The hearing of the left ear was clearly impaired and the patient also complained of a certain discomfort when exposed to noise or music. Diplacusis was suspected. It was noticed that if the patient blocked the *right* ear with a cotton wad both the stuttering and the discomfort for sounds disappeared. The effect was consistent, and at the time of report the patient had spoken normally for 2 months with a cotton wad. This case exemplifies the complex role of hearing in some cases of stuttering.

What might be the mechanisms behind the sensory effects in dystonia and stuttering? With the background of the reasoning about dysfunctional automatization and excessive gain in sensorimotor loops, two related and additive mechanisms are suggested: (a) *De-automatization*. Somatosensory and auditory feedback serve as input to the putamen (Yeterian & Pandya, 1998). The basal ganglia act to execute automated behaviors based on the habituated environmental context (Wise, Murray, & Gerfen, 1996). Therefore, it is likely that altering the feedback will result in de-automatization. (b) *Reduction of feedback gain.* As discussed above in Section 7.5.2, reducing the strength of the feedback would reduce the risk for signal overflow in sensorimotor loops.

Loss of hearing and MAF clearly implies reduced feedback gain, maybe resulting in de-automatization. FAF is likely to result in de-automatization because of the dramatic change in the character of the feedback sound. The effects of DAF might be more complex. DAF with a long delay, for example 150 ms, tends to result in reduced speech rate, implying marked de-automatization. A shorter delay, like 50 ms, usually has little effect on the speech rate but still improves fluency in many cases. A brief delay means that the feedback circuit becomes slower, and that the beginning of each speech segment will be produced with reduced auditory feedback. The effects of this change in the auditory circuit may be complex, but it seems likely that some degree of de-automatization will occur.

In summary, the symptoms of task-specific dystonia and stuttering seem to be related to automatic processing that has become dysfunctional. It is suggested that the sensory effects (e.g. the effect of frequency altered feedback in stuttering) are related to de-automatization of context dependent processing, and attenuation of the sensory feedback.

7.7. Arguments against similarity between stuttering and dystonia

7.7.1. Stuttering as a tic disorder

The concept of stuttering as a type of dystonia has recently been challenged by a study of the character of the involuntary movements related to stuttering (Mulligan, Anderson,

Jones, Williams, & Donaldson, 2003). These movements were compared with different types of movements seen in various basal ganglia movement disorders. The result of this study was that most of the involuntary movements in stuttering persons during speech could be classified as complex or simple motor tics. Only a few instances (of squeezing eye closure) were judged as dystonic. The authors suggested that stuttering is a tic disorder due to basal ganglia dysfunction.

Two main objections may be raised against the proposal of stuttering being a tic disorder. The first is related to the subjective experience. In a review of tic disorders, including Tourette syndrome, Leckman and Cohen (2003) write: ''By the age of 10 years, most individuals with tics are aware of premonitory urges that may be experienced either as a focal perception in a particular body region where the tic is about to occur (like an itch or a tickling sensation) or as a generalized awareness felt throughout the body. . . . Most patients also report a fleeting sense of relief after a bout of tics has occurred'' (p. 593). This type of ''urge'' and relief does not seem typical for stuttering.

The second objection is that the typical involuntary movements seen in stuttering are strictly task-related, emerging when trying to speak. The movements are not shown during other activities. Such strict task-specificity is often shown in dystonia but does not seem to be displayed in tic disorders.

It should also be noted that this study is based on a relatively small group, 16 stuttering adults, of which only one case was classified as very severe while the rest were regarded as being of moderate to very mild severity. The total samples of reading and free speech included 600 words for each person. The representativity of this material seems uncertain and further studies would be important. It may be the case that stuttering shares characteristics with several different basal ganglia disorders, like dystonia, parkinsonism, and tic disorders, but that it can not be defined as any of these.

7.7.2. Stuttering and cortical excitability

Another challenge against the similarities between stuttering and dystonia comes from a recent report of intracortical inhibition in developmental stuttering, by Sommer, Wischer, Tergau, and Paulus (2003). The basis for this investigation was that reduced intracortical inhibition has been found in focal dystonias like writer's cramp and blepharospasm (spasm of the eyelid), by measuring the motor response in a finger elicited by paired-pulse transcranial magnetic stimulation (TMS). The result of this study indicated that the group of 18 adults with developmental stuttering had normal intracortical inhibition and facilitation. Further, the tests with TMS pointed to a *raised* motor threshold in the stuttering group. (It may be speculated if this result is related to findings of increased cortical gyrification in the region superior of the lateral sulcus, Foundas, Bollich, Corey, Hurley, & Heilman, 2001, or to disturbances in the structure of the white matter related to the sensorimotor cortex, Sommer, Koch, Paulus, Weiller, & Buchel, 2002. These findings are discussed in more detail below, see Section 10.)

The reported normal intracortical inhibition and the raised motor threshold for the finger motor region in persons who stutter suggest a difference in pathologic mechanisms between focal dystonias and stuttering. It is too early, however, to dismiss the possible parallel between stuttering and dystonia based on this one study. For example, a dystonic

disturbance in stuttering might be related to systems not involved in finger movements, like the auditory system. Further investigations of these aspects are of importance.

7.8. Summary, dystonia and stuttering

There are several similarities between dystonia and stuttering. (a) *Lesions*: The most common locations of lesions causing dystonia are the putamen or the globus pallidus, and this may also be the case for stuttering (Ludlow et al., 1987). (b) *Pharmacology*: Some cases of dystonia are responsive to dopaminergic drugs, either by inhibiting or stimulating the dopamine system. Analogous results have been reported for stuttering (see Section 6.1). (c) *Task-specificity*: Dystonia is often limited to highly specific tasks, especially those involving highly automated sequential movements. The same is the case for stuttering. (d) *Sensory effects*: Both dystonia and stuttering are often improved by blocking or altering the sensory feedback.

Also some differences between stuttering and dystonia have been proposed: (a) that involuntary movements related to stuttering may be more similar to tics than to dystonia, and (b) that cases of focal dystonia tend to show reduced intracortical inhibition while this has not been found in stuttering.

8. Negative and positive symptoms of stuttering

Stuttering is related to a range of motor symptoms (like various types of repetitions, blocks, and accessory motor behaviors) and maybe also to temperamental traits like increased behavioral activation. Some persons who stutter show only one or a few of these symptoms, while others have many.

A classic way to structure complex symptoms, especially in basal ganglia disorders, is to differentiate between *negative* and *positive* symptoms. By negative symptoms is meant the absence of normal functions, and by positive symptoms the presence of abnormal activation of behaviors, emotions, or cognitions. This dichotomy is often used when classifying basal ganglia motor disorders, with hypo- or akinesia as negative, and chorea, dystonia, tics, tremor, and rigidity as positive. Positive symptoms can be regarded as signs of disinhibition of functional parts of the nervous system (Victor & Ropper, 2001). An analogous division is used regarding symptoms of schizophrenia, with absence of normal social and interpersonal behaviors as negative, and psychotic features as positive (Kandel, 2000).

Some symptoms of stuttering and accompanying traits may be easily classified according to this scheme. Speech blocks involving increased muscular tension and accessory motor behaviors clearly include ‘‘positive’’ symptoms. Likewise, anxiety and traits of increased behavioral activation could also be regarded as positive since they represent increased activation of a normal function (speech-related anxiety may, however, well be regarded as a normal reaction). The classification of speech symptoms like repetitions and prolongations is more complex. It is possible that similar speech disruptions can occur both as negative or positive symptoms: The inability to continue the speech sequence might appear because of a lack of cues or programming for the following

segment, or because of muscular hyperactivation that disrupts the phonation or articulation. Or, possibly, a combination of both factors, for example that deficient cues releases inappropriate muscular activation. It seems likely that these patterns differ between different persons who stutter, and maybe also between different stages in the development of stuttering. A more detailed mapping of the proximal causes of the speech disruptions in stuttering individuals and subgroups would be a valuable step for the understanding of stuttering. This type of analysis might reveal constellations of positive versus negative symptoms, indicating differences in pathology.

9. Cerebral development, aging, and degeneration

When discussing possible mechanisms of stuttering it is important to consider age- and gender-related aspects of the disorder. Stuttering has a typical pattern of onset in early childhood followed by a high rate of childhood recovery. When looking at developmental aspects it may also be interesting to study changes of stuttering in older age, and effects of neural degeneration and lesions. In this section, data regarding gender differences, development, aging, and degeneration will be briefly reviewed, and possible neural mechanisms will be discussed.

9.1. Age of onset, recovery, and gender ratio

The data regarding age of onset, frequency of recovery, and sex ratio differ somewhat between different studies, but the general tendencies are quite consistent. Based on data from some of the more recent studies (Månsson, 2000; Yairi & Ambrose, 1992, 1999) the following brief summary may be made: These studies suggest a mean age of onset between 2.5 and 3 years, a male/female ratio in children of about 2:1, a recovery rate of about 60–70% within 2 years after onset of stuttering and further recoveries later.

A study by Ambrose, Cox, and Yairi (1997) indicates that recovering and persistent stuttering may, partly, represent different subtypes. The frequency of persistent or recovered stuttering was investigated in relatives to 66 stuttering children. The analysis of the data pointed to the existence of two types of genes linked to stuttering: one type increasing the risk of transient childhood stuttering, and another type increasing the risk of persistent stuttering. The effects of these two types of genes seemed to be additive. This additive effect suggests that the genes affect the same cerebral system in the same direction. When analyzing possible causes of stuttering it is important to consider that stuttering in adults may be regarded as a subgroup of stuttering, and that the causal factors in adults may be different from the causal factors in the majority of young stuttering children. It may be the case, for example, that persistent stuttering involves a higher frequency of structural abnormalities.

An interesting finding regarding language development in stuttering children was reported by Watkins, Yairi, and Ambrose (1999). In the group of stuttering preschool children in the study summarized above (Yairi & Ambrose, 1999) their expressive language abilities were measured. The group with early onset stuttering, who entered the study at age 2–3, showed syntactic abilities and length of utterances well above what was expected for

their age. In fact, in some aspects the language abilities in this group were on a level with the norms for 2 years older children. This was true both for children who recovered and for children who persisted to stutter. Children who entered the study at a later age showed language abilities at about age expectations, except for the group of children with persistent stuttering in the oldest age group (entering the study at age 4–5), whose abilities were somewhat below the norm. These results indicate that children with early onset stuttering tend to show precocious learning of language.

9.2. Aging and stuttering

There is a paucity of research regarding the effect of aging on the severity of stuttering, but two small studies have been published. Shames and Beams (1956) sent survey forms to priests, with questions about the age and number of stuttering persons in their parish. The result suggested a drop in the prevalence of stuttering persons after the age of 50. A similar trend was indicated in a small study by Kielska (2001).

9.3. Stuttering and cerebral degeneration or lesions

The review of ''neurogenic stuttering'' in Section 4 showed that cerebral lesions can result in stuttering. Cerebral lesions or degeneration can also, however, have the opposite effect, changing lifelong stuttering to fluent speech. These paradoxical cases may provide important clues regarding the mechanisms of stuttering. At least four reports of this type have been published (Helm-Estabrooks, Yeo, Geschwind, & Freedman, 1986; Jones, 1966; Miller, 1985; Muroi et al., 1999). For example, the report by Miller (1985) described two persons with onset of severe stuttering in childhood, whose stuttering disappeared when they developed symptoms of progressive multiple sclerosis. As a further example, the author of this paper has interviewed a man who claimed that his stuttering was greatly and permanently improved after he recovered from a robbery which caused head injury. He said that he was very grateful to the robbers.

The disappearance of stuttering after cerebral lesions has been interpreted as support for the hypothesis that stuttering is the consequence of interference between the hemispheres, so that the lesion dissolved the conflict (Jones, 1966). An alternative interpretation, based on the discussion of dystonia in Section 7, could be that the lesions resulted in a decrease of gain in cerebral circuits involved in speech. All four cases reported by Jones (1966) showed bilateral speech representation before surgery, changing to unilateral afterwards. Bilateral speech representation might imply increased gain of speech related signals in both hemispheres as a result of interhemispheric connections between homologous cortical areas via the corpus callosum (see discussion in Section 10.1, regarding increased interhemispheric connections in symmetric brains). In this case the ''hemispheric interference'' might be regarded as a variant of a more general mechanism, namely overflow of speech related signals to the basal ganglia circuits.

If most cases of stuttering are the result of excessive signals in neural circuits, stuttering would be expected to improve in advanced age since aging is related to many changes in the brain, for example breakdown of myelin sheaths (Peters, 2002), leading to reduced transmission of signals. The scarce reports of stuttering and aging summarized above

do support the hypothesis that stuttering often improves at more advanced age. On the other hand, if most cases of stuttering were the result of impaired processing capacity for speech, then stuttering would be expected to become more severe by aging.

9.4. Summary of development and stuttering

The review above, of development, degeneration, etc., suggests a pattern where the causal factors for stuttering are strongest around 2.5–3 years of age. The strength of these factors drops rapidly during the preschool age in most cases. There is further decrease in late childhood and adolescence, and also a tendency for diminishing of stuttering at an advanced age. In some cases, cerebral lesions or degeneration of white matter result in normalization of speech. The causal factors are strongest in males. An interesting finding is that children with early onset of stuttering tend to show precocious language development.

9.5. Developmental changes of the nervous system

The summary in the previous section leads to the question: Are there any developmental changes in the nervous system that follow this time course, with a peak before age 3, rapid decrease in the preschool years, slower decrease until adolescence, and further decrease in old age?

The development of the human nervous system continues after birth, with major changes in many aspects during childhood (Webb, Monk, & Nelson, 2001). Postmortem studies of synaptic density (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997) and in vivo brain imaging of cerebral metabolism (Chugani, 1999) indicate a pattern where the general level of synaptic density increases from birth to about 1 to 3.5 years of age (with earlier development of for example auditory and visual cortex, and later for the frontal cortex). This high level forms a plateau lasting until about 7–9 years of age, and reaches the adult low level in late adolescence. Goldman-Rakic (1987) argued that the timing of the peak level of synaptic density in the frontal cortex is related to the time of development of expressive language abilities and cognitive functions. The timing of the peak in synaptic density corresponds well with the typical time for onset of stuttering, but the plateau lasts longer than most cases of childhood stuttering. The bulk of recovery seems to occur before the age of 5 (Månsson, 2000; Yairi & Ambrose, 1992), while the plateau of high synaptic density lasts until about 7–9 years.

However, another neurodevelopmental aspect fits better with the time course of stuttering, namely the density of dopamine receptors in the striatum. The striatal density of D1- and D2-receptors has been measured postmortem by Seeman et al. (1987), in children and adults from the general population. Fig. 2 shows the density of D1- and D2-receptors in the putamen, and the D1/D2 ratio. Both D1- and D2-receptor densities show a linear increase after birth up to a peak level at age 3 for D1 and age 2 for D2 (the correlation between receptor density and age during this phase of increase: 0.86 for D1 and 0.82 for D2). This pattern of D1- and D2-receptor development, with a marked peak, has also been shown in rats (Teicher, Andersen, & Hostetter, 1995). The density of D2-receptors falls rapidly after the peak, with about 38% reduction at age 5 compared with the peak level. The time course of D2 density development is similar to the typical time

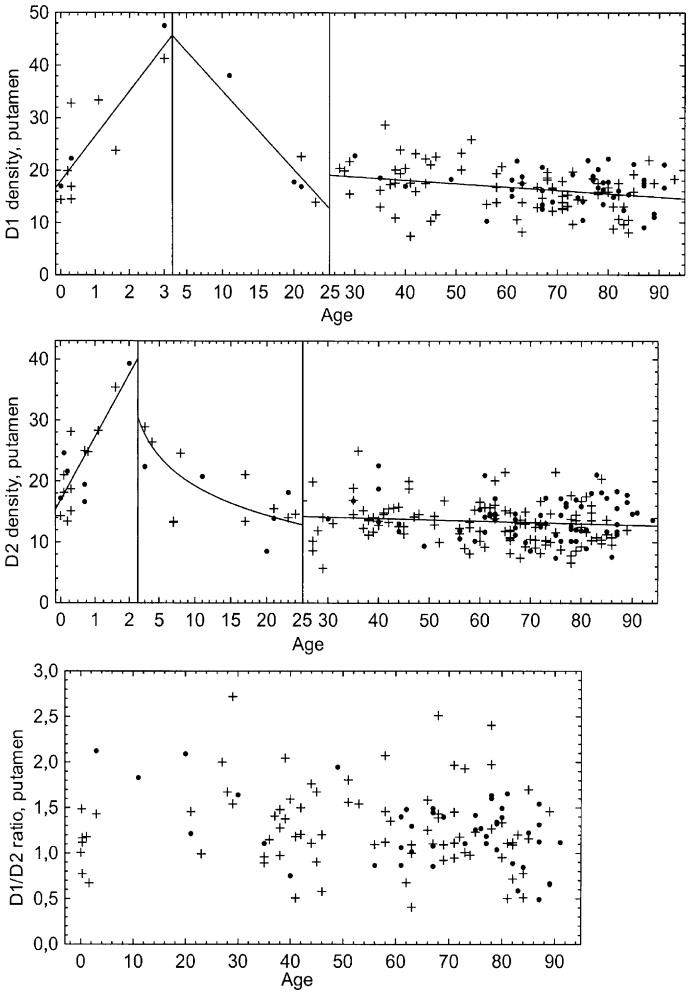

Fig. 2. Density of D1- and D2-receptors in the putamen, and D1/D2 ratio, based on postmortem data published by Seeman et al. (1987), from 244 cases in the general population. The sign ● marks females and + marks males. The regression lines are calculated for the rise, decline, and adult periods. The correlation between receptor density and age during the rise period was 0.86 for D1-receptors and 0.82 for D2-receptors. Note that for some individuals only D1- or D2-receptor density was measured, resulting in a lower number of individuals in the D1/D2 ratio plot. (In 24 of the cases the densities in the putamen were not measured, instead the figures were estimated from the available values for the caudate nucleus. The correlation between receptor density in the putamen and caudate nucleus was 0.82 in this study.)

course of onset and recovery of stuttering. For the D1-receptor there is just one case reported between 3 and 20 years, but this case suggests a slower reduction of D1-receptors.

Could dopamine receptor development explain the gender difference in stuttering? In Fig. 2 both boys and girls show similar peaks of D1- and D2-receptor density. However, when looking at the D1/D2 ratio in children one sees a separation of males and females,

with lower ratio in boys. The number of cases is very small and there are differences in age between the boys and girls, but the tendency is theoretically interesting. In the previous sections, a model of the basal ganglia was discussed, based on the principle that the indirect pathway maintains a diffuse background inhibition of impulses while the direct pathway provides a focused cue for release of the correct motor pattern. The balance between D1- and D2-receptor density may be crucial, since a high level of D2-receptors is assumed to reduce the diffuse inhibition from the indirect pathway, and a relatively low level of D1-receptors is thought to result in weaker cues from the direct pathway. A consequence of this model would be that a low D1/D2 ratio impairs the cues from the basal ganglia to the SMA (through the direct pathway) and at the same time increases the risk of unintentional movements (through reduced inhibition based on the indirect pathway). Impaired cues may result in difficulties in initiation of segments in a speech motor sequence. A hypothesis based on this reasoning would be that a low D1/D2 ratio in the putamen, in combination with a high D2 density, increases the risk for stuttering.

The time course of D1- and D2-receptor density presented in Fig. 2 suggests how changes in the D1/D2 ratio may be related to onset and recovery of stuttering. The density of D2-receptors peaks earlier than the D1-receptors. This means that the D1/D2 ratio is low when the D2 density peaks, but that the ratio will rise later since the D1 density continues to increase while the D2 density drops. This rise of the D1/D2 ratio could have a direct relation to childhood recovery from stuttering.

The level of striatal D2-receptors has been reported to have a positive correlation with cognitive performance irrespective of age (Bäckman et al., 2000; Volkow et al., 1998). Maybe early development of a high level of D2-receptors is the key factor in the group of children with early onset of stuttering and precocious language development. (The density of D2-receptors in putamen has also been reported to show a negative correlation with the temperamental traits ''detachment'' (reflecting the need for distance versus intimacy, $r = -0.68$ in Farde, Gustavsson, & Jonsson, 1997 and $r = -0.50$ in Breier et al., 1998 and ''irritability,'' $r = -0.51$ in Farde et al.).)

A further indication for a relation between high D2 density and stuttering comes from cases with Tourette syndrome (TS). Ludlow (1993) reported that 45% of persons with TS stuttered as children. A study of twins with TS found a very strong positive correlation ($r = 0.99$) between the severity of TS symptoms and the level of D2-receptor binding in the head of the caudate nucleus (Wolf et al., 1996).

If a low D1/D2 ratio in combination with a high D2 density increases the risk of stuttering, blockade of D2-receptors with for example haloperidol would be expected to balance the system. As discussed in Section 6, haloperidol is the medication that has the best documented effect on stuttering, and haloperidol is characterized by its high specificity for D2-receptors. Studies of D2-blockers in stuttering children are scarce, but the largest study (Gattuso & Leocata, 1962), involving 50 children aged between 5 and 12, reported positive effects, especially in the younger children (aged 5–8) compared with the older ones. This is in line with the suggestion that increased D2 density is a more important factor in early childhood stuttering compared with stuttering in later age.

Another report discussed in Section 6 (Fish & Bowling, 1962) claimed that amphetamine led to improvement of stuttering lasting a long time after the medication was discontinued. Against this background it is interesting that amphetamine has been shown to

give a long-lasting reduction in available D1- and D2-receptors in the striatum, as a result of the receptors being internalized into the cytoplasm (Dumartin, Caille, Gonon, & Bloch, 1998; Ginovart, Farde, Halldin, & Swahn, 1999; Sun, Ginovart, Ko, Seeman, & Kapur, 2003). It does not seem clear if the D1- and D2-receptors are affected to the same extent, there are some indications for a stronger effect on the D2-receptor type (Gifford et al., 2000). According to the suggested hypothesis of a relation between stuttering and high D2 density in the putamen, this mechanism would tend to reduce stuttering. This example shows that the pharmacological effects in stuttering might be very complex and sometimes paradoxical.

Another aspect of the basal ganglia that may be related to developmental changes is the level of the enzyme tyrosine hydroxylase (TH), which is the rate-limiting factor in the synthesis of dopamine (Feldman et al., 1997). McGeer and McGeer (1976) reported a pronounced elevation of the TH level in the putamen in the early childhood, falling rapidly to adult levels in adolescence. This would suggest an elevation of dopamine production in children. This pattern of TH level was not, however, found in a similar study by Robinson et al. (1977).

10. Anomalies of the cerebral cortex and possible relations to the basal ganglia

The review in this paper is focused on the basal ganglia system, but the functions of the basal ganglia are dependent on the functions of the cerebral cortex and the white matter connections. Some of the most interesting findings about persistent stuttering during recent years relate to the morphology of the cortex and the structure of the underlying white matter. Therefore, a discussion of these anomalies will be included here.

10.1. Increased area of planum temporale

Foundas et al. (2001) used MRI to investigate cerebral morphology in 16 adults with persistent developmental stuttering and 16 matched controls. There was no reported history of brain injury, dyslexia, specific language impairment, ADHD, or other neuropsychiatric disorders. The mean level of education was high, 16.5 years. Half of the stuttering group had a family history of stuttering. Two main findings of the study were: (a) increased total size of the planum temporale (PT), and (b) increased number of gyri in speech related areas in the stuttering group.

In the stuttering group the left PT was found to be in average 23% larger and the right 30% larger, compared with the controls. An interesting result was that the standard deviation of the PT size was lower in the stuttering group. If calculating the standard deviation in percent of the mean size for each group, the controls had 55% higher standard deviation for the left PT and 73% higher for the right, compared with the stuttering group. This indicates that large size of PT, especially in the right hemisphere, was typical for the stuttering individuals.

On average, the control group showed an asymmetry of the PT, with larger left side. The persons who stuttered showed a more symmetric pattern. It seems unlikely, however, that the lateralization in itself would be a causal factor since the groups largely overlapped, with

about 30% of the controls showing an approximately symmetric configuration and about 25% having a clearly larger *right* PT. The difference in total PT size might be a more distinctive group difference than the difference in asymmetry.

The characteristics of variations in PT size were discussed by Rosen, Sherman, and Galaburda (1992). Based on a study of 100 human postmortem brains they found that the degree of symmetry correlated with the size of the smaller PT but not with the larger PT. In other words, symmetric brains tend to have a large total PT area. Studies with rats indicated that the sizes of cortical areas mainly are determined by early events in the corticogenesis, in the progenitor cell stage, and that symmetric areas tend to have a greater number of connections through the corpus callosum.

Foundas et al. (2003) reported that DAF had the strongest fluency-inducing effect in the subgroup of stuttering persons with rightward PT asymmetry. Was this also the subgroup with the largest total PT area? As discussed in Section 7.6, the effect of altered auditory feedback might be related to excessive gain in auditory feedback loops. If this suggestion is correct, the total area of the PT might be a factor that influences this feedback gain.

10.2. Increased gyrification

In the study by Foundas et al. (2001), discussed in the previous section, 10 of 16 stuttering persons showed extra gyri along the superior bank of the lateral sulcus (3 persons bilateral, 3 left, 4 right (note, error in the original article, A.L. Foundas, personal communication, August 28, 2002)). None of the controls had extra gyri here. This region includes speech related areas, like Broca's area and the sensorimotor cortex for the articulatory organs. Further, 7 of 16 stuttering persons were found to have an extra diagonal sulcus in the posterior Broca's area, BA44 (3 persons bilaterally, 2 left, 2 right), while none of the controls showed this pattern. In fact, the left hemisphere diagonal sulcus was absent in 6 of the controls but only in 3 of the stuttering persons, making a grand total of 18 left side diagonal sulci in stuttering persons compared with 10 among the controls.

When reviewing the literature it turns out that regional increased gyrification has been found in other language disorders. Increased prevalence of extra gyri in the posterior part of the superior bank of the lateral sulcus has been reported in both developmental language disorder and dyslexia. In the general population about 10% of hemispheres show this type of extra gyrus (Steinmetz, Ebeling, Huang, & Kahn, 1990). Jackson and Plante (1996) found this extra gyri in 41% of 80 hemispheres in families with language disorder, while the control group showed extra gyri in 22.5% of the hemispheres. Leonard et al. (1993) reported extra gyri with this location in 6 of 9 adults with dyslexia, in 4 of 10 relatives, but in only 1 of 12 controls. Furthermore, 4 of these 9 cases with dyslexia had an extra Heschl's gyrus (auditory cortex), but none of the 12 controls showed this pattern.

An increased number of gyri can be a sign of a developmental disorder called *polymicrogyria*, with clearly disturbed structure of cortical layers. It is often regional and is suggested to be the result of a focal perfusion failure about the sixth-month of gestation. The symptoms are very varied, including epilepsy, spastic paresis, and mental

retardation, but there are also cases with only selective impairment of higher functions (Guerrini, Canapicchi, & Dobyns, 1999). There seem to be no reports of polymicrogyria in developmental stuttering.

10.3. Somatosensory white matter disturbance

Sommer et al. (2002) used a type of magnetic resonance imaging, *diffusion tensor*, to investigate the microstructure of the white matter in adults with persistent developmental stuttering. This method measures the *anisotropy*, an index of differences of water diffusion in three dimensions. The anisotropy is increased in white matter with a high degree of myelination and high coherence of the orientation of the axons.

The study found that the stuttering group showed reduced anisotropy in a region underlying the left sensorimotor representation of the oropharynx in the superior bank of the lateral sulcus. Increased gyrification in the superior bank of the lateral sulcus was reported by Foundas et al. (2001), as discussed above. It seems possible that these results are associated, with disorganized structure of the sensorimotor region related to the speech organs in some persons with persistent stuttering. (It would be important, however, to replicate the investigation with diffusion tensor, since Sommer et al., 2002 make the reservation that large voxel size in the study could result in influence of the gray-white border. If the stuttering group had increased gyrification in this region, the risk for gray matter influence might be higher in this group.)

If a dysfunction in the cortical sensorimotor region of the oropharynx is associated with stuttering, could this finding be integrated with the hypothesis that stuttering is related to a dysfunction of the basal ganglia circuits? At the current state of knowledge, any model will be clearly speculative, but just as examples two models will be sketched. The first suggestion is based on the principle that when a motor sequence is executed the striatum receives continuous information from the primary motor cortex (M1) about the output of the motor signals to the muscles. It is likely that this continuous input to the striatum is used as a basis for the basal ganglia to generate the cue for shifting to the next motor segment (see discussion in Section 3.6). If the signal from the M1 to the striatum is too weak or distorted the generation of the shift-cue may fail. The speech sequence becomes disrupted, resulting in repetition of the previous segment. The second suggestion is that the balance between auditory and somatosensory input to the basal ganglia may be important for a normal function of the speech automaticity. If the auditory input is strong and the somatosensory input is weak the system might become unstable.

11. Conclusions

The following tentative conclusions are proposed, with the intention of suggesting pathways for further research.

(a) There are strong indications that the basal ganglia-thalamocortical motor circuit, through the putamen to the SMA, plays an important role in the pathophysiology

of stuttering. The dysfunction may have various causes and may be the effect of interaction between several factors. Possible factors might be, for example: high density of D2-receptors and low D1/D2 ratio in the putamen; aberrant levels of dopamine release; and focal lesions of the basal ganglia-thalamocortical circuit.

(b) The core dysfunction in stuttering is suggested to be impaired ability of the basal ganglia to produce timing cues. Some of the conditions that temporarily alleviate stuttering are proposed to be effective by providing compensatory timing information. This pertains to the rhythm effect, chorus speech, and singing. The adaptation effect is mainly based on an improvement of the basal ganglia timing cues resulting from practice of a specific speech sequence.

(c) Other conditions that tend to alleviate stuttering are suggested to be effective because of de-automatization of the speech control. This would apply to novel modes of speaking and to masked or frequency altered auditory feedback. The effect of altered auditory feedback might also be related to attenuation of the effective feedback signal.

(d) Influence of emotions and stress on stuttering is well compatible with the suggestion of stuttering as a basal ganglia disorder.

(e) Concomitant symptoms, such as involuntary movements, are thought to be the result of specific mechanisms related to the basal ganglia circuits, prevalent in some but not in all cases of stuttering.

(f) A morphological study suggests the importance of cerebral cortex anomalies in persistent stuttering, possibly in interaction with the basal ganglia functions.

(g) The typical pattern of early childhood onset of stuttering and subsequent recovery in many cases is proposed to be related to a peak in D2-receptor density in the putamen about the age of 2–3, in combination with a relatively low D1/D2 ratio in some children, especially boys. This factor is suggested to be particularly important in stuttering children with precocious language development.

(h) Stuttering is a heterogeneous disorder and characterization of subtypes is an important task for research. Based on differential traits (Daly, 1996; Van Riper, 1982), and differential responses to medication (Langova & Moravek, 1964) two preliminary subtypes are suggested (it should be noticed that the proposed differential pharmacologic effects are based on very few cases):

Stuttering type 1: This group corresponds to what Daly (1996) defined as ''stuttering'' (as opposed to ''stuttering-cluttering'') and is similar to Van Riper's tracks I and III (Van Riper, 1982), and may constitute the majority of persons who stutter. There are some indications that the speech in this subgroup tends to improve on dopamine stimulants and to get worse on D2-blockers (it is too early, however, to draw any conclusions about dopamine stimulants in the treatment of stuttering). The onset of stuttering occurs after a period of fluent speech, and tense speech initiation blocks often become an important part of the problem. The stuttering tends to get worse in relation to negative emotional reactions.

Stuttering type 2: This group corresponds to what has been called ''stuttering-cluttering'' (Daly, 1996) and is similar to Van Riper's track II (Van Riper, 1982). There are indications that the stuttering tends to improve on D2-blockers and to get

worse on dopamine stimulants. Frequent behavioral traits may be increased behavioral activation, high speech rate, and talkativeness.

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Appendix A. Continuing education

1. The circuits through the basal ganglia are organized in the following way: the basal ganglia system receives its main input from
   a. The brain stem. The output from the BG interacts closely with the cerebellum.
   b. The frontal lobe. The output from the BG modulates the activity of the entire cerebral cortex.
   c. The cerebellum. The output from the BG modulates the limbic system.
   d. Almost the entire cortex. The output from the BG modulates the activity of the frontal lobe and parts of the brain stem.
   e. The limbic system. The output from the BG modulates the auditory cortex.
2. The putamen can be described as
   a. The output nucleus of the basal ganglia, projecting to the thalamus.
   b. A limbic structure, with key functions in emotional responses like anxiety.
   c. The motor part of the striatum, which is the main input nucleus of the basal ganglia system.
   d. A structure involved in the cognitive circuits of the basal ganglia, important for syntactic aspects of speech.
   e. The auditory part of the basal ganglia.
3. According to the model of the basal ganglia presented in Section 2, how do the direct and the indirect pathways interact to shape the behavior?
   a. The direct and the indirect pathways amplify each other, thereby selecting the desired response.
   b. The direct pathway provides a focused cue to the cerebral cortex for the release of the desired behavioral program, while the indirect pathway provide a diffuse background inhibition of potentially competing responses.
   c. The direct pathway provides a constant inhibition of impulses, while the indirect pathway acts as a noise filter, amplifying the strongest cortical signals.
   d. The direct and indirect pathways are only important when learning a new behavior, not when executing well-learned movements.

e. The direct pathway provides information about the muscular tension, while the indirect pathway provides spatial information.

4. What explanation of the effect of chorus speech to eliminate stuttering is suggested in this paper? Chorus speech results in
   a. De-automatization of speech.
   b. Reduced auditory feedback of the own voice.
   c. Reduced anxiety.
   d. Timing cues from the voice of the other person.
   e. A different and easier speech pattern.
5. The frequent pattern of early childhood onset and recovery of stuttering is suggested to be related to
   a. A peak in synaptic density in the cerebral cortex during childhood.
   b. Increased density of D1-receptors in putamen in some children.
   c. A peak in the size of the planum temporale during childhood.
   d. A temporary right hemisphere dominance of the auditory function during childhood.
   e. A peak in D2-receptor density in the putamen, in combination with low D1/D2 ratio in some children.

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