On the Causal Mechanisms of Stuttering

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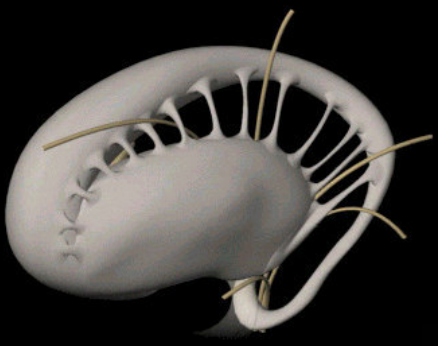

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Cover:
The striatum, the largest structure of the basal ganglia, viewed from the left side of the brain. It is suggested in this thesis that the motor functions of the basal ganglia are central in stuttering. (Illustration from the computer software InterBrain, by permission of Martin C. Hirsch, Springer Verlag, Berlin, 1998.)

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To Sahli, Schilder, and Seeman,
who related stuttering to the
functions of the basal ganglia
more than 70 years ago.

LIST OF PAPERS

This thesis is based on the following papers that will be referred to by their Roman numerals:

I. Alm, P. A. (2004). Stuttering, emotions, and heart rate during anticipatory anxiety: a critical review. *Journal of Fluency Disorders, 29*, 123-133.

II. Alm, P. A. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of Communication Disorders, 37*, 325-369.

III. Alm, P. A. (2004). Copper in developmental stuttering: a study of plasma copper, ceruloplasmin, and estimated free copper. *Folia Phoniatrica et Logopaedica.* In press.

IV. Alm, P. A. (2004). Stuttering and sensory gating: a study of acoustic startle prepulse inhibition. *Submitted.*

V. Alm, P. A. & Risberg, J. (2004). Stuttering in adults: the acoustic startle response, temperamental traits, and biological factors. *Submitted.*

Dissertation for the Degree of Doctor of Medical Science in Neuropsychology presented at Lund University in 2005.

ABSTRACT

Stuttering is one of the most common speech disorders. However, the etiology is poorly understood, and is likely to be heterogeneous. The aim of this thesis was to clarify causal mechanisms, focusing the brain. The project included theoretical development based on published data, and a broad approach of explorative studies and testing of hypotheses.

The theoretical work focused the *basal ganglia*, leading to a model based on the *dual premotor systems hypothesis* (G. Goldberg, 1985, 1991), which defines two parallel premotor systems: *the medial* (basal ganglia + SMA), and *the lateral* (lateral premotor cortex + cerebellum). Stuttering is suggested to be caused by a disturbance of the medial system, in most cases in the basal ganglia. The core dysfunction is proposed to be impaired "go-signals" from the medial system, supposed to trigger the next motor segment in speech.

Under some conditions speech control is shifted from the medial to the lateral system, thereby bypassing the dysfunction and resulting in fluent speech. The lateral system is suggested to be active when speech is combined with sensory input, like chorus speech or metronome. Also the effect of altered auditory feedback in reducing stuttering is proposed to be based on this mechanism. The lateral system is able control speech timing without sensory input, but this demands increased attention to some particular aspect of speech, as occurs in imitation of dialects, exaggerated rhythm, reduced speech rate, or role play. Also singing is suggested to be based on the lateral system.

Superfluous muscular activation accompanying stuttering may be a type of *dystonia*: involuntary contractions related to the basal ganglia disturbance. The high prevalence of stuttering at age 2.5–3 years is proposed to reflect a peak in the number of D2 dopamine receptors.

A total of 35 stuttering adults participated. Two studies, of copper metabolism and "startle prepulse inhibition", did not indicate any significant differences in comparison with matched controls.

It has previously been reported that stuttering may be associated with increased neuromuscular reactivity, measured as exaggerated eye-blink in response to noise, and that this trait may be related to a "nervous" temperament. These aspects were investigated. Based on literature it is argued in the thesis that increased anxiety in stuttering adults mainly is an effect of the speech difficulties. The stuttering group showed somewhat stronger eye-blink, though this was not statistically significant. Strong eye-blink was not related to anxiety, but was clearly related to low calcium, which is known to increase the excitability of the nervous system. The stuttering group showed somewhat lower calcium, and a weak tendency towards more severe stuttering in case of low calcium. It is possible that low calcium can increase stuttering severity and anxiety in some cases.

A subgroup reported traits of childhood ADHD, and this group typically also reported neurological incidents before the onset of stuttering. The subgroup without traits of ADHD typically reported having stuttering relatives but no neurological incident.

Keywords: stuttering, basal ganglia, dual premotor systems, dystonia, ADHD, neurological lesions, dopamine

CONTENTS

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Everything that exists in this world is a result of history, and, as such, the result of a countless number of causal factors. This basic scientific principle pertains in a very high degree to the writing of this thesis. A great number of persons have been part of the process, or part of the background. Though it is not possible to mention all, I would like to acknowledge some of them here.

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ABBREVIATIONS

5-HT	serotonin
5-HT1a	serotonin receptor type 1a
5-HT1b	serotonin receptor type 1b
AAF	altered auditory feedback
ADHD	attention deficit hyperactivity disorder
BA	Brodmann area (cortical regions)
BAS	behavioral activation system
BG	basal ganglia
BIS	behavioral inhibition system
CM	centremedian nucleus (a nucleus of the thalamus)
D1	dopamine receptor type 1
D2	dopamine receptor type 2
DAF	delayed auditory feedback
dB	decibel
ECG	electrocardiography (heart activity)
EEG	electroencephalogram (registration of electrical activity in the brain)
EGG	electroglottography (a non-invasive method of registering phonation)
EMG	electromyography (muscular activity)
FAF	frequency altered auditory feedback
FDOPA	a tracer-labeled precursor of dopamine
GABA	gamma aminobutyric acid (an inhibiting neurotransmitter)
GP	globus pallidus (a basal ganglia nucleus)
GPe	globus pallidus, external part
GPi	globus pallidus, internal part
KSP	Karolinska Scale of Personality
M1	primary motor cortex
MAF	masked auditory feedback (i.e., noise)
MDMA	3,4-methylendioxymethamphetamine, ecstasy
MIDI	musical instrument digital interface
MRI	magnetic resonance imaging
N	number of subjects
PET	positron emission tomography (a brain imaging method)
PPI	prepulse inhibition
preMC	lateral premotor cortex
PT	planum temporale (an auditory cortex area)
r	Pearson correlation coefficient
SMA	supplementary motor area (cortical area)
SD	standard deviation
SN	substantia nigra (a nucleus in the midbrain)
SNc	substantia nigra, pars compacta (produces dopamine)
SNr	substantia nigra, pars reticulata (similar function as GPi)
SSI	the Stuttering Severity Instrument
SSRI	selective serotonin reuptake inhibitor (a type of antidepressant)
STN	subthalamic nucleus (a basal ganglia nucleus)
TANs	tonically active neurons (cholinergic striatal interneurons)
Thal	thalamus
TMS	transcranial magnetic stimulation
VL	ventrolateral nucleus (a nucleus of the thalamus)
WASSP	the Wright & Ayre Stuttering Self-Rating Profile
WURS	Wender Utah Rating Scale (childhood traits of ADHD)

SAMMANFATTNING PÅ SVENSKA (SUMMARY IN SWEDISH)

A. Huvudpunkter från avhandlingen, i korthet

- *Föreslagen teori om stamning.* Hjärnan har två parallella system för "timing" av stavelser och ljud i talet: "mittsystemet" och "sidosystemet". Stamning är kopplad till mittsystemet, vilket inkluderar *basala ganglierna* (strukturer mitt i hjärnan som är inblandade i automatisering av olika beteenden). Huvudproblemet föreslås vara bristande "startsignaler" för stavelserna och ljuden i talet. Vidare föreslås att under vissa förhållanden skiftar styrningen av timing till sidosystemet, vilket göra att talet flyter eller stamningen minskar: (a) när talet kopplas till sinnesintryck, som vid körläsning eller tal i takt med metronom, (b) när någon aspekt av talet styrs med en förhöjd grad av uppmärksamhet, t.ex. vid imitation av dialekt, överdriven rytm, eller sänkt talhastighet, eller (c) vid sång. Också "förändrad hörselåterkoppling" föreslås stödja skifte till sidosystemet, baserat på sidosystemets inblandning vid bearbetning av sinnesintryck.

- Stamning baseras inte på en "nervös" läggning, men är kopplad till en sänkt tröskel för avbrott i talet. Oro för talsituationer kan utvecklas som en effekt av talsvårigheterna.

- En undergrupp av de stammande rapporterade vissa drag av uppmärksamhetstörning eller hyperaktivitet (ADHD) under barndomen. De flesta av dessa deltagare rapporterade också olika händelser av neurologisk natur före stamningen började, som förlossningskomplikationer eller hjärnskakning med medvetslöshet, vilka eventuellt kan ha påverkat basala ganglierna. Däremot rapporterade deltagarna utan tendens till ADHD under barndomen vanligen minst en stammande släkting men inga särskilda händelser av neurologisk art.

B. Definition av stamning

Förslag till definition av stamning, delvis baserat på tidigare definitioner:

> Stamning är en talstörning som kännetecknas av svårigheter att röra sig framåt i talet, när personen vet vad han eller hon vill säga.
>
> Störningen uttrycks som: svårigheter att initiera ljud; förlängningar av ljud; repetitioner av ljud, stavelser, ord eller fraser; omformuleringar; pauser; överflödiga ljud eller ord; eller undvikande av tal.
>
> I vissa fall är störningen förknippad med onormal muskelspänning eller onormala rörelser, särskilt i hals, mun och ansikte, men även i övriga kroppen.
>
> Talstörningen kan vara dold om personen lyckas använda medvetna strategier för att undvika att visa symtom.
>
> Det är typiskt för stamning att symtomen försvinner vid sång, körläsning, eller tal i takt med metronom.

C. Bakgrund

Avhandlingen är ett försök att klarlägga orsaksmekanismerna bakom en av de vanligaste talstörningarna, *stamning*, vilken i vissa fall innebär ett allvarligt kommunikationshandikapp. Orsakerna till stamning har förblivit oklara. Ett stort antal olika förklaringar har föreslagits, inriktade på psykologiska, sociala, inlärningsmässiga eller neurologiska aspekter. Avhandlingen fokuserar på hjärnan i förhållande till stamning, baserat på antagandet att alla faktorer som påverkar stamning har sin effekt genom påverkan på hjärnans funktioner.

D. Strategi för projektet

En svårighet med denna typ av forskning är att stamning verkar vara en heterogen störning, med skiftande orsaksbakgrund och skiftande symtom, men det är inte klart hur dessa skillnader ska beskrivas. Följande strategi formulerades vid planering av projektet:

- Att ge hög prioritet för teoretisk utveckling baserat på redan publicerade data.
- Att använda en bred ansats och undersöka många olika aspekter hos samma individer.
- Att använda en kombination av s.k. explorativa studier och prövning av specifika hypoteser.

E. Teoretiskt arbete

Det teoretiska arbetet var särskilt inriktat på två olika aspekter, dels *stress/oro*, dels *basala ganglierna*.

E.1. Artikel I: Stamning och förväntat obehag

Artikel I är en förnyad analys av publicerade data angående hjärtfrekvensen hos stammande personer i stressande talsituationer. Denna typ av studie har inte kunnat visa något tydligt samband mellan stamning och stress eller oro. Tvärtom har flera studier rapporterat *lägre* hjärtfrekvens och blodtryck hos stammande personer när de utsätts för stressande press att tala. Detta har lett några författare till den oväntade slutsatsen att stamning skulle *minska* stress, och att stamning skulle uppfylla någon typ av omedvetet behov hos dem som stammar. Med andra ord, resultaten av dessa studier har föreslagits stödja en psykoanalytisk förklaring av stamning.

I artikel I argumenteras för att dessa rapporter har blivit misstolkade: sänkning av hjärtfrekvens och blodtryck är en normal och vanlig reaktion hos människor och andra däggdjur i situationer där man förväntar sig att något obehagligt kommer att inträffa, när man inte vet hur man bäst ska hantera situationen. Denna typ av reaktion har också kallats "freezing", eftersom den är förknippad med varierande grad av hämning av rörelserna. Vidare föreslås i artikeln att hos stammande är denna reaktion en effekt av tidigare negativa erfarenheter av stamning, vilka kan skapa förväntan om obehag i talsituationer.

E.2. Artikel II + fortsatt diskussion i avhandlingen: Stamning och basala ganglierna

Vänster och höger hjärnhalva. Den mest spridda neurologiska teorin om stamning, under de senaste 75 åren, har varit att stamning orsakas av en konflikt mellan vänster och höger hjärnhalva angående styrningen av talet. Normalt styrs talet framför allt av vänster hjärnhalva, men hos stammande personer verkar höger hjärnhalva vara mer aktiv än normalt vid tal. I artikel II argumenteras dock för att den ovanligt kraftiga inblandningen av höger hjärnhalva inte orsakar stamning, utan istället delvis kompenserar för den grundläggande störningen.[1]

Basala ganglierna: en del av "mittsystemet". En alternativ teori, som föreslås i denna avhandling, är att stamning orsakas av en störning i den automatiska produktionen av en talsekvens. Störningen är kopplad till det *mediala premotoriska systemet* i hjärnan, eller förkortat *mittsystemet*.[2] "Premotorisk" syftar på att detta system medverkar i planering och styrning av motorik, inklusive tal. Mittsystemet är lokaliserat runt hjärnans mittlinje, och består framför allt av *basala ganglierna* och *supplementära motor-arean* (SMA). Basala ganglierna är en samling strukturer ungefär i mitten av hjärnan, med viktiga funktioner för automatisering av olika typer av beteenden, inklusive motorik vid tal. Ett välkänt exempel på en störning av basala gangliernas funktion är Parkinsons sjukdom, som orsakas av brist på signalsubstansen *dopamin* och som resulterar i svårigheter att initiera rörelser. Dopamin reglerar funktionen hos basala ganglierna på ett komplext sätt, i samspel med flera andra signalsubstanser. SMA är en del av hjärnbarken och antas ha en nyckelroll när det gäller att generera "startsignaler" för rörelser, inklusive talorganens rörelser.

Grundvalen för denna teori är att tal kan beskrivas som en motorisk sekvens, där stavelser och ljud utgör delar (segment). Det är sannolikt att basala ganglierna och SMA har en viktig funktion vid normalt tal: att basala ganglierna genererar "tidsmarkörer" vid slutet av segmenten i sekvensen, och därigenom signalerar till SMA att ge startsignal för nästa segment. Den centrala störningen vid stamning föreslås vara bristande funktion hos dessa startsignaler.

Dubbla premotoriska system. En slående aspekt av stamning är att symptomen vanligtvis inte märks under vissa omständigheter, t.ex. vid tal i takt med metronom, vid högläsning tillsammans med någon annan eller vid sång. I avhandlingen föreslås att dessa fenomen kan förklaras med att hjärnan har två parallella premotoriska system, med vissa funktionella skillnader: *mittsystemet* (diskuterat ovan) och *sidosystemet.* Sidosystemet består av den *laterala premotoriska hjärnbarken* och *lillhjärnan*. När talkontrollen växlas från mittsystemet till sidosystemet är stamningssymtomen borta eller minskade.

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[1] Detta har föreslagits tidigare, av A. R. Braun och medarbetare (1997).

[2] Denna terminologi är en översättning och förkortning av "the medial premotor system". I nästa avsnitt diskuteras även "the lateral premotor system", eller "sidosystemet". Modellen om dubbla premotoriska system är formulerad av G. Goldberg (1985; 1991), "the dual premotor systems hypothesis", dock utan koppling till stamning.

Enligt denna modell har båda systemen förmåga att styra startsignalerna för talsekvensen, men med vissa begränsningar. Vid spontant tal, som syftar till att förmedla ett budskap och som baseras på en vilja att kommunicera, så styrs startsignalerna normalt genom mittsystemet. Men om startsignalerna på något sätt kopplas till yttre signaler (t.ex. en metronom eller rösten av en annan person vid högläsning tillsammans) så tas styrningen över av sidosystemet. Detta skulle förklara varför stamning inte visas under dessa förhållanden: störningen hos mittsystemet kopplas förbi vid växlingen till sidosystemet.

Sidosystemet har förmåga att producera startsignaler även utan stöd från yttre signaler, men det kräver en förhöjd nivå av uppmärksamhet på någon aspekt av talet, vilket gör talet mindre spontant. I avhandlingen föreslås att denna effekt visas när stamningen minskar vid imitation av en dialekt, vid tal med överdriven rytm eller vid tal med medvetet kontrollerad sänkt talhastighet. Även tal vid rollspel, då uttrycken är medvetet kontrollerade, skulle enligt denna modell styras av sidosystemet. Vidare föreslås att den typiska frånvaron av stamning vid sång också är en effekt av denna mekanism: när man sjunger är den exakta tidpunkten för varje stavelse bestämd av rytmen i sången, och forskningsstudier pekar på att denna rytm produceras av sidosystemet.

En intressant aspekt av stamning är att talstörningen ofta minskas tydligt av förändring av hörselåterkopplingen, d.v.s. när en elektronisk anordning med mikrofon och hörsnäcka används för att ändra hur den egna rösten hörs. Tonhöjden av rösten kan förändras och ljudet kan fördröjas en aning. Den bakomliggande mekanismen är sannolikt komplex, men med utgångspunkt från aktuell forskning om hjärnan argumenteras i avhandlingen att denna förändring av hörselåterkopplingen understödjer skifte i talkontrollen från mittsystemet till sidosystemet. Detta är i linje med principen att sidosystemet är aktivt när tal kombineras med bearbetning av sinnesintryck.

Fluktuationer i funktionen hos mittsystemet. Det är en vanlig observation att symtom av olika motoriska störningar hos basala ganglierna tenderar att fluktuera beroende på t.ex. stress och stämningsläge. Sådana fluktuationer verkar finnas i de flesta fall av stamning. En modell föreslås där graden av stamningssymtom vid ett visst tillfället påverkas av graden av motstridiga impulser (tankar eller känslor) i situationen. En hög nivå av motstridiga impulser kan resultera i ökad stamning, medan entydiga impulser, t.ex. odelad glädje eller vrede, tenderar att öka talflytet. På samma sätt kan tal när man är ensam eller tal med husdjur ses som situationer med en låg grad av motstridiga impulser, och vanligen en hög grad av flyt i talet.

Denna modell kan leda till frågan om stamning orsakas av psykologiska konflikter. Dock pekar tillgängliga data på att stammande personer i allmänhet *inte* har en förhöjd nivå av "neurotisism" eller allmän oro. Istället finns stöd för en modell där bestående stamning är kopplad till ett neurologiskt tillstånd med sänkt tröskel för avbrott i talet.

Det bör påpekas att graden av stamningssymtom vid ett visst tillfälle sannolikt påverkas av en lång rad faktorer, t.ex. graden av uppmärksamhet på talet (ibland mer stamning vid avkoppling), tidspress, tidigare negativa erfarenheter av en viss situation, och allmäntillståndet (t.ex. förkylning). En slutsats av detta resonemang är

att det psykologiska tillståndet hos en stammande person inte låter sig bedömas utifrån mängden observerad stamning.

"Medrörelser". I vissa fall är stamningen förknippad med ofrivilliga rörelser och ökad muskelspänning. Dessa s.k. medrörelser har ofta betraktats som sekundära inlärda beteenden, vilka i början hade syftet att underlätta talet. I avhandlingen diskuteras möjligheten att dessa rörelser och den förhöjda muskelspänningen kan ses som en typ av *dystoni*, med direkt koppling till den neurologiska orsaken till stamningen.[3] Termen dystoni betecknar motoriska symtom som kännetecknas av ofrivilliga muskelsammandragningar, ofta med spridning till näraliggande muskler. Dystoni kan drabba alla delar av kroppen, är ofta begränsad till starkt automatiserade sekventiella rörelser (t.ex. att skriva eller spela ett instrument), blir ofta värre av stress, och orsakas troligen av olika typer av störningar i basala ganglierna.

Tillfällig barnstamning. Stamning uppvisar ett mönster där de flesta fall börjar tidigt i barndomen, följt av att en stor andel slutar stamma redan som barn. Tillgängliga data tyder på att orsaksfaktorerna bakom stamning är starkast och vanligast förekommande vid åldern 2,5 till 3 år. Därefter minskar styrkan av dessa faktorer i de flesta fall under förskoleåldern. I artikel II argumenteras för att detta mönster framför allt avspeglar en naturlig topp i antalet dopaminreceptorer typ D2 i basala ganglierna vid 2 till 3 års ålder.

F. Experimentella studier

Laboratorieutrustning byggdes upp för projektet. Sammanlagt 35 stammande vuxna och 40 kontrollpersoner utan stamning deltog i de olika testen (dock inte alla i alla test). Tre rapporter av de experimentella studierna ingår i denna avhandling, och två kommer att rapporteras senare (analys av talsymtom och ett test av inflytande av hörseln på talet).

F.1. Artikel III: Koppar och stamning

Det har tidigare rapporterats att stammande män skulle ha lägre nivå av koppar i blodet än normalt, och att svårighetsgraden av stamning skulle ha ett omvänt samband med nivån av koppar. Vidare är det känt att sällsynta störningar av kopparomsättningen kan ge störd funktion hos basala ganglierna, med dystoni. Det har också visats att koppar kan påverka viktiga signalsubstanser i basala ganglierna. Mot denna bakgrund undersöktes nivån av koppar och kopparbindande protein hos de stammande och kontrollpersonerna, och nivån av "fritt" koppar beräknades. Dock visade resultatet ingen skillnad mellan grupperna och inget samband mellan lågt koppar och svårare stamning. Denna studie gav alltså inte stöd för den tidigare rapporten om samband mellan lågt koppar i blodet och stamning.

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[3] Att stamning kan ses som en form av dystoni har föreslagits tidigare, av G. Kiziltan och M. A. Akalin (1996) och av M. Victor och A. H. Ropper (2001).

F.2. Artikel IV: Stamning och förmågan att undertrycka ljud

Hjärnans automatiska förmåga att undertrycka bearbetning av vissa störande ljud kan mätas med en metod som kallas "startle prepulse inhibition". Metoden innebär att en blinkreflex framkallas, som en reaktion på ett starkt och plötsligt brusljud, och styrkan av blinkningen mäts. Om det starka ljudet föregås av ett svagt ljud, med ca 0,1 sekunder, så undertrycks normalt blinkreflexen. Detta kan tolkas som ett uttryck för en filterfunktion hos hjärnan, så att hjärnan fokuserar på det första ljudet och därför undertrycker bearbetningen av följande ljud. Det har visats att denna filterfunktion är försämrad vid vissa störningar som påverkar basala ganglierna. Om stamning har samband med en störning hos basala ganglierna kanske även stammande uppvisar en sådan minskad filterfunktion. En annan möjlighet som vi ville undersöka var om denna filterfunktion kunde ha samband med effekten av förändrad hörselåterkoppling att minska stamning. Så vitt vi vet har "startle prepulse inhibition" inte tidigare testats på stammande.

Den stammande gruppen jämfördes med en grupp kontrollpersoner utan stamning. De två grupperna visade mycket lika resultat och det fanns inget samband mellan graden av filterfunktion och effekten av förändrad hörselåterkoppling på stamning. Slutsatsen blev att denna förmåga att undertrycka ljud inte har samband med stamning.

F.3. Artikel V: Neuromuskulär reaktivitet, temperament och biologiska faktorer

Artikel V är en omfattande rapport av ett flertal variabler, men med fokus på hypotesen att stamning kan ha samband med ökad "neuromuskulär reaktivitet", d.v.s. en tendens till starkare nervsignaler och kraftigare muskelsammandragningar än normalt. En sådan tendens har ibland satts i samband med ett allmänt känsligt temperampent och tendens till oro. I studien mättes neuromuskulär reaktivitet som styrkan av blinkreflexen då man utsätts för ett starkt plötsligt brusljud (på engelska: "startle reflex"). Denna blinkreflex har även setts som en indikation på ökad nivå av ängslighet och oro.

F.3.1. Översikt av tidigare rapporter

Reaktivitet och oro. En tidigare studie (B. Guitar, 2003) rapporterade i genomsnitt 81% starkare blinkreflex hos de stammande jämfört med kontroll-gruppen, och att detta drag hade samband med ett "nervöst" temperament. Även andra studier har rapporterat förhöjda tendenser till oro hos stammande vuxna. Dock pekar en granskning av litteraturen på att denna förhöjda nivå av oro är begränsad till sociala talsituationer, och framför allt är en effekt av själva talproblemet — alltså inte ett grundläggande personlighetsdrag.

Temperament hos stammande barn. Studier av temperament hos stammande barn har gett blandade och motstridiga resultat. En möjlig tolkning av tillgängliga data är att temperamentet hos stammande barn kan beskrivas som en skala med två poler: (1) Barn som är välanpassade, har god koncentrationsförmåga, och väl utvecklad språklig förmåga — ibland ovanligt tidig språkutveckling. (2) Barn med drag av

uppmärksamhetproblem och/eller hyperaktivitet (s.k. ADHD), med t.ex. impulsivitet, inlärningsproblem, och försenad motorisk utveckling.

F.3.2. Resultat

Reaktivitet och oro. Till skillnad mot den tidigare studien av blinkreflex och stamning visade denna studie ingen statistiskt signifikant skillnad mellan stammande vuxna och kontrollgruppen (i genomsnitt ca 20 % starkare blinkreflex hos den stammande gruppen, men med stor överlappning). Liksom flera tidigare studier visade ett frågeformulär en högre grad av oro i den stammande gruppen. Som diskuterats här ovan kan detta resultat vara en sekundär effekt av talproblemet.

Ett intressant resultat var att styrkan hos blinkreflexen visade ett svagt *omvänt* samband med graden av oro i den stammande gruppen. Detta tyder på att styrkan av blinkreflexen inte är användbar som mått på ett oroligt temperament. Vidare visade blinkreflexens styrka bara ett mycket svagt samband med stamningens svårighetsgrad. Sammanfattningsvis ger denna studie inte stöd för att förhöjd neuromuskulär reaktivitet skulle vara ett typiskt drag hos stammande personer, även om ett svagt samband kan finnas.

Kalcium i relation till blinkreflexens styrka. Studien visade att stark blinkreflex hade samband med låg nivå av kalcium i blodet, både hos de stammande och hos kontrollgruppen. Detta är inte förvånande, eftersom det är väl känt att nervsystemets retbarhet ökar när nivån av kalcium sjunker, med ökad risk för kramper. Totalt sett kunde skillnader i kalciumnivå förklara ungefär 28% av skillnaderna i blinkreflexens styrka i denna studie.

Kalcium i relation till oro och stamning. Det är känt att låga nivåer av kalcium kan ge ökad tendens till oro och ångest. Den stammande gruppen hade något lägre genomsnittlig nivå av kalcium än kontrollgruppen, med ett svagt samband mellan lågt kalcium och svårare stamning. Det är möjligt att låga nivåer av kalcium i blodet kan förvärra stamning. Dessa resultat behöver dock bekräftas av fortsatta studier.

Drag av ADHD i barndomen. Med utgångspunkt från ett frågeformulär uppskattades graden av drag av ADHD under barndomen (d.v.s. uppmärksamhetsproblem, hyperaktivitet, etc.). Den stammande gruppen visade i genomsnitt tydligt högre nivå av drag av ADHD under barndomen jämfört med kontrollgruppen, men i de flesta fall inte tillräckligt för att ge diagnosen ADHD. De stammande deltagarna var ganska jämt fördelade på denna skala, från avsaknad av drag av ADHD till tydliga ADHD-drag. Det mest typiska draget hos stammande deltagare med drag av ADHD under barndomen var uppmärksamhetsproblem och "dagdrömmande".

Drag av ADHD i barndomen i relation till ärftlighet och neurologiska skador. Ett intressant mönster visas om den stammande gruppen delas i två halvor, med starka respektive svaga drag av ADHD. I gruppen med relativt starka drag av ADHD rapporterade de flesta deltagare indikationer på möjliga neurologiska skador före stamningen började, men färre rapporterade stammande släktingar. Den vanligaste rapporterade incidenten var skallskada (typ hjärnskakning, ledande till sjukhusvård eller medvetslöshet), förlossningskomplikationer, eller för tidig födsel.

Detta är i linje med publicerade studier som funnit ökad risk för ADHD efter denna typ av händelser. Tvärtom rapporterade de flesta personerna i gruppen med svaga drag av ADHD minst en stammande släktning, men få rapporterade indikationer om neurologisk skada före det att stamningen började.

Neurologiska skador och drag av ADHD kan även ha samband med förhöjda nivåer av oro och ångest. Resultatet av denna studie visade en svag tendens till högre nivå av oro hos deltagare med drag av ADHD.

Sammanfattningsvis pekar resultatet på att fall med ärftligt betingad bestående stamning vanligen inte uppvisar drag av ADHD under barndomen. Däremot tenderar fall av stamning till följd av neurologiska skador att uppvisa förhöjda ADHD-drag, särskilt uppmärksamhetsproblem, dock i de flesta fall inte i tillräcklig omfattning för att ge diagnosen ADHD.

F.3.3. Diskussion

Neurologiska skador och basala ganglierna. Skallskador och förlossningskomplikationer kan öka risken för stamning. Det är möjligt att dessa skador framför allt är kopplade till basala ganglierna. När det gäller hjärnskakning verkar den centrala mekanismen som orsakar medvetslöshet vara en rotationskraft med centrum i den övre delen av *hjärnstammen*. Detta kan resultera i diffusa skador hos nervbanorna i denna region, som inkluderar basala gangliernas banor och dopaminsystemet. När det gäller förlossningskomplikationer och för tidig födsel kan basala ganglierna vara särskilt sårbara, med risk för diffus förlust av nervceller och förändringar hos signalsubstanssystemen.

Genetik och stamning. Publicerade data tyder på att flera olika gener kan bidra till ökad risk för stamning. Det är tänkbart att de flesta av dessa gener inte är specifikt kopplade till stamning, utan istället är varianter inom den normala genetiska variationen. Detta innebär att genetiskt betingad stamning kan uppstå även utan stammande släktingar, om vissa gener råkar sammanfalla hos en viss individ. I artikel V argumenteras för att ett möjligt genetiskt drag bakom stamning är en hög nivå av dopaminreceptorer typ D2 i den motoriska delen av basala ganglierna.

SUMMARY

A. Main points of the thesis, in brief

- *Suggested theory of stuttering.* The brain has two parallel systems for timing of the syllables and sounds in speech, *the medial* and *the lateral system*. Stuttering is related to the medial system, which includes the *basal ganglia* (structures in the middle of the brain involved in automatization of various behaviors). The main problem is proposed to be impaired "go-signals" for the syllables and the sounds in spontaneous speech. It is suggested that under some conditions the speech timing is shifted to the lateral system, thereby making speech fluent or reducing stuttering: (a) when speech is linked to sensory input, as during choral reading or metronome paced speech, (b) when some aspect of speech is controlled using a raised level of attention, as during imitation of a dialect, exaggerated rhythm, or reduced speech rate, and (c) when singing. Also "altered auditory feedback" is proposed to support a shift to the lateral system, based on the involvement of the lateral system in encoding of sensory input.

- Stuttering is not based on a "nervous" constitution, but is related to a lowered threshold for speech disruptions. Increased anxiety for speech situations may develop as an effect of the speech difficulties. The symptoms tend to fluctuate depending on a range of variables, of which one may be emotional responses.

- A subgroup reported some traits of attention deficit hyperactivity disorder (ADHD) during childhood. Most of these participants also reported various incidents of a neurological nature before the onset of stuttering, like birth complications or concussion with unconsciousness, possibly affecting the basal ganglia. In contrast, the participants without traits of ADHD in childhood typically reported at least one stuttering relative but no special incidents of a neurological nature.

B. Definition of stuttering

The following tentative definition of stuttering is proposed, partly based on previous definitions:

> Stuttering is a speech disorder characterized by difficulties to move forward in the speech sequence, when the person knows what to say.
>
> The difficulties are expressed as: sound initiation problems; prolongations of sounds; repetitions of sounds, syllables, words, or phrases; rephrasing; pauses; superfluous sounds or words; or avoidance of speech.
>
> In some cases the difficulties to move forward in the speech sequence are associated with abnormalities in muscular tension or abnormal movements, especially in the throat, mouth, and face, but also in the rest of the body.

The disorder may be hidden if the person manages to use conscious strategies to avoid display of symptoms.

The symptoms are typically absent during singing, chorus speech, or paced (metronome) speech.

C. Background

This thesis is an attempt to clarify the causal mechanisms behind one of the most common speech disorders, *stuttering* or *stammering*, which in some cases constitutes a severe impediment of communication. The causes of stuttering have remained obscure. A plethora of explanations have emerged, proposing psychological, social, learning, or neurological models. The thesis focuses the brain in relation to stuttering, based on the rationale that any factor affecting stuttering is likely to be expressed through the functions of the brain.

D. Project strategy

One problem in this type of research is that stuttering clearly is a heterogeneous disorder, with various causal backgrounds and varying expression of symptoms, but it is not clear how this heterogeneity should be described. The following basic strategy was outlined for the project:

- To give high priority to theoretical development based on published data.
- To use a broad approach, investigating many aspects in the same persons.
- To use a combination of explorative studies and testing of specific hypotheses.

E. Theoretical work

The theoretical work focused two main lines of interest: the role of *anxiety* and the role of the *basal ganglia.*

E.1. Paper I: Stuttering and anticipatory anxiety

Paper I is a renewed analysis of published heart rate data of stuttering persons, related to stressful speech situations. Studies of this type have failed to find any major relation between anxiety and stuttering. In fact, several studies have reported *lower* heart rate and blood pressure in stuttering persons when exposed to stressful speech demands. This has led some authors to the counterintuitive conclusion that stuttering would *reduce* stress, and that stuttering would fulfill some kind of unconscious need. In other words, the results of these studies have been suggested to support a psychoanalytic explanation of stuttering.

In paper I it is argued that the heart rate data have been misinterpreted: reduction of heart rate and blood pressure is a natural and common response in humans and other mammals in situations characterized by anticipatory anxiety and uncertainty about how to handle the situation. This type of reaction has also been termed "freezing", because it tends to be related to various degrees of movement inhibition. Further, it is suggested that in stuttering persons this response results from previous negative experiences of stuttering, causing anticipatory anxiety in speech situations because of uncertainty about how to handle possible speech disruptions.

E.2. Paper II + further discussion in the thesis: Stuttering and the basal ganglia

The left and the right hemispheres. The most widespread neurological theory of stuttering, during the last 75 years, has been that stuttering is caused by a conflict between the left and the right hemispheres of the brain, with regard to speech motor control. Normally the main control of speech is in the left hemisphere, but in stuttering persons the right hemisphere seems to be more involved than in most people. However, in paper II it is argued that this unusually strong right side involvement does not cause stuttering, but instead partially compensates for the basic dysfunction.[4]

The basal ganglia: a part of the medial premotor system. An alternative theory, proposed in this thesis, is that stuttering is caused by an impairment of the automatized execution of speech sequences. The impairment is related to *the medial premotor system* of the brain. The medial premotor system is located along the midline of the brain, and its main parts are the *basal ganglia* and the *supplementary motor area* (SMA). The basal ganglia are a set of structures located in the center of the brain, which play an important role in the automatization of various types of behaviors, including the motor aspects of speech. A well-known example of basal ganglia dysfunction is Parkinson's disease, caused by deficiency of the neurotransmitter *dopamine* and resulting in difficulties in initiating movements. Dopamine regulates the functions of the basal ganglia in a complex way, in concert with several other neurotransmitters. The SMA is a part of the cerebral cortex, assumed to play a key role in providing the "go-signal" for movements, including the movements of the speech organs.

The basis for this theory is that speech can be described as a motor sequence, where syllables and sounds constitute segments. It is likely that the basal ganglia and the SMA have an important function in normal speech: that the basal ganglia generate "timing cues" at the end of the segments in the sequence, thereby signaling to the SMA to give the go-signal for the next segment. The core dysfunction in stuttering is suggested to be an impairment of these go-signals.

The dual premotor systems model. One striking aspect of stuttering is that the symptoms typically are absent under certain conditions, like speaking to the pace of a metronome, chorus reading, or singing. It is proposed in this thesis that many of these phenomena can be explained by the existence of two parallel premotor systems in the human brain, with functional differences: *the medial* (discussed above) and *the lateral*.[5] The main parts of the lateral system are the *lateral premotor cortex* and the *cerebellum.* When the speech control is shifted from the medial to the lateral system, stuttering is absent or reduced.

According to this model both these systems are able to control the timing of the speech sequence, but with some limitations. In spontaneous speech, that is intended

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[4] This has been suggested previously, by A. R. Braun and coworkers (1997).

[5] The dual premotor systems hypothesis, formulated by G. Goldberg (1985; 1991).

to convey a message and that is based on an urge to communicate, the control of timing is normally channeled through the medial system. In contrast, when the timing of speech segments is linked to external stimuli (like a metronome or the voice of another person in chorus reading), the timing is executed by the lateral system. This would explain why no stuttering is shown under these conditions: the impairment of the medial system is bypassed by the shift to the lateral system.

The lateral system has the ability to control timing of speech without external input, but this demands an increased level of conscious attention to some aspect of speech, thereby making speech less spontaneous. This effect is proposed to be demonstrated by reduced stuttering during imitation of a dialect, in speech with exaggerated rhythm or, for example, by a consciously controlled reduced speech rate. Also speech in role play, where the expression is controlled and does not reflect the emotional state, should, according to this model, be controlled by the lateral system. Further, it is suggested that the typical absence of stuttering in singing also is an expression of this mechanism: when singing, the exact timing of each syllable is determined by the rhythm, and research indicate that this timing is produced by the lateral system.

One interesting aspect of stuttering is that it is often clearly improved by altered auditory feedback, i.e., when an electronic device with a microphone and an earphone is used in order to change the way in which the speaker's own voice is heard. The pitch of the sound can be shifted and the sound can be slightly delayed. This type of alteration has a strong fluency enhancing effect in many cases of stuttering. The mechanism is likely to be complex, but based on recent findings from brain research it is argued that this auditory alteration tends to support a shift in speech control from the medial to the lateral system. This is in line with the basic principle that the lateral system is active when speech is combined with perception of sensory input.

Fluctuations in the function of the medial system. It is a common experience that the symptoms of various motor disorders of the basal ganglia tend to fluctuate depending on the emotional state, and such an emotional variation seems to exist in most cases of stuttering. A model is suggested where the momentary severity of stuttering may be related to the degree of conflicting impulses (emotions or thoughts) in a situation. A high level of conflicting impulses tends to result in a "freezing" state with increased stuttering, whereas unambiguous impulses, like unmingled happiness or anger, tend to improve speech fluency. Likewise, speaking when alone or speaking to pets constitutes a situation with a low level of conflicting impulses, usually associated with a high level of fluency.

This model may lead to the question of whether stuttering is caused by psychological conflicts. However, available data suggest that stuttering persons typically *do not* have an increased level of "neuroticism" or general anxiety. Instead the data seem to support a model where persistent stuttering is related to a neurological constitution involving a lowered threshold for speech disruptions.

It should, however, be noticed that the momentary severity of stuttering is likely to be influenced by a wide range of factors, like the level of attention given to speech (sometimes more stuttering in relaxed situations), time pressure, previous negative experience of certain situations, and the general physiological state (having

a cold, etc.). A conclusion based on this reasoning is that the psychological state of a person who stutters cannot be deduced from the observed level of stuttering.

Accessory movements. In some cases the moments of stuttering are accompanied by involuntary movement and increased muscular tension. These movements have often been regarded as secondary learned behaviors, which initially served to support initiation of speech. In this thesis it is suggested that this superfluous muscular activation may be regarded as a type of *dystonia*, directly related to the neurological cause of stuttering.[6] The term dystonia signifies motor symptoms characterized by involuntary muscular contractions, often with spreading of contractions to adjacent muscles. Dystonia can affect all parts of the body, is often limited to highly automated sequential motor tasks (like writing or playing an instrument), is often worsened by stress, and seems to be caused by various basal ganglia disturbances.

Recovering childhood stuttering. Stuttering has a typical pattern of onset in childhood, followed by a high rate of childhood recovery. Available data indicate that the causal factors for stuttering tend to be strongest and most frequent at age 2.5 to 3 years. Thereafter the strength of these factors drops rapidly in most cases during the preschool years. It is argued in paper II that this pattern mainly reflects a naturally occurring peak in the number of basal ganglia type D2 dopamine receptors at the age 2 to 3 years.

F. Experimental studies

Laboratory facilities were set up for the project. A total of 35 stuttering adults and 40 non-stuttering controls participated in the various tests (though not all the persons in all the tests). Three reports of the experimental studies are included in this thesis, and two will be reported later (analysis of speech symptoms and one study of the influence of hearing on speech).

F.1. Paper III: Copper and stuttering

A study has previously been reported in which the stuttering men appeared to have lower levels of copper in the blood than normal, and their severity of stuttering were reversely related to the level of copper. Further, it is known that rare disorders of copper metabolism can result in dysfunction of the basal ganglia and dystonia. It has also been shown that copper can affect important neurotransmitters in the basal ganglia. Against this background the levels of copper and copper binding protein were analyzed in the stuttering persons and the control group, and the estimated level of "free" copper was calculated.

However, the result showed no difference between the groups, and no relation between lower copper and more severe stuttering. It was concluded that this study

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[6] That stuttering may be regarded as a type of dystonia has been suggested previously, by G. Kiziltan and M. A. Akalin (1996) and by M. Victor and A. H. Ropper (2001).

did not support the previous report of a relation between low blood level of copper and stuttering.

F.2. Paper IV: Stuttering and the ability to inhibit sounds

The automatic ability of the brain to inhibit processing of some disturbing sounds can be assessed by a method called "startle prepulse inhibition". A blink reflex is elicited, as a response to a sudden loud noise, and the magnitude of the blink reflex (the "startle reflex") is measured. If the loud sound is preceded by a weak sound, at an interval of about 0.1 seconds, the blink reflex is normally inhibited. This can be interpreted as an expression of a filter function of the brain, so that the brain focuses its attention on the first sound and therefore inhibits the transmission of the following sound. It has been shown that this inhibiting function is reduced in some disorders affecting the basal ganglia. Therefore, if stuttering is related to a basal ganglia disturbance it might be the case that also stuttering persons show such an impaired inhibition. Further, it was speculated whether impaired inhibition of sounds might be related to the effect of altered auditory feedback in reducing stuttering. As far as we know, startle prepulse inhibition has not previously been tested on stuttering persons.

The stuttering group was compared with a group of matched controls. However, the two groups showed very similar results, and no relation was found between the level of inhibition and the effect of altered auditory feedback in reducing stuttering. Thus, it was concluded that this type of inhibition of sounds is not related to stuttering.

F.3. Paper V: The acoustic startle response, temperamental traits, and biological factors

Paper V is a report of several variables, but with its main focus on the hypothesis that stuttering might be related to increased neuromuscular reactivity and a sensitive or reactive temperament. Neuromuscular reactivity was defined as the magnitude of the "acoustic startle reflex", and was measured as the magnitude of the eye-blink in response to sudden bursts of loud noise. The acoustic startle reflex has been regarded as an indication of a sensitive temperament and increased levels of anxiety.

F.3.1. Review of literature

Reactivity and anxiety. A previous study (B. Guitar, 2003) reported on average an 81% stronger startle reflex in stuttering adults than in the control group, and indicated that this trait was related to a "nervous" temperament. Also other studies have reported significantly elevated levels of "trait anxiety" in stuttering adults. However, a review of the literature indicates that this elevated level is limited to social situations involving speech, and that the anxiety mainly is a secondary effect of the speech difficulties — not a constitutional trait.

Temperament in stuttering children. Studies of the temperament of stuttering children have yielded mixed and contradictory results. One possible interpretation of available data is that the temperament of stuttering children can be described as a

continuum with two poles: (1) Children who are well adjusted, having good skills of concentration, with language abilities that are well developed and sometimes precocious, and being "easy children". (2) Children who have traits of attention deficit hyperactivity disorder (ADHD), showing excessive motor activity, impulsiveness, inattention, problems of learning, and delayed motor development.

F.3.2. Results

Reactivity and anxiety. In contrast to the previous study of startle and stuttering, this study did not find a statistically significant difference in startle reactivity between the stuttering adults and the control group (on average 20% higher average startle amplitude in the stuttering group, but with large overlap). In agreement with several previous studies a higher level of anxiety was found in the stuttering group. As discussed above, this group difference may well be a secondary effect of the speech difficulties.

One interesting result was that the startle reactivity showed a slight *negative* relation to anxiety in the stuttering group, thereby indicating that startle reactivity is not a valid indication of an anxious temperament. Furthermore, the level of startle reactivity was very weakly related to the severity of stuttering. In summary, this study does not support that increased neuromuscular reactivity is a typical trait of stuttering persons, even though a weak relation may exist.

Calcium in relation to startle reactivity. It was found that high startle reactivity was related to low levels of calcium in the blood, both in the stuttering group and in the controls. This is not surprising, because it is well known that the nervous system becomes progressively more reactive when the level of calcium is reduced, with increased risk of tetany. Overall, differences in the level of calcium could explain about 28% of the differences in startle reactivity in this study.

Calcium in relation to anxiety and stuttering. It is known that deficient levels of calcium may result in increased anxiety. The stuttering group had somewhat lower average level of calcium than the control group, with a weak relation between low calcium and more severe stuttering. It is conceivable that low levels of calcium may increase the severity of stuttering. However, these findings need to be confirmed by further studies.

Childhood traits of ADHD. Based on a retrospective questionnaire, the level of childhood traits of Attention Deficit Hyperactivity Disorder (ADHD) was estimated. The stuttering group showed on average a clearly higher average level of ADHD traits than the control group, though in most cases below the level for diagnosis of ADHD. The stuttering participants were quite evenly distributed along this scale, ranging from no traits of ADHD at all to marked traits of ADHD. The most typical childhood trait in the stuttering participants with high scores were being inattentive and "daydreaming".

Childhood traits of ADHD in relation to heredity and neurological lesions. An interesting pattern emerges if the stuttering group is split in two halves, with high vs. low traits of ADHD. In the high-ADHD group most of the participants had reported

indications of possible neurological lesions before the onset of stuttering, but fewer had stuttering relatives. The most frequently reported incidents were traumatic head injury (resulting in hospital care or unconsciousness), birth complications, and premature birth. This is in line with published studies which found an increased risk of ADHD after these types of incidents. In contrast, most persons in the low-ADHD group reported at least one stuttering relative but few reported indications of neurological lesions before the onset of stuttering.

Neurological lesions and traits of ADHD may also be related to increased levels of anxiety. The data showed a slight tendency towards higher levels of anxiety in participants with traits of ADHD.

In summary, the results indicate that cases with *hereditary* persistent stuttering typically do not show childhood traits of ADHD. In contrast, cases of stuttering due to neurological lesions tend to show an increased level of childhood ADHD traits, especially inattention.

F.3.3. Discussion

Neurological lesions and the basal ganglia. Head injuries and birth complications may increase the risk of stuttering. It is possible that these lesions tend to be related to the basal ganglia. In cases of concussion the principal mechanism causing unconsciousness seems to be a rotational force centered in the upper part of the *brain stem*. This may result in diffuse injuries of the pathways in this region, which include basal ganglia pathways and the dopamine system. In cases of birth complications or premature birth, the basal ganglia may be especially vulnerable, resulting in diffuse loss of nerve cells and changes in the neurotransmitter systems.

Genetics of stuttering. Published data indicate that several genes may contribute to increased risk of stuttering. It is conceivable that most of these genes are not specifically related to stuttering, but instead are variants within the normal genetic variation. This implies that genetically determined stuttering may occur even in the absence of stuttering relatives, if certain genes happen to coincide in one individual. In paper V it is argued that one possible genetic trait behind stuttering might be a high number of dopamine D2 receptors in the motor part of the basal ganglia.

1. INTRODUCTION

> *Stuttering has been called a riddle. ... It is also and perhaps primarily a puzzle, the pieces of which lie scattered on the tables of speech pathology, psychiatry, neurophysiology, genetics, and many other disciplines. ... Regretfully, but hopefully, we suspect that some of the essential pieces are not merely misplaced but still missing*. (Van Riper, 1982, pp. 1–2)

The quotation above was written by Charles Van Riper after a long life trying to understand his own and other persons' strange difficulties of speech. The thorough work of Van Riper and many others has built the foundation for continued research on stuttering. It is possible that the missing pieces Van Riper was looking for were not attainable at the time of his research, but that the general development of science and technology has put them within our reach.

Stuttering is a problem of speech. As such, it is characterized by the combination of occasions of normal speech, interrupted by temporary inability to move forward in the speech sequence. This on-and-off nature of the symptoms of stuttering makes it very conspicuous to the listener, and often frustrating for the person who stutters. The experience of stuttering is exemplified by Wendell Johnson, a colleague of Charles Van Riper. He described an occasion when he, as a young student with severe stuttering, was given a lift in a car by a teacher:

> *... he stopped to give one of his staff members a ride and as she got in the car he introduced us. ... we had gone about a mile when all of a sudden I finally managed to blurt out, "Puhleased to meet you!" They were startled, and so was I, and I wished I hadn't said it, only I would have been more embarrassed if I hadn't said anything at all* (Johnson, 1961, p. 8)

1.1. Aim of the thesis

The aim of this thesis is to elucidate the causal mechanisms of stuttering, mainly focusing the functions of the nervous system.

1.2. Definitions of stuttering

There have been many attempts to define the essence of stuttering, but there is still no consensus. Andrews and Harris (1964) suggested the following definition:

> *Stuttering is an interruption in the normal rhythm of speech of such frequency and abnormality as to attract attention, interfere with communication, or cause distress to a stutterer or his audience. He knows precisely what he wishes to say, but at the time is unable to say it easily because of an involuntary repetition, prolongation or cessation of sound.* (p. 1)

The same year another widely used definition was proposed by Wingate (1964), as a "standard definition of stuttering" (p. 488):

> *The term "stuttering" means:*
>
> *1. (a) Disruption in the fluency of verbal expression, which is (b) characterized by involuntary, audible, or silent repetitions or prolongations in the utterance of short speech elements, namely: sounds, syllables, and words of one syllable. These disruptions (c) usually occur frequently or are marked in character and (d) are not readily controllable.*
>
> *2. Sometimes the disruptions are (e) accompanied by accessory activities involving the speech apparatus, related or unrelated body structures, or stereotyped speech utterances. These activities give the appearance of being speech-related struggle.*
>
> *3. Also, there are not infrequently (f) indications or report of the presence of an emotional state, ranging from a general condition of "excitement" or "tension" to more specific emotions of a negative nature such as fear, embarrassment, irritation, or the like. (g) The immediate source of stuttering is some incoordination expressed in the peripheral speech mechanism; the ultimate cause is presently unknown and may be complex or compound.* (p. 488)

The World Health Organization (1977) put forward a shorter definition, based on Andrews and Harris (1964):

> *Disorders in the rhythm of speech, in which the individual knows precisely what he wishes to say, but at the time is unable to say it because of an involuntary, repetitive prolongation or cessation of a sound* (p. 202).

Based on the conclusions from the papers in this thesis, in combination with the definitions above, the following definition of stuttering is suggested:

> Stuttering is a speech disorder characterized by difficulties to move forward in the speech sequence, when the person knows what to say.
>
> The difficulties are expressed as: sound initiation problems; prolongations of sounds; repetitions of sounds, syllables, words, or phrases; rephrasing; pauses; superfluous sounds or words; or avoidance of speech.
>
> In some cases the difficulties to move forward in the speech sequence are associated with abnormalities in muscular tension or abnormal movements, especially in the throat, mouth, and face, but also in the rest of the body.
>
> The disorder may be hidden if the person manages to use conscious strategies to avoid display of symptoms.

The symptoms are typically absent during singing, chorus speech, or paced (metronome) speech.

1.3. Theories and research: a historical overview

1.3.1. Different types of theories

The conspicuous nature of the symptoms of stuttering has led to an abundance of speculations and theories about their causes, since ancient times. The two dominating poles in the speculations have been psychosocial versus organic causes. During the last century a third group of theories gained widespread influence, namely theories of stuttering as a learned behavior.

The different types of theories also lead to different interpretations of the symptoms of stuttering. An important distinction can be made between theories that view stuttering as a purposeful behavior versus theories viewing stuttering as merely a breakdown of speech motor control (Bloodstein, 1995). The first group is represented by psychodynamic theories of stuttering as a symbolic expression of repressed needs, and by operant conditioning theories of secondary rewards of stuttering. The second group of theories is represented both by psychological theories of breakdown as a result of emotional stress, and by neurological theories of dysfunctional speech motor control. From the learned behavior perspective stuttering can be viewed as a dysfunctional habit. This division of theories is illustrated schematically in Figure 1. However, it is important to emphasize that many theories are eclectic, combining psychosocial, organic, and learning elements. But most theories have their main focus on one of these aspects.

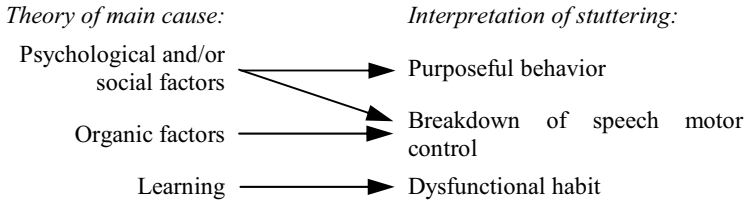

Figure 1. Schematic illustration of the main types of theories of stuttering, and corresponding interpretations of the behavior of stuttering.

1.3.2. The history of stuttering

In order to understand the current state of affairs it is important to have at least some knowledge of the history that got us here. It is also essential to learn from the ingenious efforts of the past. When studying what has been thought and written about stuttering it is striking how the same basic theories and concepts have emerged repeatedly, albeit in different formulations, over the past 200 years. Actually, it seems fair to say that most of the current ideas concerning stuttering were expressed in their initial form prior to 1930. The following historical review must by necessity be fragmentary and incomplete, but hopefully it will reflect the main lines.

1.3.3. Before the 19th century

Early hypotheses about stuttering included ideas that the strange behavior was instituted by gods or devils (Bryngelson, 1942). Another important line of thinking, from Aristotle (384 B.C.) until the first half of the 19th century, was that stuttering was caused by dysfunction of the tongue (Van Riper, 1982). In the seventeenth century Francis Bacon considered that the tongue was too stiff and cold, a condition he treated with moderate doses of wine (Bryngelson, 1942) — a treatment which might have been appreciated.[7] Other organic theories were proposed, e.g. dysfunctions of the tonsils, the uvula, the airways, or, as suggested by Hippocrates, an accumulation of "black bile" (Van Riper, 1982). Hippocrates seems to have held the opinion that stuttering persons had too many thoughts occurring too fast (Sjöholm, 1911).

In 1584 the physician Hieronymus Mercurialis differentiated between *balbuties naturalis*, stuttering due to hyperexcitability of the brain, and *balbuties accidentalis*, stuttering as a result of shock or frightening experiences (Freund, 1966). The German philosopher Moses Mendelssohn, who is said to have stuttered himself, considered stuttering to be more psychological than organic. In 1783 he suggested that stuttering may be the result of collisions between different ideas or impulses trying to use the same speech organs at the same time (Froeschels, 1961).

1.3.4. The 19th century to the beginning of the 20th century, focus on Europe

From the middle of the 19th century to the first part of the 20th century German and Austrian clinicians were very influential, proposing neurological, psychoanalytical, and learning theories of stuttering. This period in central Europe may be viewed as the cradle for the main modern theories of stuttering.

1.3.4.1. Surgery

In the first half of the 19th century scientific reasoning about stuttering started to develop, but there also emerged a number of less valuable ideas. The surgeon J. F. Dieffenbach in Berlin thought that stuttering was related to dysfunctional reflexes and tried surgery of the tongue in January 1841. A 3/4 inch wide transverse wedge was removed close to the root of the tongue, see Figure 2. After the painful surgery no stuttering could be observed in the first patient. This led to a very rapid spread of the method to France and England. It was reported that in France alone 200 stuttering persons underwent the operation in 1841. However, the enthusiasm soon faded when the effect on stuttering turned out to be very doubtful. It seems that the main effect only lasted until the wound had healed and the pain had faded. Moreover, at least two patients died after the surgery (Appelt, 1945; Sjöholm, 1911).

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[7] It can be noted that early attempts of treatment of stuttering also have been reported from Sweden. One old cure was to take the tongue of a newly slaughtered cow and unexpectedly slap it in the face of the stuttering person (Sjöholm, 1911). However, no controlled clinical trials of this method have yet been reported.

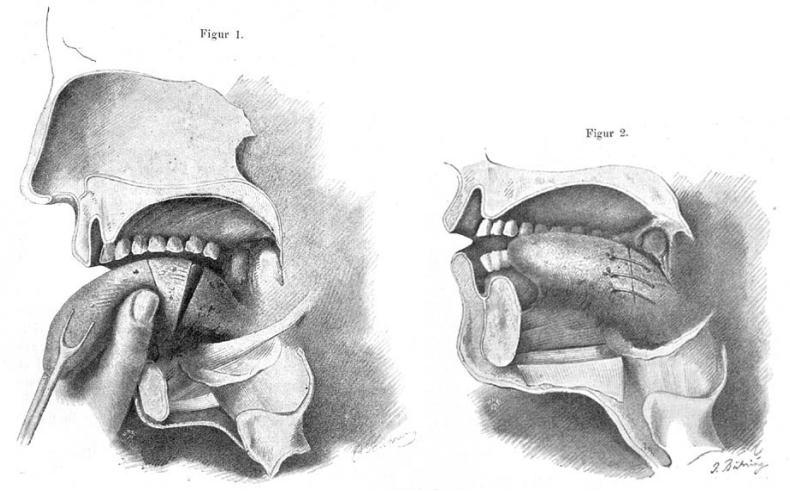

Figure 2. Surgical treatment of stuttering in year 1841. Illustration from Gutzmann (1898).

1.3.4.2. Speech exercises

In New York Mrs. Leigh practiced a secret stuttering treatment in 1825, focusing on tongue exercises, but also including psychological aspects of increased confidence in speech. This method gained much attention as a possible cure for stuttering and spread to Western Europe (Sjöholm, 1911; Smith, 1955; Freund, 1966). Another influential program was developed by the Frenchman M. Columbat (about 1830), mainly based on speech exercises with rhythm.

As early as 1846 to 1848 the German physician Schmalz is reported to have published a program for speech practice with striking similarities to modern programs of *fluency shaping*. Schmalz' program involved reduction of speech rate, smooth abdominal breathing, relaxed onset of phrases, smooth articulation, focus on the phonation, and connecting the words with each other without interruptions (Gutzmann, 1898). [8]

One of the most well-known and widespread treatment programs was developed by Albert Gutzmann around the late 1870's. Albert Gutzmann was director of a school for the deaf in Berlin, and his work with stuttering was continued by his son Hermann Gutzmann. Their program consisted of three main parts: exercises for the respiratory muscles, the phonatory muscles, and the articulation organs (Gutzmann, 1898). See Figure 3, for illustrations of respiration exercises. They also emphasized the importance of gaining psychological confidence in the ability to speak (Sjöholm, 1911; Freund, 1966). Instituting Gutzmann's program, courses for stuttering children were started in Germany in 1886, and spread to a large number of cities. The activity

[8] Alfred Appelt (1945) wrote that Schmalz also suggested "an embrocation of petroleum for the throat" (p. 47) as a treatment for stuttering. It is not clear exactly how the petroleum was used. According to Appelt this recommendation resulted in a "nearly invincible distrust of any treatment" (p. 47) for stuttering for several years, especially in Sweden.

was extensive. In Berlin alone, 24 courses were held during the winter of 1907-1908. The following year this type of course was also introduced in Sweden, in Gothenburg and Stockholm (Sjöholm, 1911).

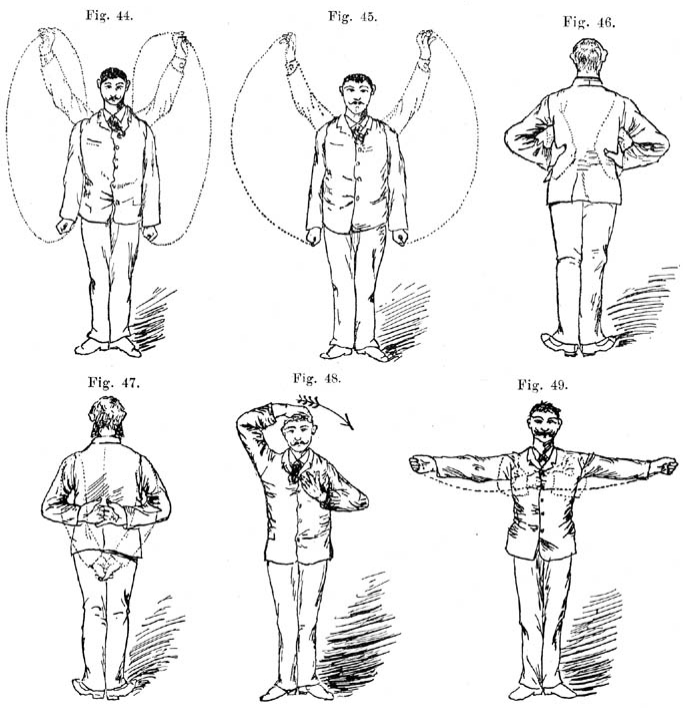

Figure 3. Exercises for the respiratory muscles according to the Gutzmann method. Illustrations from Gutzmann (1898).

1.3.4.3. Neurological theories

Examinations of the speech organs of stuttering persons did not reveal any physical abnormalities. In the first half of the 19th century a new era began, associating stuttering with dysfunction of the nervous system. Stuttering was suggested to reflect for example spasms, chorea, or respiratory incoordination.

An early widespread theory (in the 1820s to the 1840s) was that stuttering resulted from "exaggerated hastiness" of cerebral impulses (Freund, 1966), basically the idea put forward by Hippocrate (as mentioned in Section 1.3.3). In 1898 the physician Hermann Gutzmann in Berlin wrote a comprehensive and detailed book, *Das Stottern*, which became the dominant work on stuttering of his age. Gutzmann argued that stuttering often is related to a deficiency of the cerebral cortex (Van Riper, 1982), and that accessory psychological problems are a consequence of stuttering, not a cause. (See Figure 4 for an illustration by Gutzmann of cortical regions involved in speech.) An argument to support this point of view was that most very young children who stutter tend to do so without showing signs of anxiety (Sjöholm, 1911).

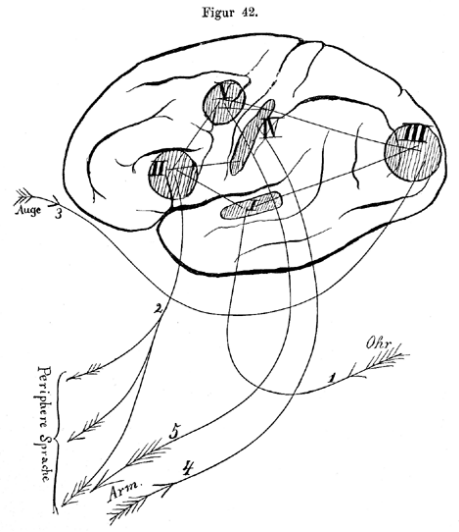

Figure 4. Illustration by Hermann Gutzmann (1898) of cortical regions involved in speech.

One of the most influential modern neurological theories of stuttering, that stuttering is related to the lateralization of the cerebral hemispheres, had an early forerunner in Germany. It is claimed that Stier, after studies of left-handedness, already in 1911 proposed that the cause of stuttering is a battle between the left and right cerebral hemispheres for dominant control of speech (Kistler, 1930, as cited in Van Riper, 1982, p. 326; Freund, 1966). This hypothesis was later made well-known by researchers in America (see Section 1.3.5.1 below).

Also the main theory of the current thesis, that stuttering is related to the basal ganglia, was proposed in Germany almost a century ago. Beginning in 1916 and lasting into the 1920s, an epidemic of encephalitis occurred in Europe, with neurological symptoms of Parkinsonism, hyperkinesia, etc. It was described in 1916 by Dr. Constantin von Economo, and was named Economo's encephalitis or encephalitis lethargica (Dickman, 2001). Freund (1966) wrote that Economo's encephalitis involved speech disturbances such as palilalia and "pseudo-stuttering", and that the disease was known to affect the striatum. The striatum constitutes the largest part of the basal ganglia system, and was regarded to be related to muscular tone and speech drive. According to Freund these observations led a German named Sahli to develop the concept that stuttering is a "striatum neurosis".

Sahli's proposal of a relation between the striatum and stuttering was supported by the German physician Schilder in 1927. In 1934 this theory found its best-known proponent in the phoniatrician M. Seeman of Prague, a former student of Herman Gutzmann. According to Seeman, the striatum is influenced by the action of autonomic centers in the hypothalamus, related to emotions. This emotional influence was thought to cause inhibition or disinhibition of the speech drive in the striatum, finally resulting in the symptoms of stuttering with difficulties in initiating speech, associated movements, and muscular tension. (Freund, 1966)

1.3.4.4. Psychological theories and learning

Carl Ludwig Merkel, professor of medicine in Leipzig and also a person who stuttered, had great influence on the development of psychological theories of stuttering. In his writings from 1842 he claimed that stuttering is based exclusively on psychological conflicts, especially those arising from early childhood traumas. Yet another German physician who stuttered himself, Wyneken, 1869, viewed the stuttering person as a "speech doubter". He considered that the will to speak is opposed by doubt regarding the ability to speak.

A similar view was expressed by Rudolph Denhardt in 1890, that stuttering persons are fixed in a belief that speaking is difficult, i.e. an "expectancy neurosis" (Freund, 1966). It is noteworthy that Denhardt associated stuttering with the motor disorder known as *writer's cramp* and with similar disorders such as a musician's sudden inability to play a musical instrument because of muscular contractions. At that time this type of disorders was regarded as psychogenic occupational neuroses, but is today considered to be neurological task-specific focal dystonias (Sheehy & Marsden, 1982), related to focal basal ganglia dysfunction (Naumann, Becker, Toyka, Supprian, & Reiners, 1996).

The view that stuttering is related to expected speech difficulties was taken up and disseminated further by Emil Fröschels, Professor of Logopedics in Vienna, and one of the most influential scientists in the history of speech pathology. Fröschels argued that repetition of syllables is quite normal in children. However, some children mistake these normal repetitions as speech difficulties, thereby initiating the development of real stuttering as they increase their effort when trying to speak (Froeschels, 1933). Fröschels left Austria for America in 1938, but even before that time he had an impact in the USA through his publications and cooperation with American clinicians (Duchan, 2004; Froeschels, 1933). His extensive work with stuttering can be exemplified by Fröschels' claim to have examined more than 16 000 cases (Froeschels, 1943).

The development of psychoanalysis was started in Vienna by Sigmund Freud. He only briefly mentioned stuttering in his writings. In *The psychopathology of everyday life*, published in 1901, stuttering was described as a sign of an internal conflict, similar to the phenomenon called a "slip of the tongue" (when an unintended word is said) (Freud, 1980). Peter Glauber (1958) summarized Freud's contributions on stuttering. According to Glauber, Freud only had one case history in which stuttering played an important role. This was the case of Frau Emmy, a woman diagnosed as having hysteria and who showed many complex symptoms, like stuttering, motor and vocal tics, and being overenergetic. The stuttering had adult onset. However, it has been argued that substantial evidence exists that Frau Emmy suffered from Tourette syndrome, not hysteria, and that she also had motor symptoms of dystonia and athetosis (Pappenheim, 1980).

In 1917, Freud expressed the view that stuttering *"could be caused by a displacement upwards of conflicts over excremental functions"* (Glauber, 1958, p. 339). There is, however, one report indicating that Freud later had started to question his psychoanalytic explanations of stuttering. Glauber (1958) stated that Sigmund Freud told Esti Freud, a speech therapist, that *"the psychoanalytic method offered neither insight nor help in this disorder"* (p. 344).

Despite the indication of Freud's doubt regarding psychoanalysis in cases of stuttering, some of the followers of Freud wrote more about this subject, for example Otto Fenichel who was born in Vienna in 1897. In 1946 he published a comprehensive textbook of psychoanalytic theory, wherein he discussed many of the human afflictions, including asthma, tics, peptic ulcers, and stuttering. He was convinced of the psychodynamic origin of stuttering. The quotation below exemplifies the characterization of stuttering persons in some psychoanalytic writings:

> *Psychoanalysis of stutterers reveals the anal-sadistic universe of wishes as the basis of the symptom. For them, the function of speech regularly has an anal-sadistic significance. Speaking means, first, the utterance of obscene, especially anal, words and, second, an aggressive act directed against the listener.*
>
> *... Unconsciously, speech in general or in certain situations is thought of as a sexualized defecation. ... The expulsion and retention of the words means the expulsion and retention of feces, and actually the retention of words, just as previously the retention of feces, may be either a reassurance against possible loss or a pleasurable autoerotic activity. One may speak, in stuttering, of a displacement upward of the functions of the anal sphincters.*
>
> *...*
>
> *The anal-sadistic significance of the symptom is also in keeping with the typically anal-sadistic personality make-up of the stutterer, which is identical with the personality make-up of the compulsion neurotic.* (Fenichel, 1946, pp. 311-313)

Similar psychoanalytic views of stuttering have continued to persist. For example, in 1999 T. Plänkers (1999) of the Sigmund Freud Institute in Frankfurt, proposed a new version of the psychoanalytic theories of stuttering. The following is a short quotation from the abstract as an example of the viewpoint:

> *The intrusive identification of parts of the self in the maternal rectum gives rise to a claustrophobic experiential world in which all obstacles that are encountered between self and object must be eliminated. The anal-sadistic object space of the claustrum is projected on to the external object space and thus also on to the mouth as the origin of the sound envelope, where it produces both a lifeless sound envelope and a torn content, i.e. stuttered sounds, words and sentences.* (p. 239)

1.3.5. The twentieth century, focus on America

1.3.5.1. Iowa City around 1930: cerebral lateralization

The work on stuttering during the 20th century was dominated by the outflow from one main centre, in Iowa City, USA. It began in the middle of the 1920s with

the work of the neurologist Samuel Orton on reading disability. He noted a kind of mirror phenomenon in many of the children with reading disability, a confusion in the left-right dimension. He found that several of the children also stuttered. One of them was naturally left-handed but had been required to shift to the right hand. A relation between stuttering and shift of handedness had frequently been suggested in the previous literature. Orton advised the patient to shift back to the left hand again, hoping that this would solve the problem of stuttering. The rationale was that stuttering might be the result of a conflict between the left and the right cerebral hemispheres, and forcing a child to change handedness was thought to result in weakening of the natural cerebral dominance pattern. It was reported that the patient started to improve after changing back to use of the left hand, and that the stuttering had disappeared entirely after seven months. These observations led to the suggestion that both reading disability and stuttering are expressions of a lack of dominance between the cerebral hemispheres (Orton, 1927; Orton, 1928). This started a period of intense research on neurological aspects of stuttering in Iowa City, during the late 1920s and the first half of the 1930s.

The work with the stuttering patients was entrusted to a young researcher in psychology and speech pathology, Lee Edward Travis. One procedure that was used was to make the nondominant arm immobile in an attempt to strengthen the cerebral dominance. Travis gathered a team of graduate students, who were to have a profound influence in the field of stuttering, lasting also today. The two most influential of Travis' students, Wendell Johnson and Charles Van Riper, were both suffering from severe stuttering when they came to Travis' clinic for therapy. They soon got involved in the research on the cerebral lateralization hypothesis, Johnson first and Van Riper later. (Williams, 1999) However, despite ingenious studies and some interesting results, the relation between handedness and stuttering was not confirmed (Daniels, 1940) and the attempts to shift the handedness were abandoned (Perkins, 1996).

1.3.5.2. The Johnson era

In 1938, Travis moved to the University of California and soon Wendell Johnson became the head of research and of the clinic in Iowa City (Williams, 1999). This was the start of a new period in the history of stuttering, lasting into the 1960s. It has been called "the Johnson era" (Perkins, 1996). In the years from 1935 to 1940, the thinking of Travis and Johnson changed dramatically, away from neurophysiology. Travis became one of the main proponents of a psychoanalytic approach to stuttering. In 1940 he published a paper with the title "The Need for Stuttering": *"It is quite true that the stutterer does fight to retain his symptoms. ... To deprive him of his symptoms might be to plunge him into the very danger which he most dreads and which his stuttering was created to avert"* (Travis, 1940, p. 193). Travis was the editor of *The Handbook of Speech Pathology and Audiology*, and in the 1971 edition he maintains the psychoanalytic view. He starts his chapter with the sentence: *"Stuttering is the consequence of the young child speaking with his mother and father"* (Travis, 1971, p. 1009). Briefly, the basic idea in this text seems to be that stuttering develops because it results in attention from the parents.

Wendell Johnson became committed to a new philosophy called "General Semantics" established by Alfred Korzybski. In short, this philosophy focuses on

how our use of language interacts with our perception of reality, and how words themselves can manipulate and limit our thinking. This led to the development of the "Diagnosogenic theory" of stuttering, presented in 1942. The theory states that stuttering usually is caused by a parent's diagnosis of normal "disfluency" in the child's speech as stuttering. This diagnosis was thought to start a negative process where the child gets the message that something is wrong with its speech and therefore starts to make a conscious effort to control it. In other words, there was nothing wrong with the child's speech until the parent started to worry about it. Stuttering was said not to begin in the child's mouth but in the parent's ear.

Johnson considered that the parent's reaction was the result of unrealistic standards of speech and a tendency towards anxious perfectionist parental attitudes in our culture. One argument for the diagnosogenic theory was a report that certain Indian tribes did not have a word for stuttering, and that no stuttering existed in these tribes. Johnson interpreted this as support for his semantic theory, that the existence and use of the word "stuttering" actually causes stuttering to develop. However, later more thorough investigations showed that these Indian tribes had both expressions relating to stuttering and persons who stuttered, but that the tribe members were embarrassed to admit this. (Bloodstein, 1995; Williams, 1999)

Johnson's ideas and subsequent variations seem to have been dominating the American debate on stuttering into the 1960s. Two of Johnson's students, Joseph Sheehan and Oliver Bloodstein, gained renown for their further development of Johnson's basic ideas, beginning in the 1950s. Sheehan's view was that stuttering is the result of an "approach-avoidance conflict" between the drive to speak and the avoidance of speaking, for example because of a fear of stuttering (Perkins, 1996; Guitar, 1998). In his textbook from 1970, Sheehan begins with the statement: *"Stuttering is a disorder of the social presentation of the self. Basically, stuttering is not a speech disorder but a conflict revolving around self and role, an identity problem"* (Sheehan, 1970, p. 4).

Sheehan often used the metaphor that stuttering is like an iceberg, implying that the behavior of stuttering that can be seen and heard is only a small part of a larger problem. The major part was assumed to exist below the surface and consisted, according to Sheehan, of false roles, fear, avoidance, guilt, and shame (Sheehan, 1970). This "iceberg" metaphor has had a great influence on how stuttering has been perceived, not least in Scandinavia. Sheehan's therapy focused on reduction of avoidance, in order to resolve the assumed approach-avoidance conflict. This included work on self-acceptance and practice to stutter openly and easily (Guitar, 1998).

Oliver Bloodstein developed a model which has been called the "anticipatory struggle hypothesis". It suggested that stuttering develops from various types of failure of communication in children, leading to anticipation of future difficulties in speech. For example, excessive communicative pressures could lead to fragmentation of speech. In the 1980s Starkweather furthered this line of thinking, with his "demands and capacities" theory. It stated, in brief, that stuttering occurs when the internal and external demands on the child exceed its capacity for fluent speech. (Starkweather, 1987; Guitar, 1998)

It can be noted that the ideas of Wendell Johnson and Joseph Sheehan still have a strong support in some persons with interest in stuttering. The following quotation

from a public Internet conference on stuttering is a recent example: *"I agree with you, these men* [Johnson and Sheehan] *had great ideas. Sheehan's iceberg analogy is still one of the best stuttering analogies today and will still be true for the next 50-100 years. Johnson and Sheehan were giants (heroes) in the field of stuttering"* (International Stuttering Awareness Day Online Conference, 2004).

1.3.5.3. Charles Van Riper

Charles Van Riper, who worked with Wendell Johnson, moved from Iowa City to Western Michigan University in 1936. In his writings Van Riper (1982) described the prevailing conflicts between different views of stuttering around this time. He had recently published a paper claiming that many of the most abnormal behaviors of stuttering are learned responses. According to Van Riper was he viciously criticized by persons with the conviction that stuttering was a neurological spasm, viewing the learning theories as heresy. Others were critical from the standpoint that *"only ignorance or stupidity could lead anyone to believe that these behaviors were something more than symbolic symptoms of a deep seated neurosis"* (p. 284). Recurring conflicts between viewpoints seem to have been common in the field of stuttering.

Through his textbooks, published from 1939 to 1982, Van Riper became a leading authority on stuttering. He was primarily a clinician, but carried out a monumental task in compiling and structuring information about stuttering. In 1982 Van Riper suggested that the essence of stuttering is the disruption of the motor sequence of the word, as a result of disturbed timing of its components. This proposal was based on several lines of reasoning, for example the striking "rhythm effect". This is the phenomenon that pacing the speech by a regular rhythm, like that of a metronome, instantly creates fluency in most cases. The deficient timing of the speech of stuttering persons might be attributed to an organic tendency or to emotional stress (Van Riper, 1982).

In his therapy Van Riper combined work with emotional aspects and speech modification. Desensitization to the stuttering was an important part; to stop hiding the stuttering and to stop avoiding speech situations. The stuttering behavior was modified through detailed monitoring of the speech and detailed techniques for control of instances of stuttering (Guitar, 1998; Williams, 1999).

1.3.5.4. Scandinavia.

Influx into Scandinavia. The view on stuttering in Scandinavia before the 1950s was mainly influenced by the German and Austrian traditions, predominantly with speech practice according to Gutzmann and others, but also with psychoanalysis (Sjöholm, 1911; Smith, 1955; Tamm, 1955). Inspired by the new ideas from America, a self-help club was initiated in Stockholm in 1954. It was started by stuttering persons who were disappointed and frustrated by the limited results of the traditional methods. In 1956 the Danish speech pathologist Victor Block worked for one year with stuttering in a speech clinic in Toronto. The clinic had a "non-avoidance" approach, working with open stuttering and self-acceptance, influenced by Wendell Johnson, Charles Van Riper, and psychoanalysis. In 1958 the method was introduced in Århus, Denmark. It was a sharp break with the established speech practice therapy in Denmark, which, according to the non-avoidance model, was a

detrimental attempt to try to hide the stuttering. (Bloch, 1958) Speech pathologists and stuttering persons from Sweden visited the clinic in Århus, and in 1962 the speech pathologist Hans Danielsson started psychotherapeutic treatment of stuttering in Sweden based on the "acceptance-ideology" from Århus (Danielsson, 1973).

In 1966, a book of Wendell Johnson was published in Sweden, based on his diagnosogenic theory (Johnson, 1966). The influx of the non-avoidance philosophy from America, in combination with previously established psychoanalytic ideas, led to a dominance of these traditions in Scandinavia during the 1970s and 1980s, and also thereafter (see discussion in Christmann, 1994).

Research in Sweden during the 1960s and 1970s. Several research initiatives were taken in Sweden. At the Karolinska Institute, Stockholm, in the Laboratory for Clinical Stress Research, a research program on stuttering and stress was carried out, involving tests of long-term treatment and pharmacological modification of stress responses (Leanderson & Levi, 1966; Edgren, Leanderson, & Levi, 1969). At Stockholm University research into the psychodynamic treatment of stuttering started in the late 1960s, resulting in a dissertation and a book on stuttering from a psychoanalytic perspective (Albert, 1980; Albert, 1982). Fritzell (1976) pursued a 10-year longitudinal study of the prognosis of stuttering in schoolchildren.

1.3.5.5. Behaviorism and fluency shaping

Operant conditioning. Associative learning, or *conditioning*, has been suggested to play an important part in stuttering. The principles of *operant conditioning*, derived from behaviorism and B.F. Skinner, were applied on stuttering in the late 1950s and 1960s. In 1958, Flanagan, Goldiamond, and Azrin reported that they had been able to reduce or increase the frequency of stuttering by the use of reinforcing or aversive changes of sound stimuli (Bloodstein, 1995). Shames and Sherrik in 1963 combined theories of operant conditioning with the diagnosogenic theory and psychodynamic ideas. According to their model, stuttering developed through a complex chain of behavior reinforcements. The stuttering behavior served to terminate certain types of environmental punishments, but it would also result in rewards in the form of increased attention from other persons, and serve as an excuse for failure or inadequacy. Ayllon and Azrin, in 1965, followed this type of reasoning and argued that "masochistic" behaviors may be maintained by negative reinforcement, if the behavior ends a punishment. (Van Riper, 1982)

Combination of classical and operant conditioning. In 1967, Brutten and Shoemaker proposed a two-factor theory of stuttering largely based on classical conditioning. Their view was that all children could have speech disruptions if exposed to negative external events when speaking. This might cause certain words or situations to become associated with stress and speech disruptions. This conditioning might lead to a vicious circle where more and more words and situations become associated with stuttering and negative emotions. Associated behaviors of stuttering, like head movements, were suggested to be established by negative reinforcement (operant conditioning). The head movement may initially have the effect of terminating speech blocks, so that the behavior is reinforced. However, the behavior soon loses its fluency enhancing effect, but then it has

already become a habit. New accessory behaviors are added, with the result that advanced cases of stuttering may show a conglomeration of old automatized behaviors. (Van Riper, 1982; Bloodstein, 1995) The theory of Brutten and Shoemaker may be an important contribution to explain the situational variability of stuttering, and the changing display of accessory behaviors. Guitar (1998) suggested that this process of classical conditioning may start after a child has begun to show the first signs of stuttering. In this case Brutten and Shoemaker's theory can be regarded as a useful model of how stuttering may become more severe by associative learning, but it does not explain the basic cause of stuttering.

Operant conditioning in modern therapy. The principles of conditioning have also been applied in different types of stuttering therapy, especially in Australia (see Ingham & Andrews, 1973, for an early review). The currently most well-known example is the Lidcombe program for stuttering children, developed in Sydney. The main principle might be summarized as systematic reinforcement of fluent speech, in a situation where the child should associate speech with positive experiences (Onslow, Menzies, & Packman, 2001).

Fluency shaping. Another line of behavior change in stuttering is based on work with modification of the speech pattern, often referred to as *fluency shaping*. In the 1960s several researchers found that delayed auditory feedback (DAF) had a fluency enhancing effect in many cases of stuttering (Lotzmann, 1961). Long delay, like 250 ms, forced the stuttering persons to talk at a reduced speech rate and to prolong the speech sounds. In the middle of the 1960s this type of slowed speech was used in therapy by Goldiamond, first with DAF, but later it was found that this way of speaking and its fluency enhancing effects could be learned also without DAF. Goldiamond stated that he taught the clients a new speech pattern that they could choose to use or not to use, *"like a new coat that can be worn or left hanging in the closet"* (as cited in Gregory, 1979, p. 5). In the 1970s similar procedures were used by William Perkins, Ronald Webster (the Precision Fluency Shaping Program), and others (Gregory, 1979). The development of various types of fluency shaping programs has made this approach one of the most widely used in the treatment of stuttering today.

1.3.5.6. The renewed neurological interest

Stuttering as an epileptic disorder. Around the end of the 1950s, the discussion about a possible neurological basis of stuttering slowly gained renewed impetus. Robert West (1958) proposed that stuttering might be a type of epileptic disorder: that the speech arrests could be the symptom of a special type of focal petit mal.

Stuttering as a disorder of perseveration. Jon Eisenson (1958) viewed stuttering as a disorder of *perseveration*, which he defined as *"the tendency for a mental or motor act to persist for a time longer than normal after the stimulus which brought about the behavior is no longer present"* (p. 225). He believed that this tendency for perseveration was not limited to speech. Eisenson suggested that the majority of stuttering persons have an organic inclination for perseveration, whereas others start

to perseverate when, at the moment of speaking, they are confronted with certain influences.

Stuttering as a disorder of feedback circuits. Mysak (1960) outlined a complex "servo theory" of stuttering, based on "cybernetic" automatic control principles. The main idea was that stuttering is a failure of the automaticity of speech. According to this model, speech automaticity is dependent on several feedback circuits, and disturbances in these circuits may result in stuttering (Bloodstein, 1995). The interest in the effects of delayed auditory feedback (DAF) in the 1960s provided increased support for this type of ideas.

Stuttering as a disorder of cerebral lateralization. The cerebral lateralization theory, made well-known by Orton and Travis around 1930, found renewed interest in 1966 following a remarkable report by R.K. Jones (1966). Four adult patients with severe stuttering since childhood underwent brain surgery for different reasons, not related to the stuttering. Wada-tests before the surgery indicated bilateral speech representation in all cases. After recovering from the surgery all four patients spoke without stuttering, and in all cases the post-surgery Wada-test indicated unilateral speech control. During the follow-up period, between 15 months and 3 years, their speech remained fluent. The observations were interpreted as giving strong support to the cerebral lateralization theory, implying that interference between the hemispheres resulted in stuttering. However, the initial stir faded when subsequent Wada-tests of a number of adults with developmental stuttering all showed unilateral speech representation (Bloodstein, 1995).

There are now several reports of cases were lifelong stuttering has disappeared after different types of damage to the brain (Lebrun & Bayle, 1973; Helm-Estabrooks, Yeo, Geschwind, & Freedman, 1986; Muroi et al., 1999; Miller, 1985). 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 thesis 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. There is no established explanation of this paradoxical phenomenon, but possible mechanisms are discussed in paper II of this thesis.

Several versions of the cerebral lateralization theory of stuttering have been suggested, for example by Yeudall (1985), Heick (1986), and Webster (1993). Since the late 1960s, there has been an almost continuous stream of reports indicating that stuttering persons, on average, tend to have greater right hemisphere involvement in speech and language than controls. A range of different methods has been used, like dichotic listening, tachistoscopic viewing, bimanual hand tasks, sequential finger tapping, EEG alpha asymmetry, event related potentials, and brain imaging. See reviews in Moore (1990), Watson and Freeman (1997), and in Ingham (2001). For example, in a PET study of cerebral metabolism Wu and coworkers (1995) found reduced activation of left hemisphere speech areas in stuttering persons. In another PET study Fox and Ingham (1996) reported right side dominance of the cerebral motor system in stuttering persons. In a later report (Fox et al., 2000), these

researchers concluded that their results supported theories that stuttering is related anomalous lateralization of speech motor regions, but they also discussed other possibilities, like relations between stuttering and the auditory system and the cerebellum. Similarly, the results of a PET study by De Nil, Kroll, Kapur, and Houle (2000) was reported to support atypical lateralization of language processes in stuttering adults.

Also Braun et al. (1997) found a right-shift of cerebral activity in stuttering adults. However, they also found indications that the right hemisphere activation reflects *compensatory* processes that *reduce* stuttering. This suggestion leads to the possibility that the right-shift of activation might be an epiphenomenon, only indicating left hemisphere impairment of speech control.

Stuttering as a disorder of impaired processing capacity for speech motor control. A more general neurological model of stuttering was proposed by Megan Neilson, namely that stuttering is related to diminished central capacity for speech motor control, causing difficulties in handling the relation between motor activity and sensory feedback during speech (Andrews et al., 1983). This hypothesis is well compatible with the suggestion by Braun et al. (1997) that the right hemisphere activity represents compensatory processes. However, this theory seems less congruent with observations of improved stuttering after cerebral damage.

Stuttering as a disorder of disturbed motor reflex control. Zimmermann (1980) suggested a hypothesis of stuttering as a movement disorder, focusing on the lower parts of the brain. In brief, this model attributes stuttering to disturbed reflex interaction between respiratory, laryngeal, and supralaryngeal structures, as a result of increased gain in brain stem nuclei.

Stuttering as a disorder of the basal ganglia. Another group of theories, with special relevance for this thesis, concerns the possible relation between the basal ganglia circuits and stuttering. The main input nucleus of the basal ganglia is the striatum, which can be divided into three parts related to different functions: the *putamen* (motor), the *caudate nucleus* (associative/cognitive), and the *ventral striatum* (limbic/emotional), see details in paper II. As mentioned in Section 1.3.4.3, German theorists in the 1920s suggested that stuttering is a "striatum neurosis".

The earliest proposal of a link between stuttering and the basal ganglia that I have found in more contemporary literature was by Rosenberger (1980). He discussed a possible relation between dopamine and stuttering, partly based on experiences with treatment of stuttering using the dopamine-receptor blocker haloperidol. Dopamine is one of the key transmitter substances regulating the functions of the basal ganglia. In a PET-study Wu et al. (1995) found significantly reduced metabolism in the left caudate nucleus in the stuttering persons. In a later study of three stuttering persons, using FDOPA-PET, the same team reported about three times higher uptake of FDOPA in many parts of the brain, compared to controls (Wu et al., 1997). They concluded that this result was *"compatible with the hypothesis that stuttering is associated with an overactive pre-synaptic dopamine system"* (p. 767).

Stuttering as a type of dystonia. Another line of reasoning, also related to the basal ganglia, associates stuttering with the movement disorders known as *dystonia*. 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 (Friedman & Standaert, 2001).

An interesting aspect of focal dystonia is that it is often task-specific, being present for example when 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. 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). There is strong support for a relation between basal ganglia dysfunction and dystonia (Naumann et al., 1996).

As pointed out in Section 1.3.4.4, similarities between stuttering and occupational cramps were noted already in 1890, but then in a psychological context. That stuttering may be regarded as a type of dystonia has been suggested by Kiziltan and Akalin (1996) and Victor and Ropper (2001). It is interesting to note that the neurologist Charles Bluemel (1930) actually described what is now called task-specific dystonia as *"stammering in walking", "stammering in writing",* and *"stammering with instruments (piano, violin, typewriter, telegraph)"* (pp. 34-37). In this writing Bluemel viewed all of these types of "stammering" (or stuttering) as impediments of thought.

Modern developments of altered auditory feedback. As mentioned above, it was discovered in the 1960s that delayed auditory feedback (DAF) enhanced the fluency in many cases of stuttering, especially with a short delay of about 50 ms (Lotzmann, 1961). It has also been known for a long time, at least since the 1930s, that masking noise tends to temporarily improve stuttering (Van Riper, 1982). With the new possibilities of digital sound processing it was found that shifting the frequency of the speaker's own voice, in headphones, actually had even stronger fluency enhancing effect than DAF (Howell, El-Yaniv, & Powell, 1987). This effect of frequency-shifted auditory feedback (FAF[9]) was shown to be independent of the speech rate (Kalinowski, Armson, Roland-Mieszkowski, Stuart, & Gracco, 1993), and to be equally effective for shifts up or down (Hargrave, Kalinowski, Stuart, Armson, & Jones, 1994).

Recently a combination of DAF and FAF has been implemented in a commercially available miniature device, fitted in the ear canal in one of the ears (Stuart et al., 2003). The reported evaluations so far suggest a fairly stable effect after an average of 4 to 8 months of use (Stuart, Kalinowski, Rastatter, Saltuklaroglu, & Dayalu, 2003; Kalinowski, Guntupalli, Stuart, & Saltuklaroglu, 2004; Rainmaker & Sun, 2004). Treatment effects of DAF and FAF is discussed further in Section 4.2.3.

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[9] Also called FSF, Frequency Shifted Feedback.

Theories on the effect of altered auditory feedback. The phenomena of altered auditory feedback are of major theoretical interest for the understanding of stuttering. There is no established explanation of the effects. Kalinowski and Saltuklaroglu (2003b) and the company providing the miniature device suggest that DAF/FAF results in an emulation of the well-known effect of choral (unison) speech on stuttering. It is assumed that the shift of pitch and the slight delay creates an illusion of another speaker. Kalinowski and Saltuklaroglu (2003a) argued that choral speech reduces stuttering through activation of a system of "mirror neurons". These questions are discussed in more detail in Section 3.2.9.2.

1.3.6. Research on psychophysiology and temperament

1.3.6.1. Psychophysiology

As outlined in the historical review given above, there have been recurrent suggestions of a link between emotions and stuttering. However, the existence or nature of such a relation is not yet clear. One way to investigate emotional aspects of stuttering is to measure physiological correlates of emotions, like heart rate changes, skin conductance, or pulse volume in fingers. This type of studies have yielded mixed results, but two of the most thorough studies failed to find physiological indications of stronger emotional responses before or during speech tasks in stuttering persons (Peters & Hulstijn, 1984; Weber & Smith, 1990). The conclusion from these two studies was that stuttering persons generally do not show higher levels of autonomic arousal than non-stuttering persons.

There are even reports suggesting that stuttering would *reduce* stress. Dabul and Perkins (1973) found that a speech task with provoked stress/anger (electroshock) increased stuttering but reduced the mean blood pressure when the subjects were not permitted to exhibit their frustration. Reduction of blood pressure was regarded as an indication of reduced stress. Perkins (1996) concluded that this study *"confirmed the counterintuitive interpretation that stuttering has a powerful stress reducing, hence, reinforcing, effect"* (p. 101) and that *"empirical evidence does exist that suggests a psychodynamic role for stuttering"* (p. 5). The results of psycho-physiological studies of stuttering are further discussed in paper I of this thesis, where it is argued that the results of studies of heart rate and blood pressure have been misinterpreted.

1.3.6.2. Temperament

A renewed interest in temperamental traits and stuttering has also emerged. Oyler (1994) reported increased "sensitivity" in a group of stuttering school children. Embrechts, Ebben, Franke, and van de Poel (2000) found a higher level of gross motor activity and impulsivity, and a lower level of attentional focusing and inhibitory control in preschool children with stuttering. Interestingly, Embrechts and coworkers also found a nonsignificant tendency of *lower* scores of shyness, fear and sadness in the stuttering group. Guitar (2003) reported higher scores on a "nervous" temperament scale in a group of stuttering adults. This trait was correlated with increased magnitude of acoustic startle eyeblink responses. Finally, the stuttering preschool children studied by Anderson, Pellowski, Conture, and Kelly (2003) were

said to show less adaptability to change and having irregular biological functions. This group was also reported to show "less distractibility", based on low scores on questions like *"the child stops an activity because something else catches his/her attention"* [p. 1225]. (In the article this trait was also referred to as "hypervigilance", based on a reasoning that these children might have been overly attentive or engaged in a task. There is a risk of misinterpretation of the term "hypervigilance" in this context, since it usually refers to a state of increased responsiveness).

Peters and Guitar (1991) suggested that stuttering may be related to the *freezing-response*, an innate reaction pattern elicited by potential threats. This reasoning is furthered in Guitar (1998), suggesting the possibility that temperamental traits of sensitivity and high emotional reactivity may be risk factors for development of stuttering in children.

In brief summary, research on temperament and stuttering has yielded mixed results. This aspect is discussed in more detail in paper V of this thesis.

1.3.7. Subtypes of stuttering

It is clear that stuttering is a heterogeneous disorder in many respects, however, there is no established way to categorize subtypes. It is likely that subtyping will be a prerequisite for a detailed understanding of stuttering. Heterogeneous groups are a major problem in research based on group average data, for example in brain imaging studies. Despite this, only a few studies on subtypes of stuttering have been published.

In the literature, some attempts of subtyping have been made. These can broadly be divided into two levels of subtypes: subtypes based on type of onset and symptoms, versus subtypes based on background factors.

1.3.7.1. Subtypes based on onset and symptoms

The European subtyping. Based on the European tradition Freund (1966) discussed different types of stuttering. One distinction that has a long history in Europe is between "developmental" and "traumatic" stuttering. However, the main distinction focused by Freund was between "pure stuttering" (or "common stuttering") and "stuttering-cluttering". Cluttering is a speech disorder characterized by hasty, erratic, and poorly intelligible speech. Persons with cluttering tend to be unconcerned and unaware of the speech problems (Encyclopædia Britannica, 2004). Stuttering-cluttering is described by Freund as stuttering with traits of cluttering, also regarding traits of personality. Freund also described another type of stuttering, called "hysterical stuttering", a term which is likely to have been based on Sigmund Freud's case Frau Emmy (discussed above in Section 1.3.4.4). In brief, cases of "hysterical stuttering" were reported to show a highly stereotyped stuttering, sometimes with bizarre behaviors, and a marked indifference and detachment in relation to the symptoms. However, as mentioned above there are strong indications that Frau Emmy suffered from Tourette syndrome and not hysteria.

Van Riper's tracks. In 1971, Van Riper published a system with four different subtypes, called "tracks". It seems clear that this classification is based on the European tradition described by Freund (1966), when comparing the descriptions of

the different subgroups: track I corresponding to "developmental pure stuttering", II corresponding to "stuttering-cluttering", III corresponding to (emotionally) "traumatic pure stuttering", and IV corresponding to "hysterical stuttering". Freeman (1999) considered Van Riper's proposal of categorization "perhaps the single most significant neglected area for research in the field of stuttering".

Preus (1981) and Daly (1981) found roughly similar proportions of the different tracks to those of Van Riper, with about 55%, 20%, 10%, and 2% for each of the four tracks respectively. In a later publication, Daly (1996) wrote that about 40% of the persons who stutter may be classified into the stuttering-cluttering group. Dalton and Hardcastle (1977) estimated the size of this subgroup to about 25% of their stuttering patients. There are reports of about 33 to 40% prevalence of articulation disorders in school age children with stuttering (St Louis, Murray, & Ashworth, 1991; Blood, Ridenour, Qualls, & Hammer, 2003). It is possible that the "stuttering-cluttering" group is dominant among the cases with articulatory problems.

According to Van Riper (1982), most children in track II (stuttering-cluttering) were late in starting to use phrases and sentences. In order to exemplify the heterogeneity of stuttering it can be mentioned that Watkins, Yairi, and Ambrose (1999) reported that children with early onset stuttering tend to have *precocious* language development. This group of children showed syntactic abilities and length of utterances well above what was expected for their age, in some aspects on level with the norms for children two years older.

Are the subgroups suggested by Freund and Van Riper valid? It is questionable whether the described "hysterical stuttering", corresponding to Van Riper's track IV, should be regarded as stuttering. The descriptions might better reflect Tourette syndrome with complex vocal and motor tics and palilalia (Pappenheim, 1980; Bruun, Cohen, & Leckman, 1984; Graybiel & Canales, 2001). Dalton and Hardcastle (1977) found the distinction between stuttering and stuttering-cluttering to be quite valid. However, they were critical of the generalization regarding traits of personality attributed to cases of stuttering versus cluttering, as described by for example Weiss (1964). My personal experience is that the suggested categorization often is quite difficult to apply to stuttering adults, but may possibly be easier to apply to stuttering children. In summary, the tracks I, II, and III outlined by Van Riper might offer a valuable basis for further work on subtyping.

1.3.7.2. Subtypes based on background factors

Another way of subtyping is to look at possible causal background factors, such as heredity and indications of neurological lesions. Poulos and Webster (1991) reported that 66% of 169 adults and adolescents with stuttering had a family history of stuttering. In the group with a family history of stuttering only 2.4% reported birth or early childhood factors which might be related to neurological damage. In contrast, 37% of those without family history of stuttering did report such early factors. This suggests the existence of two subgroups, with stuttering related to genetic versus neurological traumatic factors. This distinction is supported by an older study by West, Nelson, and Berry (1939), who found that in 85% of 100 stuttering persons without stuttering relatives special events were associated with the onset of stuttering (like serious infectious diseases, diseases of the nervous system,

or injuries). This type of events was only reported in 33% of the cases with stuttering relatives. This pattern is supported by the results of paper V in this thesis.

In turn, there are indications of two main subtypes of heritable stuttering. A study of families with stuttering by Ambrose, Cox, and Yairi (1997) found support for a model where transient childhood stuttering and persistent stuttering are related to different genes. According to this model transient childhood stuttering should not be regarded as a genetically milder form of persistent stuttering. However, the two types of genes seemed to have an additive effect, so that the effects of genes increasing the risk of persistent stuttering are added to the effects of genes increasing the risk of transient stuttering.

1.4. Assessment of stuttering severity: reliability and validity [10]

In research on stuttering it is often important to make some type of quantification of the severity of stuttering. For example, in studies of causal mechanisms the correlation between the severity of stuttering and possible causal variables may be investigated. However, there are several problems of reliability and validity related to quantification of stuttering.

1.4.1. Content validity

A main issue for all methods of assessment of stuttering severity is *content validity*. This aspect refers to how well a test is able to measure the behavior for which it is intended. As discussed below, there are several threats against content validity in this context:

1.4.1.1. The variability of stuttering

An important problem for any assessment method based on recorded speech is the variability of stuttering. The severity of stuttering may change vastly depending on the situation and the emotional state, but also from day to day or month to month. Also the type of speech task is important. For example, it has been reported that the severity of stuttering during reading often is unrelated to the severity during communication (Johnson et al., 1963, as cited in Ludlow, 1990).

In some cases the stuttering occurs infrequently, but when it occurs it can be very severe. Van Riper (1982, p. 196) gives an example of this, a video recording of a stuttering adult who was able to read a long text fluently except for the first word. At this word he had a severe silent block with contorted face. All viewers agreed that this block showed that the person had very severe stuttering. However, if this single word had not been included in the video the person would have been rated as a fluent speaker. This aspect is very important when considering the psychological and social effects of stuttering. A single unexpected very severe block on social occasions, like when reading aloud in the classroom or when answering the phone, is likely to have a profound psychological impact. This means that also persons who speak fluently most of the time may experience a real problem of stuttering, causing

[10] This discussion of assessment of stuttering severity is partly based on an unpublished paper by the author of this thesis (Alm, 1997), performed at the University of Alberta, Edmonton, Canada.

anxiety and avoidance of certain speech situations. A conclusion is that limited speech samples make the content validity uncertain.

1.4.1.2. Voluntary control and "covert severity"

Covert severity? Another problem of assessment is that some stuttering persons have a partial voluntary control of the symptoms, for example by use of fluency enhancing techniques like reduced speech rate and soft onsets. If a person is using fluency techniques the recorded speech sample will not reflect the severity of the "basic" stuttering disorder. This leads to the question: if a person achieves complete fluency by use of fluency enhancing techniques, should he still be considered to be a stuttering person? The basic dysfunction of speech fluency may still prevail, but there are no overt symptoms. For neuroscientific research regarding the causal mechanisms of stuttering this is an important issue: in this case the severity measures should, preferably, reflect the basic level of dysfunction, not solely the severity of the overt symptoms.

Dysphemia? In the late 1920s, Robert West from the University of Wisconsin, used the term "dysphemia", to signify *"the general nature of the disorder of which stuttering is the chief symptom"* (West & Nusbaum, 1929, p. 469).[11] The term was important during the era of neurological research on stuttering around the 1930s, but seems not to have been used very much thereafter. The need for such a term has emerged again with the renewed interest in neural correlates of stuttering, to make it possible to distinguish between the overt symptoms, which may be controlled by voluntary strategies, and the underlying dysfunction.[12]

Summary. It is suggested that in research on the causal mechanisms of stuttering the severity measure should ideally reflect the severity of "dysphemia", i.e., the severity of the underlying dysfunction, not the severity of overt symptoms. This is of course very difficult to achieve, but one step in this direction is to try to base the measurements on instances of speech without use of voluntary fluency enhancing strategies.

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[11] The original meaning of dysphemia is the opposite of "euphemism", i.e., to substitute a normal word or expression with a "vulgar or derogatory" one (Online Etymology Dictionary, 2004).

[12] In this discussion it can be mentioned that Charles Van Riper seems to have coined a word that he used informally, to stand for the essence of stuttering: "gluency". I have only found two instances of this word. One is in an excerpt from a letter from Van Riper to his old friend Wendell Johnson, in the context of a discussion about the word "disfluency" coined by Johnson. Van Riper wrote: *"Not disfluency but gluency is the essence of our disorder. Dammit, we get stuck when we stutter and you know that as well as I do"* (Van Riper, 1992, p. 83). The other example is in a interview of Van Riper, written in Spanish (Entrevista a Van Riper, 2004). Here the word "gluency" stands for the "glue" that causes the lips of stuttering persons to get stuck, as opposed to "fluency". The word gluency is an ingenious invention. Too much gluency makes the speech sticky, and a person may have problem with gluency even if no overt symptoms can be noticed in speech. The gluency may still be there when the speech flow is controlled by voluntary use of fluency enhancing techniques to avoid getting stuck.

1.4.1.3. Which aspects of stuttering should be assessed?

Another question refers to which aspects of stuttering symptoms that should be assessed. For example, should repetitions of whole words and phrases be included, or only part-word repetitions? The result of the assessment will vary depending on which aspects that are attended to.

1.4.2. The purpose of assessment: relative or absolute scores?

It is also important to consider the purpose of the assessment of stuttering severity. For instance, in correlational research on causal factors it is the *relation* between scores for different participants that is important, not the *absolute level* of the scores. This means that the reliability of the severity scores can be described by the interrater agreement calculated as the Pearson correlation coefficient.

1.4.3. Methods for assessment of stuttering severity

1.4.3.1. The possibility of making objective judgments

Behavioral studies of stuttering usually evaluate the severity of stuttering on the basis of the overt speech behavior. Theoretical aspects relating to this type of judgments are discussed in Ludlow (1990) and in Cordes and Ingham (1994). It has been found that experienced authorities on stuttering working in different clinics tend to show considerable differences in their assessment of which words are stuttered or not (Kully & Boberg, 1988; Cordes & Ingham, 1995).

1.4.3.2. Counting stuttering frequency

A commonly used measurement is to count the *percentage of stuttered syllables* (%SS). However, the content validity of this measurement may be questioned since it only reflects the number of instances of stuttering, not the severity of each instance. For example, the duration and muscular effort differ vastly between different instances of stuttering. The frequency of stuttering and the tension during instances of stuttering are not highly correlated (Van Riper, 1982).

Ludlow (1990) recommended that all types of disruptions of speech are included in frequency counts, also "normal disfluencies". In this way the problem of defining and segregating different types of disfluencies is avoided.

1.4.3.3. Duration of stuttering

Starkweather, Gottwald, and Halfond (1990) suggested the use of *percent-time disfluency* (PTD), i.e., the percent of the speaking-time that is disfluent, as an alternative to frequency counts. This measure would be expected to have higher content validity than frequency counts, because it reflects both the frequency and the duration of instances of stuttering. However, when the author of this thesis attempted to measure percent-time disfluency it turned out to be more difficult and time-consuming than expected.

1.4.3.4. Rating scales

Several versions of rating scales have been used. Van Riper (1982) suggested a 7-point profile with four separate aspects: frequency of stuttering (in percent), level

of tension or struggle, average duration of instances of stuttering, and level of postponement-avoidance. Martin, Haroldson, and Woessner (1988) claimed satisfactory intrajudge and interjudge reliability for ratings of overall severity using a single scale with the end points labeled "mild" and "severe".

1.4.3.5. Compound measures of overt aspects of stuttering

The Stuttering Severity Instrument (SSI) (Riley, 1972) is an attempt to create a more comprehensive and valid measure of overt stuttering severity, and it has become widely used. This instrument requires estimation of three aspects: (a) the percent stuttered syllables, (b) the estimated length of the three longest blocks, and (c) perceptual rating of associated behaviors, like facial grimaces, on a 5-point scale. These three measures are then to be fused to give an overall severity score.

However, the validity and reliability of SSI has been questioned. Mowrer (1991) argued that a limitation of SSI is that it only considers audible prolongations and sound or syllable repetitions as stuttering. Broken words, revisions, interjections, and repetitions of words or phrases are overlooked. Lewis (1995) carried out a thorough evaluation of SSI. This study reported a rather modest interjudge agreement for number of syllables stuttered (73.9%) and for the mean duration of the three longest instances of stuttering (73.7%). Riley (1991) reported an interjudge reliability of $r = 0.62$ for the perceptual rating of associated behaviors, and $r = 0.82$ for the resulting global SSI score.

In the SSI procedure the global score is converted to the labels "very mild", "mild", "moderate", "severe", and "very severe". Hall, Lynn, Altieri, and Segers (1987) reported an evaluation where ten judges rated speech samples from two stuttering adults. The result showed that one of the two subjects got classified as mild, moderate, or severe. I.e., the same person may be classified as either mild or severe when different judges are using SSI.

Lewis (1995) compared the interjudge agreement of the severity level resulting from SSI with a purely subjective severity rating, using a five-point rating scale. It was found that the interjudge agreement was "essentially identical" (p. 55) for the SSI rating and the purely subjective rating. Lewis argues that if these two methods result in the same level of reliability there are arguments against the use of SSI: (a) SSI resulted in the same outcome as the use of a purely subjective rating scale, but *"the SSI-3 data collection and coding procedures entailed considerably more expenditure of time and effort."* (p. 55); and (b) *"clinicians and researchers are likely to interpret subjective ratings of severity with some caution as compared to the relatively greater confidence placed in severity levels derived from the SSI-3's purportedly reliable quantification of stuttering behaviors."* (p. 55).

1.4.3.6. Self-rating of stuttering severity

One way to overcome the limitations of severity measurements based on overt speech is to use self-rating questionnaires, like WASSP, The Wright & Ayre Stuttering Self-Rating Profile (Wright & Ayre, 2000). There may be several potential advantages with self-reports. It gives the possibility of getting a severity rating that (a) is based on all speech situations, (b) can account for the use of voluntary strategies to reduce stuttering, and (c) indicates emotional experiences. However, subjective severity reports also have their limitations. Van Riper (1982)

notes that persons who stutter are often poor judges of the objective severity of their own stuttering. One problem is the lack of a common yardstick. Another problem may be a psychological tendency to over- or underestimate their own problems. In some cases the awareness of instances of stuttering seems to be low, possibly due to habituation.

1.4.4. Severity rating used in the current project

In the current project severity ratings are only used for correlational analysis, thus only the relative level of the ratings is important. Based on the reasoning above a rating scale procedure was chosen, for scoring of video recorded speech samples of reading aloud and self-formulated monologues.

As mentioned above, the frequency of stuttering and the tension during instances of stuttering are not highly correlated (Van Riper, 1982). Therefore it was hypothesized that the severity of stuttering may be described by two main dimensions: (a) the proportion of speech time with symptoms of stuttering, and (b) the instance of the highest level of superfluous muscular activity or movements during speech. These two aspects were estimated on rating scales ranging from 0 to 7.

Further, it has also been reported that the severity of stuttering during reading often is weakly related to the severity during communication (Johnson et al., 1963, as cited in Ludlow, 1990). For that reason, the speech time with symptoms of stuttering was rated separately for reading aloud and self-formulated speech.

Finally, a global severity score was estimated as an approximate composite of the sub-scores. Possibly this procedure, with estimation of sub-scores before estimation of the global score, has potential to be more reliable than a single global rating scale. This is because a global severity score is more abstract than the more behaviorally related sub-scores. The resulting rater agreement was $r = 0.91$ for the global scores, indicating good reliability. For further details about the procedure, see Section 2.2 below.

1.5. Strategy in research on mechanisms of stuttering

The review of research on stuttering above reflects a situation where almost no pieces of the jigsaw puzzle have yet fitted into a certain place in relation to other pieces. In his book *Stuttering and Science* William Perkins (1996) discussed why the research on stuttering has not advanced farther in the understanding of the disorder: *"Out of this plethora of research directions, no definitive experimental evidence constrains the research to even a few leads."* (p. 19). One of the problems discussed by Perkins is the scarcity of comprehensive testable theories of stuttering: *"The function of a theory is to provide ... guidance to the most profitable research directions, given the current state of knowledge"* (p. 25). *"With stuttering, we have cycled round and round the same assumptions so that we are literally no closer to a solution now than when Travis launched scientific inquiry* [around 1930]*"* (p. 23). Perkins argued that advancement of testable theories, with the aim of including all observed aspects of stuttering, is a prerequisite for the advancement of the understanding of causal mechanisms.

Another problem highlighted by Perkins is the dominance of group data in studies of stuttering: *"Group results have been mandated, so single subject research ... has all but disappeared. All individual scores are summed together, which effectively eliminates evidence of causes operating within individuals. The irony is that groups do not stutter. Causes of stuttering operate only within individuals"* (Perkins, 1996, p. 108). Perkins was also critical of the focus on statistical significance as the main guide for research: *"when statistical significance is the criterion for whether a lead is strong enough to pursue, as it has been for decades, the effect of methodical refinement is to weaken the strength of differences that pass tests of statistical significance"* (p. 109).

A central task for research on causality is to try to separate which observations indicate causal factors, and which observations only reflect various epiphenomena. In a heterogeneous disorder such as stuttering it can be expected that the underlying dysfunctions also will appear as various subtle differences when a group of stuttering persons are compared with a nonstuttering control group. Such differences might for example be shown if analyzing language development in stuttering children, even if there is no causal link between the language system and the speech disruptions in stuttering. In addition, it can be expected that the speech problem in itself will result in secondary group differences, for instance in social attitudes. Therefore, the most parsimonious interpretation of observed group differences would be to primarily regard them as either epiphenomena or secondary effects of stuttering. Claims that a factor may be involved in the causal chain resulting in the speech disruptions should be supported by well-founded arguments.

The ultimate goal of research on the causal mechanisms of stuttering is to be able to describe the causal factors on an individual level. There is compelling evidence that stuttering, at least in some respects, is a heterogeneous disorder. It is not yet clear how this heterogeneity is best structured, into subtypes or continuous dimensions, but it is clear that group average studies will not solve this question. On the other hand, as long as we do not have meaningful criteria for subtyping, group average studies will continue to be important. In order to obtain information about possible subtypes a good practice would be to analyze and discuss the distribution of the data in group studies. How representative is the significant tendency? If the stuttering group shows a high standard deviation, the distribution should be commented on. If the result indicates the existence of subgroups the publication of graphs, such as histograms and scatterplots, is valuable.

A key aspect in research is to reveal relations between variables. When studying a heterogeneous population it is important to get as many variables as feasible from the same group of individuals, to be able to relate the variables on an individual level. As Perkins (1996) noted, causes of stuttering operate only within individuals, not within groups. To move forward in this direction it is important to gather as much relevant information as possible about as many stuttering individuals as possible. It goes without saying that such an endeavor will demand a great deal of work and time.

Some methods, for example some types of brain imaging, can only be interpreted on the group level, not on the individual. In order to get as clear results as possible from these methods it is of great importance to find meaningful criteria for the subtyping of stuttering persons.

1.6. Overview of the current project

The following is an overview of the current project, also including studies in which the analysis is not yet finished. Consequently, the results of these studies are not reported in this thesis, and are planned to be published later as separate papers.

1.6.1. Basic ideas

The current project was planned on the basis of the reasoning outlined above. In summary, the following ideas guided the planning of the project:

- To give high priority to theoretical development based on published data.
- To use Van Riper's description of subgroups type I-III as a starting point for the analysis of subgroups.
- To include persons with cluttering without stuttering, because of the assumed relation between cluttering and stuttering in some cases.
- To limit the study to adults, so as to reduce possible ethical issues of experimental studies.
- To use methods which lend themselves to interpretation on an individual level.
- To use a broad approach, because of the unclear theoretical state and because of the assumed heterogeneity of the stuttering population.
- To use a combination of explorative studies and testing of specific hypotheses.
- To gather as much relevant data as possible in one visit of the test persons, to be able to relate different variables on an individual level.

1.6.2. Survey to participants

Contact with persons with stuttering or cluttering was mainly obtained through the clinic of phoniatrics and logopedics, Malmö University Hospital. The clinic sent a survey to adult previous patients, based on a register of patients with these diagnoses, starting 1971. The survey was also distributed by *Skånes stamnings-förening*, the association for stuttering persons in Scania[13], to known stuttering adult members. The survey questions related to symptoms and possible background factors. (See Section 2.1 for details regarding participants.)

1.6.3. Overview of experimental studies in the current project

As mentioned above, one of the basic ideas of the project was to gather as much data as possible in one visit of the test persons. The result of this strategy is that only a part of the data has yet been analyzed and is included in the current thesis. For example, the registrations of symptoms of stuttering, with video and electroglottography, have not yet been analyzed and are planned to be reported later. In this Section (1.6.3), all experimental studies included in the total project are summarized. The next section (1.7), is an overview of the work reported in this thesis.

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[13] Scania, or *Skåne*, is a province in the South of Sweden, an area including the cities of Malmö and Lund.

1.6.3.1. Aspects of principal interest

The experimental studies were planned with four different aspects of principal interest:

- *Motor speech behavior.* What exactly happens on a motor level when the speech sequence is disrupted? Different types of stuttering? The role of adduction or abduction of the vocal folds?
- *Emotions and stress*. Studies of the hypothesis that the "freezing response" may be related to stuttering blocks.
- *Dopamine and basal ganglia functions.*
- *The role of auditory feedback in stuttering.*

1.6.3.2. Equipment

To be able to carry out the project, laboratory facilities for this type of experiment were planned. The laboratory was designed to be multi-purpose, with the following functions:

- Computerized video recording, including electroglottography (EGG) of vocal cord waveforms during phonation.
- Recording of heart rate (ECG), muscular activity (EMG), etc.
- Tests of altered auditory feedback.
- Production of sound stimuli with controlled amplitude and frequencies.

Digital sampling of various signals was accomplished by a Biopac MP100 system, allowing up to 16 channels. For recording of video, sound, and EGG, a Winnov Videum AV computer capture card was used. Altered auditory feedback effects were produced by a Digitech Studio Quad 4 effects processor (Harman Music Group Inc). The effects processor was controlled by MIDI-codes from a computer, allowing programming of test sequences. Filtering of sound frequencies was attained by an Ultra-Curve DSP8024 equalizer (Behringer), also controlled by MIDI-codes.

1.6.3.3. Psychophysiological pilot study of "freezing"

A pilot study of physiological aspects of speech stress was performed, using telephone and other speech tasks for stress induction. The study focused on parasympathetic effects on heart rate related to "freezing" (such as reduction of heart rate and change of respiratory sinus arrhythmia), during inhibition of the sympathetic nervous system with beta-blocking medication (metoprolol 50 mg). However, the preliminary results did not indicate clear stress responses, possibly because most participants already were quite "desensitized" through therapy or other life experiences. There are also ethical problems of stress induction, and the medication with beta-blockers made the recruitment of test persons more difficult. Since the test program included so many other aspects the study of "freezing" was excluded from the project.

1.6.3.4. Studies of acoustic startle (included in this thesis)

One important part of the program was tests of "acoustic startle". The principle of this method is that the blink responses caused by loud sound stimuli are measured by EMG. This basic principle can be used for several types of test, related to

different aspects of neural functioning. The *amplitude* of the blink response can be used as an indication of neuromuscular reactivity and sensitivity for sounds. The amplitude is also influenced by the emotional state and conditions like social phobia (Vrana, Spence, & Lang, 1988; Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Larsen, Norton, Walker, & Stein, 2002). Exaggerated startle may be a part of various neurological or psychiatric syndromes (Howard & Ford, 1992).

Another aspect of startle is called *prepulse inhibition* and is regarded as a measure of auditory "sensory gating", i.e., the ability of the nervous system to inhibit disturbing stimuli. The term "prepulse inhibition" refers to the effect that a weak sound immediately before the laud sound tends to reduce the startle response. Studies of animals and humans have indicated that impairment of startle prepulse inhibition is related to dysfunction of the basal ganglia system, and that the level of prepulse inhibition can be modulated through the dopamine system (Swerdlow & Geyer, 1999). Increased dopamine synthesis in stuttering persons, as suggested by the study by Wu et al. (1997), would be assumed to result in reduced prepulse inhibition. In our study the blink response was measured for both eyes, providing the possibility of finding differences in lateralization, for example caused by left hemisphere dysfunction (Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000).

1.6.3.5. Blood sample analyses (included in this thesis)

Analyses of blood samples were included in order to investigate biochemical variables possibly related to stuttering:

- *Prolactin*. The FDOPA-PET study of three stuttering adults (Wu et al., 1997) suggested a strong global increase of dopamine synthesis in some cases of stuttering. The level of prolactin in the peripheral blood is regulated by the level of dopamine release from the hypothalamus (Guyton & Hall, 1996). Analysis of prolactin was therefore included in the study in order to investigate if it might be used as a rough indication of subtypes of stuttering.
- *Copper* and the copper binding protein *ceruloplasmin* was included because Pesak and Opavsky (2000) had reported significantly low copper levels in stuttering men. It is also known that disorders of the copper metabolism can affect the basal ganglia.
- *Calcium* and *magnesium* levels were checked since there are reports of deficiency of these minerals in stuttering persons (Costa, Antoniac, Berghianu, & Marinescu, 1986; Schleier, Schelhorn, & Groh, 1991). Reduced level of plasma calcium results in increased excitability of the nervous system, and thereby a lowered threshold for muscular contraction. Low concentration of magnesium causes increased irritability of the nervous system (Guyton & Hall, 1996). In this way deficiency of calcium or magnesium might, theoretically, worsen stuttering.
- *Thyroid hormones* were included in order to be able to exclude hyperthyroidism in cases with symptoms like anxiety and agitation.

1.6.3.6. Study of the "audio-phonatoric coupling" (reported later)

Auditory feedback means that the speaker hears the own voice when speaking. The role of auditory feedback in stuttering might be investigated by tests of the "audio-phonatoric coupling", as put forward by Kalveram and Jäncke (1989) and Jäncke (1991). In brief, Kalveram and Jäncke got experimental results which

indicated that in non-stuttering persons the duration of stressed (long) vowels is influenced by auditory feedback whereas the duration of unstressed (short) vowels is almost unaffected by auditory feedback. This was shown by measuring the effect of a brief delay in the auditory feedback (about 40 ms) on the duration of produced vowels. Stuttering persons tended to show a stronger influence of the auditory feedback, also on unstressed (short) vowels. Furthermore, the effect of the feedback was reported to be increasing with increased severity of stuttering.

These findings may be interpreted as being in accord with the suggested hypothesis of a relation between stuttering and the basal ganglia: Impairment of the basal ganglia can be expected to result in reduced capacity for motor automatization, therefore resulting in increased dependence on feedback control of speech. I hypothesized that problems of speech might arise when feedback control is applied on short and fast speech segments, which are too brief to be controlled by the relatively slow feedback circuit.

Kalveram and Jäncke proposed the prosodic distinction between stressed and unstressed variables as the determinant for feedback versus feedforward control. My hypothesis was that the determinant factor is the duration of the vowel, irrespective of prosodic stress. An experiment for the test of this hypothesis was included in the project.

Further, it was speculated that persons with cluttering or stuttering-cluttering might show subnormal influence of auditory feedback. If this is correct, this measurement may be used as a test for separation of subtypes of stuttering.

The result of this study is not yet analyzed, and is not included in this thesis. It will be reported later in a separate paper.

1.6.3.7. Analysis of speech symptoms (reported later)

In an attempt to elucidate the "molecular" events in the moment of stuttering, speech samples were recorded using computerized video, including the electro-glottography (EGG) waveforms showing aspects of phonation. As a part of the project a computer program is being developed, for analysis of the "open quotient" in the EGG signal. The open quotient reflects the closing and opening of the glottis. The video recording can be displayed and analyzed together with the waveforms for the microphone signal, the EGG signal, and the open quotient.

The analysis program is also intended to report statistics for: the mean open quotient, variability of the open quotient, low frequency EGG variations (reflecting difficulties of phonation), duration of phonation segments, and duration of the intervals between phonation segments.

One general aim is to investigate if subtypes of stuttering can be identified based on this analysis of symptoms. A more specific question is if it is possible to use this technique in order to analyze the role of abductory versus adductory vocal fold movements in the moment of stuttering.

As mentioned above will the result of this study be reported later, and is not included in this thesis.

1.6.3.8. Summary of aspects included in the total project

In summary, the test program came to include the following aspects:

- Interview, case history.

- Questionnaires for temperament and personality traits.
- Self-rating of stuttering severity (WASSP).
- Registration of speech symptoms (video, sound, and electroglottography).
- Analysis of vowel durations in spontaneous speech (reading text with only unvoiced consonants and no consecutive vowels).
- Test of effects of altered auditory feedback on the severity of speech symptoms.
- Test of the effect of auditory feedback delay on long and short vowels.
- Acoustic startle: amplitude and prepulse inhibition.
- Blood samples.

1.7. Overview of the thesis

The theoretical work based on published data led to two main lines of interest: the role of the basal ganglia and the role of emotions. The interest in the relation between emotions and stuttering was based on the contradictory results and theories presented by different writers, and indications that some observations may have been misinterpreted. The interest in the basal ganglia was based on the author's impression that an understanding of this neural system may be essential for the understanding of stuttering.

The papers presented in this thesis can be divided into two main parts, the theoretical papers I-II and the empirical papers III-V:

I. *Stuttering, heart rate, and "freezing"*. An analysis of published data regarding the relation between stuttering and responses of the autonomic nervous system, reflecting emotional reactions. The author argues that some conclusions about stuttering have been based on an incomplete model of the psychophysiology of the autonomic nervous system.

II. *Stuttering and the basal ganglia.* Analysis of brain mechanisms related to stuttering, with focus on the basal ganglia system.

III. *Stuttering and copper.* Study of a possible connection between stuttering and copper.

IV. *Stuttering and sensory gating.* Study of auditory sensory gating, using "startle prepulse inhibition". This measure has been suggested to be related to the functions of the basal ganglia and the level of dopamine activation (Swerdlow & Geyer, 1999).

V. *The acoustic startle response, temperamental traits, and biological factors.* Study of neuromuscular reactivity, using acoustic startle and measurement of EMG blink amplitude, in relation to the severity of stuttering, temperamental traits, the effect of altered auditory feedback, and biochemical analyses.

2. METHODS

2.1. Participants and recruitment procedures

2.1.1. Participants with stuttering and/or cluttering

In summary, a total of 35 stuttering adults and 5 adults diagnosed as having cluttering participated in all or part of the experimental studies presented in this thesis. The stuttering group consisted of 27 men and 8 women, whereas the cluttering group included 4 men and 1 woman. The participants were selected in two steps.

2.1.1.1. Recruitment step 1: survey

First a survey with questions about symptoms and background factors was sent to persons with stuttering or cluttering. In the survey they were asked if they would be interested in receiving information about participation in further research studies. The survey was sent to the following groups:

Previous patients. The majority of the participants were patients examined at the clinic of phoniatrics and logopedics, Malmö University Hospital between 1971 and 1997 with the diagnosis of stuttering and/or cluttering. The survey was sent to persons who did not match the following exclusion criteria:

- Present age below 18 or over 65 years.
- Age below 13 at last visit at the clinic.
- The symptoms noted as mild.
- Uncertain diagnosis noted.
- Mental retardation.
- No available address.

As a result, the survey was sent to 155 persons diagnosed as stuttering and to 30 persons diagnosed as cluttering but not stuttering. The resulting response rates were 51% (79 persons) and 47% (14 persons) for the stuttering and cluttering groups respectively.

Association for stuttering persons. The survey was also sent by Skånes Stamningsförening, the association for stuttering persons in Skåne, to 39 adult stuttering members. In this group the response rate was 77% (30 persons).

Persons showing interests in participating. In addition, 11 stuttering persons contacted the author of this thesis and showed interest in participating, resulting in 10 persons who answered the survey.

Summary. In total, the survey was sent to 205 persons with stuttering (or with previous stuttering) and to 30 persons with only cluttering. The total response rates were 58% (119 persons) in the stuttering group and 47% (14 persons) in the group with cluttering.

2.1.1.2. Recruitment step 2: selecting participants for experimental studies

Stuttering. A total of 109 of the 119 stuttering persons who answered the survey wanted to receive information about participation in further research (i.e. 92%). Of these were 36 excluded because they had reported having only minor speech problems, or because of more than 100 km traveling distance. As a result, 73 persons with stuttering were contacted regarding further studies. In some cases the telephone contact indicated only minor overt speech problems, and these cases were excluded. Other cases reported difficulties to attend, and some cases failed to attend the scheduled tests. In summary, the inquiries resulted in 35 stuttering persons (27 men and 8 women) who participated in all or parts of the experimental studies.

Cluttering. In the cluttering group 12 persons of the 14 who answered the survey wanted to receive information about participation in further research. Of these were 2 excluded because they reported absence of current speech problems and 1 because of more than 100 km traveling distance. As a result, 9 persons were contacted regarding participation in experimental studies, leading to a total of 5 persons (4 men and 1 woman) with cluttering who participated in the experimental studies.

2.1.2. Control persons

A total of 40 persons were included as non-stuttering controls in the project, to achieve gender- and age-matched control groups for the different studies. Exclusion criteria were: stuttering or cluttering now or previously; stuttering or cluttering in close relatives; neurological or psychiatric disorder; or medication affecting the nervous system. For some of the studies further exclusion criteria were applied, like notable impairment of hearing. The controls were recruited in the following ways: 15 medical students (from a class of 17 possible participants, implying low selection bias), 10 persons through public notice boards in the hospital, 9 persons through stuttering participants, and 6 persons through research staff.

2.1.3. Ethical approval

The project was approved by the Lund University Research Ethics Committee.

2.2. Estimation of stuttering severity

Background. As discussed above (see Section 1.4) it is difficult to achieve a measure of the severity of stuttering with high reliability and validity. However, the wide range of severity in stuttering makes it possible to at least achieve a rough indication of the severity level, which is important in research on causal mechanisms.

Speech samples. Speech samples from the participants were recorded by computerized video. The samples involved reading aloud a text of 100 words and self-formulated monologues (retelling the text in own words, describing the way to the hospital, describing their house, and describing pictures). The length of the

monologues was about 2.5 to 5.5 minutes, with longer samples in case of infrequent stuttering.

Rating procedure. The severity of stuttering was estimated as a global severity score based on rating of the video recordings, ranging from 0 (no stuttering) to 7 (very severe). The global rating was determined by first estimating sub-scores for the following aspects: (a) The proportion of speech time with symptoms of stuttering, with separate scores for spontaneous speech and reading aloud (0 = none, 1 = minimal, 4 = stuttering about half of the time, 7 = almost continuous stuttering). (b) The instance of the highest level of superfluous muscular activity or movements during speech (0 = none, 1 = minimal, 7 = very high).

Thereafter the global score was rated as an approximate composite of the sub-scores (0 = no stuttering, 1 = very mild, 7 = very severe). Scoring was done independently by two raters, and the mean of the two ratings was used for the final analysis.

The design of this procedure is based on the suggestion that the global severity of stuttering can be described by two main dimensions: (a) the percentage of the speech time related to stuttering behaviors, and (b) the highest level of muscular effort or concomitant movements related to an instance of stuttering. These two dimensions are more closely related to observable behaviors than an abstract global severity score.

Reliability. The rater agreement for the global score was indicated by the Pearson correlation coefficient $r = 0.91$ (based on scoring of 32 stuttering adults). The severity rating is only used for correlational analysis, why the mean scores of the raters (i.e. rater bias) do not influence the reliability. The mean stuttering severity score for the total stuttering group was 3.3 ($N = 32$, $SD = 1.9$, range 0.5—7).

Analysis of the ratings indicated that the main difference between the judges was related to estimation of the highest superfluous muscular activity in cases of stuttering with silent blocks. Clearer criteria for rating of silent blocks and more training of the raters are likely to increase the inter-rater agreement of this method further.

2.3. Altered auditory feedback index (AAF index)

All participants were tested for the effect of altered auditory feedback on the stuttering, during reading aloud. The effect of each condition was rated both by the participant and the experimenter according to a Likert scale ranging from -4 to +4. The different scores were described as: "Can not talk", "Much worse", "Worse", "Somewhat worse", "No difference", "Somewhat better", "Better", "Much better", "Completely without speech problems".

The following conditions were tested and merged to an index: delayed auditory feedback (DAF) 50 ms and 80 ms, and frequency altered auditory feedback (FAF) up- and down-shift 1/3 and 1/2 octave. For the test of FAF, the score for either 1/3 or 1/2 octave shift was used, depending on which one had the best effect. This resulted in a total of 8 scores for each participant: DAF50self, DAF50judge, DAF80self, DAF80judge, FAF-up-self, FAF-up-judge, FAF-down-self, FAF-down-judge. The

Altered Auditory Feedback Index (AAF index) was calculated as the mean of these 8 variables.

Only participants with marked stuttering during normal auditory feedback were included in the analysis (n = 20). The reliability of this index, calculated as Cronbach's alpha for internal consistency, was 0.91. (Also masking noise was included in the testing of the participants, but the item analysis showed that the ratings of the effect of masking noise slightly decreased the internal consistency of the AAF index.)

2.4. Scales of temperament and personality

The following personality scales were included as part of a larger battery of tests and questionnaires.

2.4.1. The BAS scale

The *BAS scale* is a subscale from the *BIS/BAS scales*, a self-report questionnaire developed by Carver and White (1994). These scales are based on the theories of Jeffrey A. Gray about two general motivational systems, a behavioral inhibition system (BIS) and a behavioral activation system (BAS). The BAS scale is intended to reflect differences in *"proneness to engage in goal-directed efforts and to experience positive feelings"* (Carver & White, 1994, p. 319). It consists of 13 items with a four-point Likert-scale, from 1 to 4. Translated to Swedish by the author of this thesis.

2.4.2. Detachment and irritability

The *Karolinska Scale of Personality* (KSP) inventory consists of 15 subscales with a total of 135 items, with answer alternatives in a four-point Likert-scale format, from 1 to 4 (Schalling, Asberg, Edman, & Oreland, 1987). The *detachment scale*, reflecting the need for distance vs. intimacy, consists of 10 items. The *irritability scale* includes 5 items.

2.4.3. Anxiety

This scale consists of 5 items from the *BIS scale*, a subscale of the BIS/BAS scales (Carver & White, 1994), see Section 2.4.1 above, and 3 items from the *KSP psychic anxiety scale*, a subscale of the *Karolinska Scale of Personality* (Schalling et al., 1987). According to the underlying theory, high BIS scores would be reflected in proneness to anxiety (Carver & White, 1994). The items from the original scales were chosen with the intention of measuring trait anxiety, and of excluding items which could be expected to be affected by the consequences of stuttering, for example by anxiety for social situations. One item from the BIS scale was excluded because a pilot study suggested difficulties with the syntax, and one item because item analysis showed that it reduced the reliability of the scale. The resulting items were # 8, 13, 16, 19, and 24 from the BIS/BAS scale, and # 36, 74, and 121 from the KSP.

2.4.4. WURS, childhood ADHD scale

The *Wender Utah Rating Scale* (WURS) is a scale for retrospective diagnosis of childhood attention deficit hyperactivity disorder (ADHD; Ward, Wender, & Reimherr, 1993). The original form included 25 questions with special relevance to childhood ADHD. Seven of these questions were excluded, mainly because they referred to aspects which can be expected to be influenced by stuttering.

2.4.5. Reliability of scales

The reliability of the scales, calculated as Cronbach's alpha for internal consistency, was: 0.74 for BAS, 0.76 for detachment, 0.51 for irritability, 0.74 for anxiety, and 0.85 for WURS.

2.5. Acoustic startle

2.5.1. General procedure

The participants were seated in a comfortable chair and gave written informed consent to their participation on the understanding that they had the right to discontinue participation at any time if there was any part of the tests that they did not approve. Before the startle test the persons were told the following: "The experiment is concerned with measuring auditory reflexes. You will get short bursts of noise in the headphones, at about a half to one minute intervals. The response we measure cannot be influenced by will, so you do not have to do anything but to sit and watch a video with nature sceneries, with open eyes. There will be a continuous low-level background noise." The participants were informed about details of the test design afterwards.

2.5.2. Issues related to sensitivity to loud sounds

Because a pilot study had indicated that some persons with stuttering may be unusually sensitive to loud sounds, extra care was taken to avoid unpleasant experiences. The participants were asked about their sensitivity to loud sounds, like shots. Further, the test was introduced by two pulses with somewhat reduced sound level (100 and 103 dB (A), at 30 seconds intervals), and after these two pulses the participants were asked if they wanted to continue the test. If they agreed the longer test sequence was started.

One woman with stuttering did not try the test because of assumed sound sensitivity, and one control woman interrupted the test after the initial trial. This means that the exclusion because of sound sensitivity is balanced between the stuttering group and controls, causing no exclusion bias.

2.5.3. Stimuli and procedure

This test of the amplitude of the acoustic startle response was performed in combination with a test of *startle prepulse inhibition*, a method for investigation of *sensory gating* (Swerdlow & Geyer, 1999). The test of prepulse inhibition implied

that some of the pulses were preceded by a weak acoustic prepulse 90 ms before the pulse, at the sound level 71 dB (A), 50 ms duration, and 10 ms rise time.

In order to minimize the risk of negative experiences, also the longer test sequence was started with two trials with reduced sound level, 100 and 103 dB (A). Thereafter followed a sequence of 8 pulses without prepulse and 8 pulses with prepulse, at the sound level 106 dB (A), making a total of 12 pulse-alone trials (including the pulses in the introduction). The prepulse trials and the pulse-alone trials (indicated by P and 0 respectively) were sequenced in a pseudo-random and counterbalanced order: P00PP0P00P0PP00P. The two + two initial pulse-alone trials also served the purpose of achieving the most rapid habituation of the startle response before the sequence used for measurement of PPI. The intervals were on average 45 seconds, with a pseudo-random variation between 30 and 60 seconds. During the longer test sequence, lasting about 13.5 minutes, the participants viewed a video of nature sceneries.

2.5.4. Data collection, reduction and analysis

Eyeblinks were measured by electromyography (EMG) of activity over the orbicularis oculi beneath each eye, using 10 mm circular EMG surface electrodes (Nicolette Biomedical, #019-411800) with conducting paste, mounted in a plastic holder for a constant centre-centre distance of 20 mm. The ground electrode was placed on the forehead. EMG was recorded using the digital sampling system Biopac MP100A and amplifiers EMG100 (Biopac Systems Inc), with the sample frequency 1000 samples per second. The EMG was registered with the gain 5000 for all participants. Before applying the electrodes the skin was prepared with alcohol pads and abrasion.

The data reduction and analysis was first performed manually using the software AcqKnowledge 3.5 (Biopac Systems, Inc), and subsequently as automatic analysis using Matlab 6.5 (MathWorks, Inc). The amplitude data used in the statistics are from the Matlab analysis, and the manual analysis was used to verify the results. The analysis of response latencies was only done manually.

2.5.4.1. Response amplitude

The EMG-signal was band pass filtered with the cutoff frequencies 25 and 250 Hz. The effect of 50 Hz noise in the EMG signal was reduced with an adaptive filtering algorithm: A 20 ms noise profile was created using a stepwise moving window which was continuously updated with a forgetting factor of 0.7 (i.e., the profile was determined as 70% of the accumulated result and 30% the new values). The updating was discontinued at the start of the startle pulse, and the noise profile was subtracted from the EMG signal during the response window. The signal was rectified and smoothed using root mean square over a 100 ms moving window. For each trial the baseline EMG level for each eye was measured, as the root mean square of the unsmoothed EMG during the period from 0 to 20 ms after the onset of the pulse (the baseline period). The peak amplitude was defined as the peak of the smoothed EMG signal during the period from 20 to 150 ms after the onset of the pulse (the response period). The response amplitude for each eye was calculated as the difference between the baseline level and the peak amplitude. The EMG

waveform was visually inspected and trials with excessive baseline level were excluded and treated as missing data. A total of 11 trials (1.6%) were excluded. In addition, in 9 trials only the left or right value was excluded, and in 2 cases the complete left or right channel was excluded due to high noise level. The response amplitude is reported for the first introductory trial and as the mean of the last 10 pulse-alone trials (i.e., the introductory trials 1 and 2 excluded).

2.5.4.2. Calculation of prepulse inhibition (PPI)

Prepulse inhibition (PPI) was calculated as the percentage reduction in startle amplitude caused by the prepulse: 100 x ([mean pulse-alone trial amplitude] - [mean prepulse trial amplitude]) / [mean pulse-alone trial amplitude]. This means that persons with impaired PPI will get low scores. (Negative values imply facilitation of startle by the prepulse.)

2.6. Calculation of effect sizes

The term *effect size* refers to a statistical index that measures the magnitude of a treatment effect (Becker, 2000). The effect size measure is used to indicate the magnitude of the difference between two groups, and *Cohen's d* is used for this purpose. Cohen's *d* can be said to represent the difference between the means of the two groups, divided by the standard deviation, i.e., $d = M_1 - M_2 / \sigma$. There are various ways to calculate the standard deviation used in this formula. Commonly the pooled standard deviation of the two groups is used, calculated as

$$\sigma_{\text{pooled}} = \sqrt{\left(\left(\sigma_1^2 + \sigma_2^2\right)/2\right)}$$

Cohen hesitantly described an effect size of $d = 0.2$ as small, $d = 0.5$ as medium, and $d = 0.8$ as large. Another way to describe these effect sizes is to look at overlap of the two groups. An effect size of 0.2 indicates an overlap of about 85% for the two groups, whereas an effect size of 1 indicates about 45% overlap. (Becker, 2000)

In contrast to significance tests, effect size measures are independent of the group sizes. This makes the effect size an especially valuable index in explorative clinical studies, where small group sizes often are used.

The effect sizes in this thesis are calculated as Cohen's *d*. If negative effect size values are presented it means that the direction of the difference was opposite to the expected direction.

3. OVERVIEW AND DISCUSSION OF THE PAPERS

3.1. Paper I: Stuttering, emotions, and heart rate during anticipatory anxiety: a critical review

Paper I is a theoretical article making a renewed analysis and interpretation of published heart rate data of stuttering persons, related to stressful speech situations. Psychophysiological studies of stuttering have focused on the activity of the sympathetic nervous system. This type of study has failed to find any major association between stress and stuttering. In fact, several studies have reported *lower* heart rate and blood pressure in stuttering persons when exposed to stressful speech demands, in comparison with nonstuttering controls. This has led some authors, like Perkins (1996), to the counterintuitive conclusion that stuttering persons tend to experience a stress-reducing effect when stuttering is exhibited. Based on psychodynamic models, such an effect has been suggested to indicate that stuttering fulfils some kind of unconscious need.

In this paper it is argued that the heart rate data have been misinterpreted in the published psychophysiological studies of stuttering: that reduction of heart rate (and blood pressure) in fact is a natural and common response in humans and other mammals in situations characterized by anticipatory anxiety and uncertainty about how to handle the situation.

The relative reduction of heart rate is the result of a coactivation of the sympathetic and parasympathetic nervous systems, where the parasympathetic system reduces the heart rate. In other words, it is a physiological response characterized by simultaneous "gas and brake" in the control of the heart. This coactivation of both branches of the autonomic nervous system is typical of the "freezing response". The freezing response is a natural response pattern in mammals, in situations involving potential and poorly understood threats, without clear information about the best way to act. The freezing response tends to suppress movements and vocalization, in order to avoid being detected by potential threats, while at the same time preparing the organism for sudden action if needed — like fight or flight. The fastest way to suddenly increase the heart rate is to remove the parasympathetic (vagal) brake. In this way the autonomic coactivation can be seen as a physiological preparation for sudden action. It should be emphasized that the freezing response is not "all or nothing", instead it refers to a state with varying degrees of inhibition of movement and vocalization.

The review of research data suggests that the tendency to a freezing response in stuttering adults in stressful speech situations is likely to be a result of the speech problems they actually experience. There are no indications that stuttering persons show an increased tendency to freezing in non-speech situations.

Case reports and clinical experience suggest that stuttering often tends to be worsened by situations characterized by a combination of pressure and ambivalence about the best way to act. Conflicting impulses may result in a tendency to freezing. On the other hand, fight or flight responses, where there is no doubt about what to do, seem to facilitate fluency. For instance, there are reports of stuttering persons speaking perfectly fluently in dangerous combat situations in wars. Such observations are likely to be central to the development of psychodynamic theories

of stuttering, i.e., that stuttering is caused by psychological conflicts. One version of these conflict theories was formulated by Joseph Sheehan in the 1950s. He argued that stuttering is the result of an "approach-avoidance conflict": a conflict between the drive to speak and the fear of speaking, for example because of a fear of stuttering (Perkins, 1996; Guitar, 1998). When a person gets stuck within this conflict, the result would be stuttering.

Another way to look at this emotional influence is that it is not the emotional reactions that usually differ between stuttering and nonstuttering persons, instead it is the threshold for speech disruptions that is different. A strong argument for this interpretation is that established stuttering tends to be very persistent, and seldom is cured by psychotherapy or changed environment. This point was also expressed by Perkins (1996): *"... it is tempting to assume a neurological explanation because it seems to be the only credible reason why stuttering is so persistent, once acquired"* (p. 13). This view is also supported by studies indicating that stuttering persons in general do not have an increased level of neuroticism (Bloodstein 1995).

This model of different threshold for speech disruptions implies that any person can experience speech disruptions of a stuttering type if the situational pressure exceeds their threshold. However, for stuttering persons the threshold can be exceeded also in neutral and non-emotional situations. In this case, undisrupted speech is only achieved in circumstances which are especially favorable for fluency and which impose a minimum of conflicting impulses. Such circumstances may be: speaking when alone, speaking to pets or infants, unambiguous fight or flight situations, strong feelings of happiness, etc.

In summary, it is likely that the momentary severity of stuttering tends to be modulated by emotional responses, with increasing stuttering when conflicts are experienced. This does not, however, imply that the speech disorder called stuttering is related to emotional problems. Instead there are strong arguments for a neurological basis in most cases of this disorder. It should also be mentioned that there may well be subtypes of stuttering where situational and emotional variations have minimal impact. Further research is needed in order to map the relation between emotional states and stuttering in subtypes of stuttering.

3.2. Paper II: Stuttering and the basal ganglia circuits: a critical review of possible relations

Paper II is a theoretical analysis of the possible relation between stuttering and the functions of the basal ganglia system. Neurophysiological research on stuttering has been dominated by investigations of the lateralization hypothesis. In paper II it is argued that the observed displacement of processing from the left to the right hemisphere is an epiphenomenon. It is suggested to reflect two different factors: (a) Impaired automaticity of speech motor control tends to result in compensatory voluntary control of speech, which especially is dependent on right hemisphere processing. (b) Some cases of stuttering are related to lesions of the left hemisphere, resulting in a group average displacement of functions from the left to the right hemisphere.

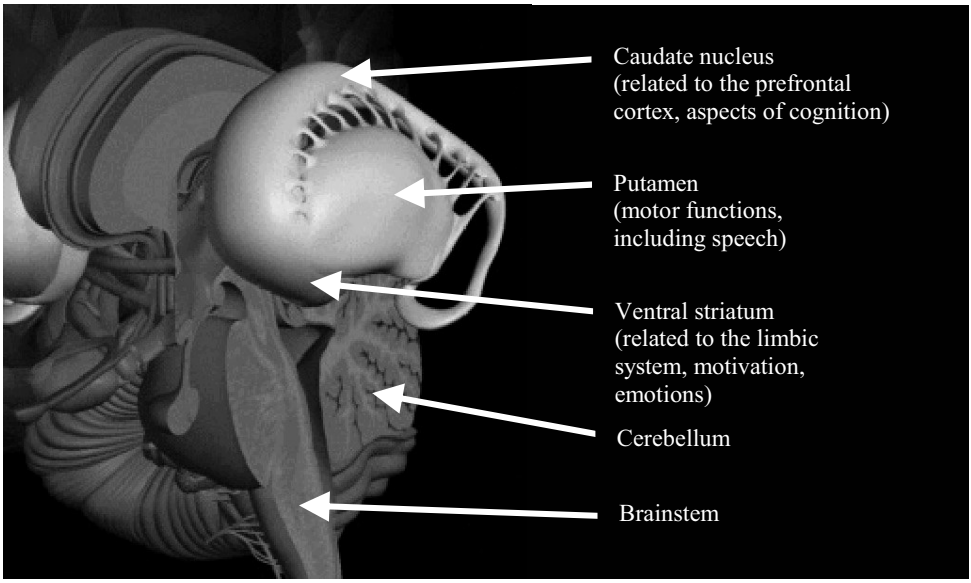

Figure 5. The left striatum, viewed in angle from the front and the side of the brain. (Illustration from the computer software InterBrain, by permission of Martin C. Hirsch, Springer Verlag, Berlin, 1998. Arrows and text added.)

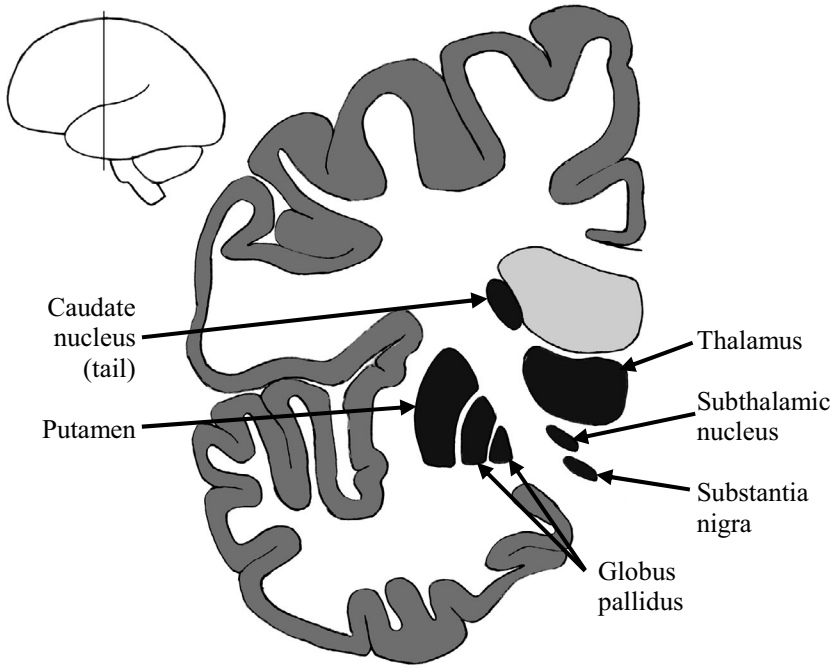

Figure 6. Coronal cross-section of the brain, one hemisphere, showing basal ganglia nuclei and the thalamus.

Instead a model is suggested where stuttering is a symptom of various types of dysfunction of the basal ganglia motor circuits, related to automatic sequencing of the submovements of speech.

3.2.1. The basal ganglia

The basal ganglia are a set of subcortical nuclei, receiving input from almost the entire cerebral cortex and the limbic system, in turn modulating the activity of the frontal cortex. (See Figure 5 and Figure 6 for basal ganglia anatomy, and page 328 in paper II for a diagram of basal ganglia circuitry.[14]) The pathways through the basal ganglia nuclei to the cortex are organized in parallel, with separate "channels" for different functions related to the motivational, the cognitive, and the motor systems. The motor system of the basal ganglia exerts its effects largely through modulation of the supplementary motor area (SMA). This basal ganglia-SMA premotor system works in parallel with a premotor system consisting of the lateral premotor cortex and the cerebellum.

The channels through the basal ganglia are organized in a direct and an indirect pathway, which are assumed to exert opposite effects on the frontal cortex, thereby balancing each other in order to obtain optimal function. The indirect pathway is thought to result in a diffuse inhibition of cortical impulses, whereas the direct pathway is assumed to give focused activation of specific frontal cortex areas in order to release specific behavioral impulses.

3.2.2. Basal ganglia cues

A general function of the basal ganglia system seems to be to provide context-dependent automatization of well-learned behaviors. In the motor system, the basal ganglia-SMA is thought to be especially involved in the timing of submovements of learned movement sequences, like speech. At the end of a completed submovement the basal ganglia system is assumed to automatically produce "cues" for the release of the next submovement in the sequence. This type of cue has been recorded from the basal ganglia neurons in monkeys who had learned a sequential wrist movement task, see Figure 7. It was shown that the basal ganglia generate this cue when the sequence is well-learned and can be predicted, see the left graph in the figure. However, if the required sequence of movements can not be predicted, no such cue is produced, see the right graph.

Impairment of self-initiated movements. In Parkinson's disease the ability of the basal ganglia to produce this type of cue is impaired. However, if external sensory cues (auditory, visual, or tactile) are provided they compensate for the deficient internal cues, thereby facilitating execution of movement sequences. This type of dysfunction, with impaired ability for self-initiated movements but preserved ability for externally cued movements, has also been observed after experimental lesions to

[14] For a relevant, thorough, and recent review of the basal ganglia, not mentioned in Paper II, see Saint-Cyr (2003).

the basal ganglia or the SMA. In contrast, this type of impairment is not shown after lesions of the lateral premotor cortex.

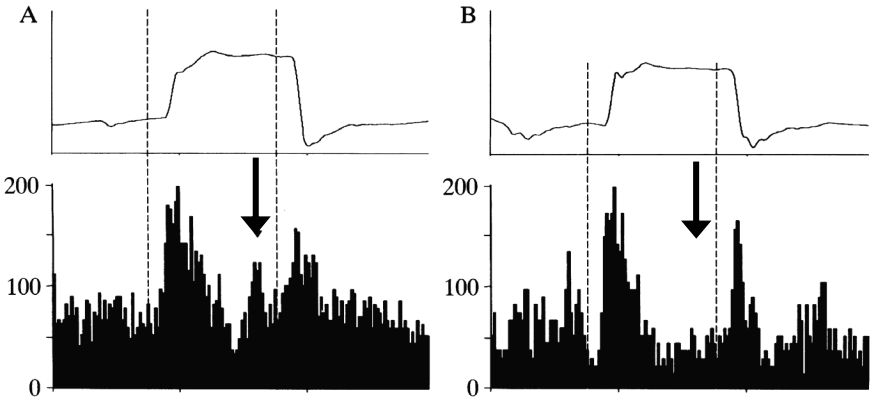

Figure 7. The upper graphs show tracings of wrist movements in a monkey (flexion and extension). The lower graphs show recordings of neuronal activity in the basal ganglia. The left graphs (A) represent a well-learned movement sequence. It can be noted that the basal ganglia discharge at the end of the first segment in the sequence (at the arrow), just before the start of the second movement. The right graphs (B) show an unpredictable sequence, that is not learned. In this case is there no cue from the basal ganglia. Illustration from Brotchie, P., Iansek, R., & Horne, M. K. Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. (*Brain,* 1991, 114, Pt 4, 1685-1702., by permission of Oxford University Press. Arrows added in illustration.)

The rhythm effect. These observations are especially interesting when discussing neural mechanisms of stuttering. One of the most striking characteristics of stuttering is the "rhythm effect", i.e., the fact that external cues for the initiation of syllables, like a metronome, usually result in instant fluency. This phenomenon strongly indicates that stuttering is related to an impairment of self-generated cues for submovements in the speech sequence, but with preserved ability for externally cued speech sequencing. As discussed above, studies of patients with Parkinson's disease and lesion studies in animals have shown that this type of dysfunction is related to the impairment of the basal ganglia-SMA system. Thus, the rhythm effect indicates that stuttering is a basal ganglia-SMA disorder.

Chorus speech and song. In paper II it is also suggested that the effect of chorus speech (reading in unison with someone else) is based on the rhythm effect, so that the voice of the other person serves as external timing-cues, for the sequencing of speech. Furthermore, stuttering persons are almost always able to sing without stuttering. The mechanism behind this effect is proposed to be that the timing of syllables is an essential part of all melodies, so that cerebral structures outside the basal ganglia provide the cues for initiation of syllables when singing.

The effect of increased attention. Persons with Parkinson's disease can often achieve improved motor ability merely by being instructed to consciously attend to a particular aspect of a movement. In a similar way, stuttering persons are often able to speak fluently for a while if changing to a way of speaking which requires increased attention, like imitation of a dialect or role playing. It is proposed in paper II that this effect is based on de-automatization of speech, resulting in decreased involvement of the basal ganglia and increased cortical processing, in other words, corticalization of the speech control.

Basal ganglia cues and motor practice. It has been found that certain "tonically active neurons" (TANs) in the basal ganglia show widely dispersed and temporally coordinated signals in relation to learned behaviors. The responses of the TANs grow stronger and more well-defined after practice of a certain behavior. It is proposed in paper II that the function of the TANs is related to the motor cueing in speech, and that practice of a certain speech sequence tends to result in reduction of stuttering as an effect of improved cueing. This phenomenon is shown by: (a) the "reading adaptation" (that the stuttering tends to be reduced if the same text is read several times), and (b) the observation that stuttering tends to be less likely on words which occur frequently in speech.

3.2.3. Dopamine

All functions of the basal ganglia are strongly influenced by the complex modulating effects of dopamine release. In brief, excessive release of dopamine in the basal ganglia tends to result in reduced inhibition of cortical impulses, whereas reduced dopamine release (as in Parkinson's disease) tends to have the opposite effect. A well-regulated level of synaptic dopamine is essential for the proper function of the basal ganglia. Various types of disturbances of the dopamine system will result in impaired signal-to-noise ratio in the target frontal cortex areas. Impaired signal-to-noise ratio will, in turn, imply increased risk of deficient motor cues from the basal ganglia. The result may be that the intended submovement is not properly initiated, while, instead, unintended motor activity may be released.

In brief, there are several indications of links between the dopamine system and stuttering, mainly from brain imaging with FDOPA-PET and from pharmacological trials. The few published reports of effects of dopamine stimulants suggest the existence of two subgroups of stuttering. Roughly one third of stuttering adults have been reported to show improvement on drugs blocking the dopamine D2 receptor (like haloperidol) whereas roughly one half of the adults have been reported to show improvement on dopamine stimulants (like amphetamine). In one study these two different groups were diagnosed as "stuttering-cluttering" and "stuttering", respectively. However, it should be noted that most cases who improved on D2 blockers did not continue the treatment due to side effects or merely slight improvement. It should also be noted that the reports of the effects of dopamine stimulants on stuttering are very scarce. Furthermore, both dopamine stimulants and D2-blockers have been reported to temporarily induce stuttering in some non-stuttering individuals.

3.2.4. "Neurogenic stuttering"

Stuttering with adult onset after brain lesions, often called "neurogenic stuttering", may provide leads to the mechanism of developmental stuttering with childhood onset. The lesions resulting in stuttering are often related to the basal ganglia motor circuit through the putamen, the VL nucleus of the thalamus, or the SMA. Typically, the lesions are located in the left hemisphere, but there are also a few reports of stuttering after right hemisphere lesions.

Another type of stuttering seems to be related to the CM nucleus of the thalamus. A few cases have been reported where the subjects showed a combination of neurogenic pain and stuttering, where the examination showed pathological electrical discharges in the left CM nucleus. When the pain and the electrical discharges were successfully treated with an electrode implant, also the speech was normalized. The main target of the signals from the CM nucleus is the putamen. It is suggested in paper II that the mechanism behind the stuttering in these cases was that the pathological firing from the CM nucleus disturbed the functions of the putamen, or more specifically, that the ability of the putamen to produce timing-cues for speech was disturbed.

3.2.5. Emotional modulation of stuttering

The common experience that many cases of stuttering are influenced by emotional reactions and stress is well compatible with the hypothesis of stuttering being a basal ganglia disorder: emotional influence is claimed to be characteristic of all basal ganglia motor syndromes (Victor & Ropper, 2001). This emotional effect on the basal ganglia system might partly be a result of emotional variations in dopamine release.

3.2.6. Stuttering and dystonia

The term *dystonia* signifies motor symptoms characterized by involuntary muscular contractions, often in the form of co-contraction of antagonistic muscles, with spreading of contraction to adjacent muscles. Dystonia can affect various parts of the body. Of special interest in relation to stuttering is the type of dystonia called *task-specific focal dystonia*. This motor disorder affects a focal part of the body, but only when a specific task is performed, for example contractions of the hand when writing or when playing a musical instrument. The affected behaviors are typically highly automated, fast, and sequential movements. Furthermore, task-specific dystonia tends to worsen under stress, an observation which led to the incorrect conclusion that it is a psychogenic problem. In fact, as discussed above in Section 1.3.5.6, Bluemel (1930) described this disorder as *"stammering in walking", "stammering in writing",* and *"stammering with instruments (piano, violin, typewriter, telegraph)*" (pp. 34-37). Further parallels between stuttering and dystonia are that: (a) both disorders often are improved if the sensory (or auditory) feedback is blocked or altered, and (b) cases of both disorders have been reported to be improved or worsened by dopaminergic drugs, either by inhibiting or stimulating the dopamine system.

There are clear indications that the symptoms of dystonia are related to disturbances of the basal ganglia motor circuits, but that also reorganization of the sensory and/or motor cortex is involved. There have been arguments against the proposal of a parallel between dystonia and stuttering: (a) that the involuntary movements of stuttering persons may not typically be dystonic, and (b) that reduced intracortical inhibition has been found in various types of dystonia, but not in stuttering. At all events, the striking parallels between stuttering and task-specific dystonia indicate that the same neural systems are involved, i.e. the basal ganglia motor circuits.

An interesting model of the pathophysiology of dystonia is that the symptoms occur when the gain of a cerebral sensorimotor loop is too high (>1). The gain might be increased as a result of several factors, like: (a) focal lesions in the putamen resulting in reduced inhibition of the cortex, (b) neurochemical anomalies in the basal ganglia, (c) expanded cortical representation of the affected body part, in the sensory and/or motor cortex. This last factor, expanded cortical representations, might, in turn, develop as a result of a combination of reduced inhibition of the cortex and extensive repetition of a certain movement.

In summary, it has been proposed that a key mechanism in dystonia is excess gain in the sensorimotor cerebral loops through the basal ganglia, leading to signal overflow. It seems conceivable that such a mechanism also may be a factor in some cases of stuttering.

3.2.7. Cerebral development, aging, and degeneration

When discussing possible causal mechanisms of stuttering it is important to consider age-related variations of the disorder. Stuttering has a typical pattern of onset in childhood, followed by a high rate of childhood recovery. The review of studies indicates that causal factors for stuttering tend to be strongest and most frequent around 2.5 to 3 years of age. Thereafter the strength of these factors drops rapidly in most cases during the preschool years. There tends to be a further decrease in stuttering in late childhood and adolescence, and probably also a tendency for stuttering to diminish at an advanced age.

Two other findings may also be relevant in this context: (a) It has been reported that children with early onset of stuttering tend to show precocious language development. (b) There are several reports of life-long stuttering which have disappeared after cerebral lesions, or as a result of degenerative symptoms of multiple sclerosis.

3.2.7.1. Childhood changes of the number of dopamine receptors in the putamen

A review of published data regarding the time course of various developmental changes in the nervous system pointed to the possibility that changes in the number of dopamine D2 receptors may be an important factor underlying stuttering. The number of D2 receptors peaks around the age of two and drops rapidly during childhood. Furthermore, the crucial aspect in relation to stuttering is suggested to be a low D1/D2 ratio in the putamen.

The rationale for this suggestion is that a high level of D2 receptors is assumed to reduce the diffuse cortical inhibition provided by the indirect pathway from the

striatum, whereas a low level of D1 receptors is thought to result in weaker activating cues from the direct pathway to the cortex. According to this model a low D1/D2 ratio would tend to result in a low signal-to-noise ratio from the basal ganglia to the cortex. For example, weak cues and low background inhibition of the SMA might lead to impaired activation of submovements in speech, whereas the risk of release of unintentional movements increases.

Available data suggest that the number of D1 receptors may peak somewhat later than the number of D2 receptors, around the age of three, and that the D1 receptors decrease in number more slowly during childhood. If this is the case, the D1/D2 ratio would be lowest when the D2 receptors peak, around the age of two, and then the D1/D2 ratio will increase when the child grows older. It is suggested that this pattern may be an important factor behind the frequent onset of stuttering around the age of 2.5 years, and subsequent spontaneous remission in many cases. Stuttering with later onset is suggested to be less related to this mechanism. This suggestion is supported by: (a) a report that D2 blocking medication has a stronger fluency enhancing effect in young stuttering children than in older ones, and (b) that the number of D2 receptors has been reported to correlate with cognitive performance, which is in accord with the report of precocious language development in children with early onset of stuttering, as mentioned above.

3.2.7.2. Cerebral degeneration or lesions

As discussed in Section 1.3.5.6, it has been suggested that stuttering is related to impaired processing capacity for speech motor control. However, this suggestion is difficult to reconcile with the reports of lifelong stuttering disappearing after cerebral lesions or degeneration. These cases have been interpreted as supporting the hypothesis that stuttering results from a conflict between speech motor control in the left and the right hemispheres. The lesion which resolved the stuttering was assumed to have established a clear dominance of one hemisphere.

In paper II an alternative explanation is suggested: that the mechanism behind the disappearance of stuttering after cerebral lesion or degeneration is that the gain of speech-related signals to the basal ganglia is reduced. According to this model, the key problem in these cases is an overflow of speech-related signals to the putamen, resulting in a ceiling-effect in the basal ganglia circuits. The risk of such an overflow might be increased in persons with bilateral speech motor control, because homologous cortical areas are connected via the corpus callosum, which might result in amplification of the signals. In such a case the hypothesis of "hemispheric interference" could be viewed as a variant of the more general mechanism: overflow of speech-related signals to the putamen.

3.2.8. Cortical and white matter anomalies in stuttering?

The review in paper II focuses 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. Some recent reports suggest anomalies of the cortex and the white matter pathways in some stuttering adults, and these findings will briefly be discussed.

One of the most interesting reports on stuttering during the last years is an MRI study of brain anatomy in stuttering adults. The most striking aspect of this report is

that many of the stuttering participants were reported to show extra gyri in speech-related cortex areas. For example, 10 of 16 stuttering persons were reported to have extra gyri along the superior bank of the lateral sulcus, whereas none of the control persons showed extra gyri in this region.

Another research team has reported impaired structure of the white matter in this part of the brain in stuttering adults, more specifically in the white matter underlying the left sensorimotor representation of the oropharynx. These two reports might reflect the same anomaly. (However, there are some reservations regarding the finding of a white matter anomaly; because of large voxel size it is possible that the analysis of the white matter has been influenced by gray matter.) Another result of the MRI study was a fairly strong tendency for larger planum temporale (an auditory cortex region) in the stuttering group.

It is not clear how these findings should be interpreted and there is a need for replication. It is possible that these reported cortical anomalies influence the function of the basal ganglia circuits. For example, if the auditory cortical areas are larger than normal, the gain of the input to the basal ganglia might also be stronger than normal.

3.2.9. Addendum: the "dual premotor systems hypothesis" as an explanation of fluency enhancing conditions

In paper II, Section 3.2, the distinction between *externally* and *internally cued* movements was discussed. Functional studies in combination with anatomical data indicated that the timing of internally cued movements is related to the basal ganglia-SMA system, whereas externally cued movements are related to the cerebellar-preMC system. This distinction between two parallel cerebral systems will here be discussed further. Furthermore, recent data regarding the effect of auditory input will be related to the effects of altered auditory feedback (AAF) on stuttering.

3.2.9.1. Goldberg's model of two parallel premotor systems

A relevant article, not included in paper II, is the thorough review of the functions of the SMA by Goldberg (1985). He developed the distinction between a *medial* premotor system, including the basal ganglia and the SMA, and a *lateral* premotor system, including the cerebellum and the lateral premotor cortex. He termed this model *"the dual premotor systems hypothesis"* (Goldberg, 1991).

According to Goldberg the medial system operates with actions derived from an internal model of the world. This medial system is proposed to be involved in speech that is *propositional* and *dependent on semantics*. In contrast, the lateral system is suggested to operate *"in a responsive mode in which each action is dependent upon an explicit external input"* (p. 568). The lateral system was suggested to be involved in speech that is *nonpropositional* and related to *auditory self-monitoring*. Furthermore, he proposed that these two premotor systems are *"in a state of mutually inhibitory balance that may shift with context"* (Goldberg, 1991, p. 41).

Goldberg (1985) also mentioned "repetitive speech" as a function of the lateral system. It is not specified exactly what was meant by "repetitive", but it seems likely that he was referring to speech where heard words or phrases are mechanically

repeated or "parroted". It is interesting that this type of speech has been shown to result in almost perfect fluency in most stuttering persons (Van Riper, 1982; Bloodstein, 1995). In the stuttering literature this phenomenon is called *shadowing*. One way to practice shadowing is for the stuttering person to hear a passage of prose in headphones, and to listen and repeat the words concurrently. It has been noticed that when the stuttering person does this, it is with an emotionless voice, and very little semantic content is extracted by the repeating person. It is just a mechanical repetition.

The theoretical work of Goldberg is partly paralleled by the experimental work of Deecke and Kurnhuber. Their conclusions placed further emphasis on the role of SMA in the timing of speech: *"The important role of the SMA for speech can well be understood if one imagines that speaking is a sequential task and needs exact timing. ... We really mean timing in the literal sense: the temporal ordering of the sequence and the delivery of the 'go-signal' for every single element."* (Deecke, Kornhuber, Lang, Lang, & Schreiber, 1985, p. 152)

Emotional expression and premotor systems. In a comment to the review of SMA-functions by Goldberg (1985), Antonio Damasio (1985) wrote that "[the SMA] *provides the royal avenue, into the cerebral cortex, of the limbic input that pertains to willed movement"* (p. 589). In his book *Descartes' Error* Damasio (1994) developed this theme further. Here Damasio points out the distinction between a "true" smile and a voluntary nonemotional attempt to smile. According to Damasio the true smile is produced by activity from the basal ganglia and the anterior cingulate cortex, i.e., the medial premotor system. In contrast, the voluntary controlled "smile" is produced by the lateral motor system. This is claimed to be the reason why it is difficult to smile naturally for photographers. This model is in line with a recent brain imaging study by Lau, Rogers, Haggard, and Passingham (2004), showing that the subjective level of urge to perform an action was related to the activity in the pre-SMA area, a part of the medial premotor system.

3.2.9.2. The effect of altered auditory feedback

De-automatization? The mechanism behind the often striking effect of altered auditory feedback (AAF) in reducing stuttering has appeared as one of the most confusing enigmas of stuttering. In paper II it was suggested that the effect is partly related to *de-automatization* of speech control. The concept of de-automatization may lead to the prediction that for example the effect of FAF ought to be temporary, disappearing when the brain has adapted to the new feedback frequencies. However, as discussed in Section 4.2.3 below, the available evaluations of long-term use of FAF points to a fairly stable and lasting effect. The question remains, of how the effect of AAF can be understood.

Listening to speech sounds excites the lateral premotor system. Four recent studies may provide important information, related to the effect of altered auditory feedback on stuttering (Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Watkins, Strafella, & Paus, 2003; Wilson, Saygin, Sereno, & Iacoboni, 2004; Watkins & Paus, 2004). In very brief summary, by using the methods of transcranial magnetic stimulation (TMS), motor-evoked potentials, and functional brain imaging it has

been shown that when hearing a speech sound, the lateral premotor cortex responds as if the person actually were articulating the sound. This phenomenon has been described as an expression of "resonance" or that the perception of speech sounds "primes" the lateral premotor system for speech production.

It has been suggested that this effect is based on certain "mirror neurons" located in the lateral premotor cortex. "Mirror neurons" have been described as forming a part of the visuo-motor system, characterized by discharge both when an individual performs a particular action, and when the individual observes someone else performing a similar action (Rizzolatti & Craighero, 2004). It is possible that a similar system exists as a part of the audio-motor system. These findings are in agreement with the model formulated by Goldberg (1985), in which the lateral premotor system is responsible for actions guided by external stimuli.

AAF as an illusion of chorus speech? Kalinowski and Saltuklaroglu (2003a), working with stuttering and altered auditory feedback, proposed that chorus reading and shadowing exert their effect on stuttering through engagement of the mirror neurons. Chorus reading and shadowing can be viewed as a direct and simple form of imitation. They then extended this explanation to also encompass the effects of FAF and DAF — stating that these effects are derivatives of the chorus speech effect, so that the altered auditory feedback signal creates an illusion of a second speaker and fools the brain into *"engaging gestural mirrors"* (p. 345). However, a problem with this model is that the second speech signal is created by the speaker himself, resulting in a circularity of the "mirror".

AAF triggers a shift to the lateral premotor system? A slightly different formulation of this model could be that the AAF triggers a shift from the medial to the lateral premotor system, according to Goldberg's dual premotor systems hypothesis. In this way bypassing the proposed dysfunction of the medial premotor system.

AAF-effects in other disturbances of the medial system. This model is supported by studies of AAF-effects in Parkinson's disease and in vocal tremor. Downie, Low, and Lindsay (1981) reported dramatic improvement of intelligibility as an effect of DAF in two of eleven patients suffering from Parkinsonism. These two cases had speech difficulties with some traits of stuttering. This effect of DAF in Parkinson's disease was confirmed by Brendel, Lowit, and Howell (2004). Furthermore, this study showed even greater improvements from FAF than DAF, in the speech of patients with Parkinson's disease. The core dysfunction in Parkinson's disease is located to the medial premotor system, and this effect of DAF and FAF is in agreement with the suggestion that the effect of AAF is based on a shift to the lateral premotor system.

DAF has also been shown to significantly reduce vocal tremor caused by psychological stress (Mendoza & Carballo, 1999). As discussed above, emotional motor expressions seem to be channeled through the medial premotor system. Thus, the observation that DAF reduces stress-related vocal tremor is also in agreement with the model of a shift in motor control from the medial to the lateral premotor system under the influence of AAF.

Continuous auditory stimulation reduces stuttering. The suggestion that listening to speech sounds reduces stuttering is further supported by the results of Kalinowski, Dayalu, Stuart, Rastatter, and Rami (2000a). Stuttering adults read a text during various conditions, like normal auditory feedback or continuous /a/ or /s/ sounds in headphones. The sound level in the headphones did *not* mask the auditory feedback of the participants' own speech. The result showed that the mean frequency of stuttering was reduced by 72% during the /a/ sound and by 52% during the /s/ sound. This finding is in accord with the model that hearing speech sounds activates the lateral premotor system, thereby improving fluency.

The AAF-effect may be related to auditory attention. Goldberg (1985) proposed that the lateral system is involved in speech with auditory self-monitoring. As a consequence, all changes increasing the attention to the auditory feedback would be predicted to facilitate the shift from the medial to the lateral system, thereby reducing stuttering. If a stuttering person attends to the auditory feedback, the effect of FAF and DAF would be expected to increase. Conversely, ignoring the sound would be expected to reduce the effect.

3.2.9.3. Summary, mechanisms supporting a shift to the lateral premotor system

The following mechanisms are proposed to support a shift of speech control from the medial to the lateral premotor system:

Speech guided by external stimuli with timing cues: (a) metronome speech, (b) chorus speech, and (c) "shadowing" (i.e., immediate repetition).

Rhythm generation in the lateral premotor system: (a) singing, and (b) speech with rhythm. (Experimental studies suggest that the right lateral premotor cortex acts as a rhythm generator for singing and rhythmic speech (Riecker, Ackermann, Wildgruber, Dogil, & Grodd, 2000; Riecker, Wildgruber, Dogil, Grodd, & Ackermann, 2002).)

Increased voluntary control of speech: (a) imitation of a dialect, (b) role playing, and (c) "prolonged speech" (i.e. reduced speech rate and prolonged vowels).

Listening to speech sounds activates the lateral premotor system: (a) chorus speech, (b) "shadowing", (c) FAF and DAF, (d) continuous speech sounds in headphones.

Low semantic and communicative content of speech: (a) speech when alone, speech to an infant or animal, and (b) singing. (This mechanism was proposed by Goldberg (1985), implying that propositional speech, with strong semantic dependence, is based on the medial motor system, whereas nonpropositional speech is more related to the lateral system.)

3.3. Paper III: Copper in developmental stuttering: a study of plasma copper, ceruloplasmin, and estimated free copper

This study was initiated because of a previously published study claiming significantly low levels of copper in the blood of stuttering men, and a negative correlation between the copper level and the severity of stuttering. The low level of copper was supported by a small pilot study in our laboratory. A review of possible links between copper and stuttering revealed several conceivable mechanisms for how disturbances of the copper metabolism might increase the risk of stuttering. It is known that disorders of copper metabolism can result in dysfunction of the basal ganglia system and dystonia. It has been shown that copper ions have a potent inhibitory effect on GABA(A) receptors, and also a pronounced effect on the dopamine system. Therefore it seemed possible that variations in the concentration of copper ions (also called "free copper") can affect the functions of the basal ganglia and thereby influence the risk of stuttering.

Against this background we investigated the plasma level of copper, the copper binding protein ceruloplasmin, and the estimated level of free copper in stuttering adults. Sixteen men with developmental stuttering were compared with 16 men without speech problems. No significant differences were found between the stuttering men and the control group in any of the biological variables, and no negative correlation between copper and the severity of stuttering was shown. On the contrary, an explorative analysis resulted in a positive correlation, between *high* plasma copper and superfluous muscular activity and movements during stuttering ($r = 0.51$, $p = 0.04$). However, this correlation may well be a haphazard result. In summary, this study does not support the previous report of a relation between low plasma copper and developmental stuttering.

3.4. Paper IV: Stuttering and sensory gating: a study of acoustic startle prepulse inhibition

As discussed above, stuttering is related to motor control and somehow also to aspects of auditory processing. Further, stuttering has also been suggested to be linked to the functions of the basal ganglia, the brain stem, and the dopamine system. One research method which may be sensitive for disturbances of these systems is called *acoustic startle prepulse inhibition* (PPI). The startle reflex is a normal reaction to strong and sudden sensory stimuli, like sounds, resulting in rapid muscular contraction elicited at the brain stem level. For research in humans usually the magnitude of the eyeblink reflex is measured, using EMG.

It has been found that if the loud sound is preceded by a weak sound, with 15 to 400 ms time difference, the startle response is usually reduced. This phenomenon has been interpreted as reflecting *sensory gating* or *perceptual filtering*, i.e. a function for inhibition of disturbing stimuli. Impairment of this inhibitory function has been found in persons with schizophrenia, Huntington's disease, obsessive-compulsive disorder, and Tourette syndrome. The degree of PPI is assumed to be determined by pathways from the basal ganglia to the pons. Pharmacological facilitation of dopamine tends to reduce PPI, whereas blockage of dopamine

receptor type D2 tends to increase PPI. Startle PPI has not yet, as far as we know, been tested on persons who stutter.

It may be speculated whether impairment of auditory sensory gating is related to the effect of altered auditory feedback (frequency altered and delayed) in stuttering. Therefore an index of the effect of auditory feedback on the stuttering (AAF index) was included in the study, in order to analyze the correlation between PPI and the AAF index.

Another aspect of PPI is that it may be sensitive to unilateral cerebral disturbances, i.e. those affecting only one hemisphere. The degree of PPI expressed by the left and the right eyeblinks is assumed to be controlled by the contralateral hemisphere. In stuttering a higher frequency of left than right hemisphere disturbances can be expected. This might result in asymmetry of PPI, with weaker PPI for the right eye in the case of left hemisphere dysfunction.

Startle PPI was analyzed in a group of 22 stuttering adults (17 men and 5 women) and compared with an equal sized group of persons without speech problems, matched for sex and age. The two groups showed very similar means and distribution of PPI, with no significant difference ($p = 0.60$). Further, no significant correlation was found between PPI and the AAF index.

The stuttering group showed a tendency towards PPI asymmetry in accord with the hypothesis, with lower right side PPI, implying possible left hemisphere dysfunction in a few cases. In 4 out of 26 stuttering cases the PPI asymmetry was outside the range of asymmetry for the control group, all in the direction assumed to indicate left hemisphere dysfunction. It can be noted that 3 of these 4 cases reported closed head injuries occurring soon before the onset of stuttering, in 2 cases leading to hospital care. A total of 6 out of 26 participants reported head injuries before the onset of stuttering. The Fisher exact test resulted in $p = 0.03$ for the probability that 3 out of 4 persons with PPI asymmetry outside the range of the control group would report pre-onset head injury.

In summary, the study does not support a relation between impairment of PPI and stuttering or the effect of altered auditory feedback. One interesting result was that 3 out of 6 cases who reported pre-onset head injury showed PPI asymmetry outside the range of the control group, indicating left hemisphere dysfunction.

3.5. Paper V: Stuttering in adults: the acoustic startle response, temperamental traits, and biological factors

3.5.1. Variables

The main aspect of this report is an investigation of whether the magnitude of the acoustic startle eyeblink response is increased in stuttering persons. The paper also includes an explorative investigation of several other variables:

- Habituation of startle, and the time from sound to eyeblink.
- Questionnaires of trait anxiety, childhood traits of attention deficit hyperactivity disorder (ADHD), and behavioral activation (BAS).
- An index of the effect of altered auditory feedback on stuttering (AAF index).
- Biochemical analyses: calcium, magnesium, prolactin, free thyroxine (T4), free triiodothyronine (T3), and thyrotropin (TSH).

- Background data: stuttering relatives and indications of neurological lesions occurring before the onset of stuttering.

The study included a total of 32 stuttering adults and 28 persons without speech problems. However, for different reasons, not all participants were included in all aspects of the study (see details in paper V).

3.5.2. Background and hypotheses

The main hypothesis in this study was that persons who stutter tend to have increased neuromuscular reactivity, either related to temperamental traits or reflecting neurological aspects of the sensorimotor function. Neuromuscular reactivity was measured as the magnitude of the EMG signal resulting from the startle eyeblink reflex elicited by brief pulses of white noise at the sound levels 100 to 106 dB (A). By using this procedure the reactivity of both the auditory system and the neuromuscular system is assessed.

It was speculated whether the effect of altered auditory feedback in reducing stuttering in many cases is related to heightened reactivity of the auditory system, so that masking, distortion, or delay of the auditory feedback reduces the problem. Therefore an important part of the explorative study was to investigate whether the AAF index is related to the magnitude of the acoustic startle response.

Another important aspect was to investigate whether there are indications of subgroups. The review of literature in paper II suggested that the stuttering population may consist of at least two major subgroups.

Analyses of calcium and magnesium were included because some older studies have reported tendencies towards low levels of these minerals in stuttering persons, and because such deficiencies can result in increased excitability of the nervous system. Abnormalities of thyroid hormones are known to affect temperament, and thus these analyses were included in the study. Prolactin was included based on the the dopamine hypothesis of stuttering (see paper II), because the blood level of prolactin is regulated by the dopamine release in a part of the brain (Guyton & Hall, 1996).

When the data collection was under way the results of a similar study were published (Guitar, 2003). Based on a group of 14 stuttering adults it was reported that the stuttering group showed significantly stronger acoustic startle eyeblink responses, especially for the first trial of the sound. The mean startle amplitude for the first trial was 81% higher in the stuttering group than in the controls. Furthermore, the amplitude of the startle eyeblink correlated with a scale of "Nervous" temperament (r = 0.39). The stuttering group also had significantly higher scores on the Nervous scale. This result supported the hypothesis that stuttering is related to heightened neuromuscular reactivity, and, furthermore, that this trait may be linked to a sensitive and reactive temperament with proneness to anxiety.

3.5.3. Conclusions from the review of literature in paper V

The introduction of paper V includes a review of published studies regarding temperament and anxiety in stuttering persons. In summary, the following conclusions were suggested:

Temperament. Studies of temperament in persons who stutter have yielded conflicting results, indicating a heterogeneous population. In brief, the published data seem to be in accord with the existence of at least two subgroups: One group with childhood traits of attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD), and one group characterized as "easy children", with good skills of concentration.

Anxiety. Stuttering adults tend to obtain higher scores than controls on questionnaires regarding trait anxiety. However, in paper V it is concluded that these studies is likely to have been affected by questions referring to aspects which can be assumed to be influenced by the fact that a person has a stuttering problem. For instance, a question like *"I am 'calm, cool and collected' "* is included in a commonly used questionnaire intended to reflect trait anxiety. It would be quite surprising if a stuttering group did not differ from a control group on such an item, considering the unpredictable nature of their difficulties of communication.

In summary, the studies indicate that stuttering adults, as a group, tend to experience increased levels of anxiety in relation to social situations because of fear of negative evaluation as a result of their speech difficulties. The conclusion that this increased anxiety mainly is a secondary effect of the stuttering is supported by: (a) the result from Craig (1990), that stuttering adults after stuttering therapy showed somewhat *lower* scores of "trait anxiety" than the control group; (b) the result from Messenger, Onslow, Packman, and Menzies (2004), that the increased anxiety is limited to social situations; and (c) the result from Embrechts et al. (2000), that stuttering preschool children obtained somewhat *lower* scores for shyness and fear than the nonstuttering controls.

3.5.4. Results of the planned testing of hypotheses

Startle eyeblink amplitude. No statistically significant difference was found between the stuttering and nonstuttering groups regarding startle eyeblink amplitude (n = 17 in both groups). There was a nonsignificant tendency in that the stuttering group had a 20% higher amplitude on the first trial. The size of this difference can be put in the perspective that the mean startle response of the females in the control group was higher than the mean response of the total stuttering group. In other words, the mean startle response of the stuttering group was well within the normal range. The study had a power of 0.93 to detect a difference in population means of the size reported by Guitar (2003).

Anxiety. The stuttering group showed significantly higher scores on the anxiety scale (effect size 0.77).

3.5.5. Explorative analysis and discussion

3.5.5.1. Correlations of startle eyeblink amplitude

Anxiety, stuttering severity, and the AFF-index. One interesting result was that the startle amplitude showed a slight *negative* correlation with the anxiety scale in the stuttering group (r = -0.11), indicating that startle amplitude is not a valid indication of an anxious temperament. Furthermore, startle amplitude was very weakly correlated with the severity of stuttering. In addition, startle amplitude showed a slight negative correlation with the AAF index (r = -0.07), and not a positive correlation as suggested by the hypothesis.

In summary, the result of this study does not support the hypotheses that startle reactivity typically is related to trait anxiety, stuttering, or to the effect of altered auditory feedback on stuttering.

Calcium and prolactin. A strong negative relation was found between startle amplitude and the plasma level of calcium, especially for the first startle trial and for women. In women (stuttering and nonstuttering merged) the startle amplitude for the first trial showed a correlation of r = -0.75 (p = 0.002) with the level of calcium. In men the correlation was r = -0.50 (p = 0.008). The strong relation between startle amplitude and calcium is not surprising, considering the well-known effects of the calcium level on the nervous system, with progressively increasing excitability if the level of free plasma calcium is reduced. Hypocalcemia increases the risk of tetany and may even cause seizures.

Startle amplitude was also correlated with the plasma levels of prolactin, again especially for the first startle trial. The women showed a correlation of r = 0.41 (p = 0.15) and the men almost the same, r = 0.42 (p = 0.03). The mechanism behind such a relation is not clear. However, binding sites for prolactin are found in the substantia nigra (Muccioli, Ghe, & Di Carlo, 1991), which is the source of dopamine for the basal ganglia motor system. This might be a pathway for influence of prolactin on startle reactivity.

Multiple regression analysis of the influence of calcium and prolactin on the amplitude of the first startle trial resulted in an adjusted R^2 value of 0.68 for the female group (p = 0.0008). In other words, in this study 68% of the variations of startle amplitude of the first trial in the female group (stuttering and nonstuttering, n = 14) might be explained by individual variations in the plasma levels of calcium and prolactin. In the male group the relations were not that strong, resulting in an adjusted R^2 of 0.22 (p = 0.02).

It can be noted that it is the level of free ionized calcium that influences the neuromuscular reactivity, and that this level may change rapidly because of changes in plasma pH. In turn, plasma pH is highly sensitive to changes in respiration, with hyperventilation resulting in a rapid increase in plasma pH and a concomitant reduction of the proportion of free calcium. This means that the neuromuscular reactivity measured by the eyeblink startle amplitude may change quickly in relation to the momentary breathing pattern. For example, anxiety may induce hyperventilation in some persons, which would tend to increase the startle amplitude. In summary, tests of startle amplitude may be affected by the individual breathing pattern immediately before the test.

3.5.5.2. Calcium in relation to anxiety and stuttering

Calcium and anxiety. It is known that low levels of calcium may result in increased anxiety. In the present study only a weak linear correlation was shown between calcium and anxiety (r = -0.18). However, the data indicate a possible threshold effect, with higher mean anxiety in the stuttering group with a calcium level below 2.28 mmol/L, with a large effect size 1.3 (p = 0.01). This explorative observation requires confirmation by further studies.

Calcium and stuttering. Stuttering severity showed a slight negative correlation with the plasma level of calcium (r = -0.28), though not reaching statistical significance (p = 0.18). Both the groups of stuttering males and females had somewhat lower levels of calcium than the controls, with the effect sizes 0.53 and 0.42. This is in line with a report by Costa, Antoniac, Berghianu, and Marinescu (1986), claiming low levels of calcium in stuttering children and adults. It can not be excluded that low levels of calcium in some cases may aggravate stuttering as a result of increased nervous system excitability. Such an effect might be both peripheral and central, with influence on peripheral neuromuscular reactivity and central sensorimotor circuits.

3.5.5.3. Magnesium and thyroid hormones

No remarkable or significant differences were found between the stuttering and the nonstuttering groups regarding magnesium or thyroid hormones.

3.5.5.4. Childhood traits of ADHD

Increased childhood traits of ADHD in the stuttering group. The WURS scale is intended to reflect childhood traits of attention deficit hyperactivity disorder (ADHD). The stuttering group showed a higher mean level of childhood ADHD traits than the controls, with a large effect size, 1.0 (p = 0.002). A total of 41% of the stuttering persons had WURS scores above the maximum score for the controls. However, most of these cases had scores below the level for diagnosis of ADHD. This means that these cases with high WURS scores showed traits of ADHD, but should not be regarded as having this diagnosis.

Analysis of the data from the stuttering group with high WURS scores showed that their increased traits of ADHD referred to the following aspects, in descending order: (a) being inattentive, daydreaming; (b) tense, restless; (c) concentration problems, easily distracted; (d) tendency to be or act irrational; (e) anxious, worrying; (f) hot- or short-tempered, low boiling point; (g) acting without thinking, being impulsive; and (f) having trouble with mathematics or numbers.

Traits of childhood ADHD related to early neurological lesions. An interesting pattern emerges if the stuttering group is split in halves, based on the WURS scores indicating traits of childhood ADHD (n = 16 in both groups). In the high-ADHD group a total of 81% reported indications of possible neurological lesions occurring before the onset of stuttering, in contrast to 25% in the low-ADHD group. This group difference was statistically significant (p = 0.004, Fischer's exact test). The frequency of stuttering relatives showed the opposite pattern, i.e. 50% of the high-

ADHD group reported at least one stuttering relative, to be compared with 87% in the low-ADHD group. The reported indications of possible neurological lesions were of various types. The most frequently occurring were (in descending order): traumatic head injury, resulting in hospital care or unconsciousness; perinatal birth complications; or premature birth.

These data indicate that the childhood ADHD traits in the stuttering group mainly were related to early neurological lesions. This indication is further emphasized when looking only at the cases with "pure" indications of background factors, that is, cases with *either* at least one stuttering relative *or* reporting indications of possible preonset neurological lesions. In the first group, with at least one stuttering relative but no indication of preonset neurological lesion, 11 of 13 persons belonged to the low-ADHD group. In sharp contrast, in the second group, with indication of preonset neurological lesion but no stuttering relative, 7 of 8 persons belonged to the high-ADHD group. This distribution of cases results in $p = 0.002$ (Fisher's exact test, two-tailed).

Anxiety in relation to traits of ADHD and lesions. There may also be a relation between pronounced traits of childhood ADHD and high levels of trait anxiety. If one outlier is excluded there was a correlation of $r = 0.41$ ($p = 0.02$) between traits of ADHD and anxiety in the stuttering group. The review of literature indicates that increased anxiety may be a secondary effect of a neurological lesion. Thus, a possible interpretation is that neurological lesions in the stuttering group tend to result in childhood traits of ADHD as well as increased trait anxiety.

3.5.5.5. Discussion of genetics and neurological lesions in stuttering

Genetics of stuttering: the role of the D2 receptor. Based on a review of the literature in relation to the result of this study it is suggested that a high number of D2 dopamine receptors in putamen may be an important factor in many cases of hereditary stuttering, especially in early onset and recovering stuttering. A high number of D2 receptors might also be related to the following traits: (a) Temperamental traits of low detachment (i.e., ease in making close emotional contact with other people, and appreciation of such contacts), low irritability, and being "easy children". (b) High cognitive performance, for example expressed as precocious language development. (c) Low level of childhood traits of ADHD.

Neurological lesions and ADHD. The result of the present study indicates that a large proportion of the stuttering adults showed increased childhood traits of ADHD as a result of early neurological lesions. This finding is in agreement with published studies showing increased risk of ADHD after childhood neurological lesions such as traumatic brain injuries, stroke of the basal ganglia, perinatal hypoxia, or preterm complications. The exact mechanisms behind the development of ADHD after neurological lesions are not known, but disturbed function of the striatum is suspected. The lesions might be subtle, of biochemical nature, and undetectable by MRI. Striatal dysfunction might also be suspected to be related to the development of stuttering in these cases.

Neurological lesions and stuttering. Previous studies have reported indications that stuttering may develop secondarily to early neurological lesions, like those arising from premature birth, perinatal complications, or concussion. The causal relation between neurological lesions and development of stuttering is supported by the difference in the number of reported indications of possible preonset neurological lesions in cases with and without stuttering relatives. Such difference has also been reported in two previous studies.

Effects of concussion on the basal ganglia. The principal mechanism in concussions resulting in unconsciousness seems to be a rotational force centered at the brainstem, at the level of the midbrain and the subthalamic nucleus. This rotation may result in diffuse axonal injuries. Such an effect is especially interesting in relation to the basal ganglia hypothesis of stuttering, since several crucial basal ganglia pathways are located in this region. It is conceivable that a severe concussion could result in disturbed basal ganglia functions, leading to both traits of ADHD and development of stuttering.

Pre- and perinatal hypoxia affecting the striatum. The pattern of dysfunctions following hypoxia depends on several factors, such as the degree and duration of hypoxia, whether it is intermittent or not, and the age of the fetus or child. It has been shown in animal studies that early intermittent hypoxia tends to result in loss of neurons in the striatum, and may lead to a chronic hypodopaminergic state in this structure. There are indications that the striatum may be especially vulnerable to hypoxia due to its high content of dopamine, and that the hypoxic lesions in part are mediated by D1 and D2 dopamine receptors.

Factors related to the sex ratio of stuttering. Stuttering shows a typical sex ratio with higher prevalence of stuttering in males, and this ratio tends to increase from early childhood to adulthood. The possible influence of various factors on this sex ratio is discussed based on the results from the present study and previously published data.

An interesting result of the present study, which is supported by Drayna et al. (1999), is that the male-to-female ratio in stuttering adults is much higher in the group without stuttering relatives than in the family history group. In the present study the group without stuttering relatives showed a 4.3 times higher male-to-female ratio than the family history group, and the corresponding figure in the study by Drayna et al. (1999) was 3.6. In other words, these results indicate that non-genetic events (for example lesions) are especially important in the etiology of persistent stuttering in males, compared with females and children.[15] What factors may be related to this sex difference in stuttering adults?

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[15] It may be possible that this pattern is the opposite in young stuttering children, because a study of Ambrose, Yairi, and Cox (1993) reported 2.6 times higher male-to-female ratio in the children *with* stuttering relatives compared with children without family history. The mean age of these children was 3.3 years. One factor which might contribute to such age-related difference is a higher mean onset age of stuttering due neurological lesions. There is a need for further studies.

As discussed above, it is likely that severe concussion can lead to development of stuttering. Statistics from hospitals point to a doubled frequency of head injuries in boys compared to girls. Thus, a higher incidence of concussions in boys would contribute to the sex differences in stuttering.

Another factor might be that the higher level of testosterone in newborn males could lead to an increased risk of hypoxic striatal lesions in male infants. Androgenic steroids have been reported to increase the release of dopamine in the striatum. Considering the indications of dopaminergic neurotoxicity discussed above, this mechanism might make males especially vulnerable to hypoxic lesions of the striatum. Furthermore, it has been reported that male gender is a risk factor for hypoxia at birth, with higher risk of encephalopathy in males than in females.

Lastly, estrogen is suggested to reduce tendencies to stuttering in females after the onset of puberty. In paper II, discussed above, it was proposed that one main feature of stuttering is an impairment in the capacity of the basal ganglia system to support the performance of speech motor sequences. It has been shown that the ability to perform fast motor sequences is greatly facilitated by increased levels of estrogen, and this has been suggested to be an effect of estrogenic modulation of the basal ganglia dopamine system. In line with this reasoning, estrogen treatment has been shown to improve the motor symptoms of parkinsonian postmenopausal women.

4. GENERAL DISCUSSION AND CONCLUSIONS

Wendell Johnson, who argued that stuttering is the result of cultural, social, and psychological mechanisms, formulated a list of aspects of stuttering which an organic theory should be able to encompass. The main items are listed below.[16]

An organic condition that causes stuttering should be compatible with:

- *infrequent stuttering, with most of the speech normal*
- *interpersonal and intrapersonal variability*
- *onset of stuttering at approximately three years of age*
- *recovery of stuttering without treatment*
- *elimination of stuttering under certain conditions:*
  - *a) talking alone*
  - *b) talking to pets*
  - *c) talking with a dialect*
  - *d) acting on the stage*
  - *e) talking with masking* [noise] *in the ears*
  - *f) singing*
  - *h) talking with a given rhythm*
  - *i) whispering*
  - *j) shouting*

(Johnson 1948, 1967, as cited by Hamre, 1972)

Most of these items have been discussed in this thesis. It seems clear that the cerebral premotor systems possess sufficient complexity to be well compatible with the aspects of stuttering listed above. Many of the details are still not well understood; however, in broad outline the characteristics of stuttering fit very well with the suggestion that the core of stuttering is a dysfunction of the basal ganglia-SMA motor circuits.

4.1. An integrative model of the nature of stuttering (outline of a working hypothesis)

This thesis began with a quotation of Charles Van Riper, comparing stuttering to a puzzle with scattered pieces. Now, at the end of the thesis, it is time to try to turn the puzzle into a picture. Any such attempt today must be regarded as tentative, open to revision when new pieces are found. Hypotheses are guesses, and I have aimed to make the hypotheses as specific and detailed as possible, in order to make it possible to disprove them. In line with this, the hypotheses are often formulated in an assertive way. With these reservations in mind, a preliminary picture may provide an important foundation for the planning of new studies and for interpretation of observed data.

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[16] The complete list included some items with questionable validity or relevance today, such as "normalcy of stutterers' blood pressure heart rate, and basal metabolism". The items in the list presented above were selected by the author of this thesis.

4.1.1. Basic neurological mechanisms

Stuttering is a *speech motor disorder* caused by disturbance of *the medial premotor system*. The medial premotor system consists of neural pathways originating in widespread areas of the *cerebral cortex*, passing through the *putamen*, the *globus pallidus*, the *subthalamic nucleus*, the *VL nucleus of the thalamus*, and finally including the *supplementary motor cortex* (SMA). The disturbance causing stuttering may be related to any part of this system.

The core functional deficit of the medial premotor system is suggested to be *impaired timing cues* from the basal ganglia to the SMA. These timing cues normally have the function of *initiating a shift to the next motor segment* in the speech sequence.

Thus, repetitions in stuttering indicate the inability to continue to the next segment in the speech sequence. Consequently, the final segment of utterances is not repeated in stuttering.

In some cases of stuttering, but not all, the disturbance of the medial premotor system results in impaired motor inhibition in moments of stuttering, causing superfluous muscular tension and movements. This muscular over-activation may be regarded as *dystonia*.

The stuttering population is clearly *heterogeneous regarding pharmacological effects*. For example, reports indicate that both D2-blockers and dopamine stimulants can improve or aggravate stuttering, in different cases.

One study of adults indicated that *increased cortical folding* in speech-related regions may be related to of stuttering. However, the functional implications of this finding are not known.

4.1.2. The fluctuations of stuttering

The brain has *two parallel premotor systems* for speech motor control: a *medial system* consisting of the *basal ganglia and the SMA*, and a *lateral system* consisting of the *lateral premotor cortex* (including *Broca's area*) and the *cerebellum*. These two systems are related to different modes of speech. In stuttering persons the disturbance affects the medial system, while the lateral system usually functions normally. There are two basic mechanisms behind the frequently observed fluctuations of symptoms in stuttering: *variations of the level of dysfunction in the medial system* vs. *bypassing the dysfunction by shifting to the lateral system*. These two mechanisms are discussed in the sections below.

4.1.2.1. Conditions resulting in a shift from the medial to the lateral system

Some conditions are proposed to result in a *shift of speech motor control from the medial to the lateral system,* thereby bypassing the disturbance of the medial system. The mechanisms suggested to induce a shift toward the lateral system are summarized in Table 1.

Table 1. Summary of mechanisms proposed to enhance fluency in stuttering persons, by shifting speech motor control from the medial to the lateral premotor system.

Mechanisms	Conditions
Speech guided by external stimuli with timing cues	- metronome speech - chorus speech - shadowing (i.e., immediate repetition)
Rhythm generation in the lateral premotor system	- singing - speech with exaggerated rhythm
Increased voluntary motor control	- imitation of a dialect - role playing - "prolonged speech"
Listening to speech sounds activates the lateral premotor system.	- chorus speech - shadowing (i.e., immediate repetition) - FAF and DAF - continuous speech sounds in headphones (e.g. "a")
Low semantic and communicative content of speech	- speech when alone - speech to infant or animal - singing

In a few cases also the lateral system may be disturbed, so that shifts from the medial system have less fluency enhancing effect in this group. It is suggested that these persons also have difficulties using fluency enhancing techniques like reduced speech rate.

4.1.2.2. Conditions affecting the level of dysfunction of the medial system

Some conditions, like emotional responses and pharmacological influence, may affect *the level of dysfunction of the medial system,* making stuttering milder or more severe. In Section 3.1 a model of psychological influence on stuttering was outlined. This model implies that the momentary severity of stuttering is modulated by the degree of conflicting impulses in the situation. A high level of conflicting emotions or thoughts tends to result in a "freezing" state, with increased stuttering. On the other hand, situations with strong but unambiguous emotions, like anger or happiness, tend to improve fluency. Likewise, speaking when alone or speaking to pets constitutes situations with absence of conflicts related to speech output, thus associated with a high level of fluency. (However, certain cases of stuttering may not show any marked relation between variations of psychological or emotional factors and speech fluency.)

Is stuttering caused by psychological conflicts? There are, however, several indications that psychological conflicts are not the basic cause of stuttering: the high degree of persistence of stuttering in teenagers and adults; the limited effects of psychotherapy or anxiolytic drugs on stuttering; the reports that stuttering persons on average does not have an increased level of neuroticism; and finally the many

indications of neurological and hereditary factors. Instead it is suggested that persistent stuttering is related to a neurological constitution involving a lowered threshold for speech disruptions in situations with conflicting impulses. Any person may experience stuttering-like speech disruptions in extreme situations, whereas the threshold of stuttering persons may be exceeded also in neutral and non-emotional situations.

Conclusions based on fluctuations of stuttering? Though many cases of stuttering may show a relation between the degree of conflicting impulses and the momentary level of fluency, it is important to caution against attempts to draw inferences regarding the psychological state of a stuttering person based on his or her level of stuttering. This is because the variation of stuttering is very complex. For instance, the level of fluency in a certain situation may vary depending on the level of attention given to speech (sometimes more stuttering in relaxed conditions and less stuttering in demanding conditions), previous conditioning of certain situations (i.e., negative experiences of for example telephone calls), time pressure, or the general state of health (for instance fatigue or a common cold).

4.1.3. Background factors

Stuttering in adults can be related to *genetic factors*, to *neurological lesions*, or to *combinations* of these two factors.

The neurological lesions can be of various origins. The dominating causes of lesions are suggested to be *intermittent pre- or perinatal hypoxia* affecting the putamen, or severe *concussion* resulting in rotational injuries of basal ganglia pathways in the brain stem at the level of the midbrain and the subthalamic nucleus. (It should be emphasized that it is likely that several other mechanisms also may result in neurological lesions leading to stuttering. However, a discussion of these possible factors lies outside the scope of this thesis.)

Neurological lesions resulting in stuttering *may well be mainly neurochemical* in nature, both in cases of hypoxia and concussion. Hypoxia may result in neurochemical changes in the putamen, and concussion might affect the dopaminergic pathways or the regulation of dopamine release.

It should be noticed that genetic factors may result in stuttering even in the absence of stuttering relatives. This is because the hereditary factors are likely to be polygenetic, so that an accumulation of certain genes in one individual may cause stuttering. Furthermore, it is conceivable that most of these genes are not specific "stuttering genes", but instead variants within the normal range of gene variation. For example, genetic variants resulting in a high level of D2 expression might increase the risk of stuttering but at the same have advantageous effects on learning ability.

4.1.4. Sex ratio

The *typical sex ratio* of stuttering, with higher prevalence of persistent stuttering in men, is suggested to largely be an effect of non-hereditary factors, such as *higher frequency of concussion and pre- or perinatal hypoxia in boys*. Furthermore, it is

proposed that *estrogen* reduces the prevalence of stuttering in females, starting at puberty, as a result of *facilitation of sequential movements* controlled by the medial premotor system.

4.1.5. Anxiety and temperament

An increased level of anxiety is frequent in the stuttering population seeking treatment. However, this *increased anxiety* is largely limited to situations involving speech and social evaluation, and can be assumed to mainly be *a secondary effect* of negative experiences of stuttering. Excessive neuromuscular reactivity is not a typical characteristic of stuttering, even if it may be shown by some cases of stuttering.

4.1.6. Temperament and background factors

Cases of stuttering with *indications of preonset neurological lesions*, without stuttering relatives, tend to have *increased traits of childhood attention deficit hyperactivity disorder (ADHD)* or attention deficit disorder (ADD) without hyperactivity. However, in most cases this is only a mild tendency, not leading to the diagnosis ADHD or ADD. The most typical trait in these cases is being inattentive and "daydreaming". The neurological lesions may also result in increased levels of anxiety in some children.

In contrast, cases of *stuttering related to hereditary factors*, without indications of neurological lesions, tend to have *low traits of ADHD or ADD*. Furthermore, it is suggested that many of these children are characterized as "easy children", showing good skills of concentration and often precocious language development. It is proposed that a factor behind both the stuttering and the temperamental traits of these children is a *high number of dopamine D2 receptors in the putamen*. More specifically, stuttering might be related to a low ratio of D1/D2 receptors in this structure.

4.1.7. Recovering childhood stuttering

The typical pattern of early childhood onset of stuttering and subsequent recovery in many cases is proposed to be based on *a peak in the number of D2 receptors in the putamen about the age of 2 to 3*, in combination with a low D1/D2 ratio. A low D1/D2 ratio may be more common in boys, contributing to the higher incidence of stuttering in boys.

It is conceivable that *low levels of calcium might contribute to an increased risk of stuttering and to increased levels of anxiety*. Reduction of the calcium level increases the excitability of the nervous system, both in the brain and in the peripheral neuromuscular system.

4.2. Treatment of stuttering and proposals for research

This thesis focuses on the causal mechanisms of stuttering, but the possible implications for treatment will briefly be discussed. Can the suggested models of the nature of stuttering shed new light on the mechanisms behind the effect of

treatment? Can possible new treatment methods be suggested, proposing pathways for further research?

When discussing methods of treatment both the effects and the "costs" need to be evaluated. The costs can be of various kinds, such as side effects of pharmacological treatment, need for conscious monitoring of speech techniques, disturbing sound of altered auditory feedback, or financial costs of electronic devices, medication, or therapy.

4.2.1. Speech practice and operant conditioning

Speech practice in adults. In most cases of stuttering adults the effects of speech practice will become only partially automatic, even after long practice. When continuous monitoring of speech is required to maintain the technique, the treatment effect can be said to be of the "bypass type" (i.e., shifting speech control from the medial to the lateral premotor system). But even so, the acquisition of the fluency skills may be very valuable for the individual. For example, even if a stuttering person chooses not to use the monitoring in most situations in everyday life, the knowledge of having this tool may result in a considerable improved sense of security in speech situations.

The Lidcombe program. One of the most interesting developments in stuttering therapy for children in recent years is the Lidcombe program (Onslow, Menzies, & Packman, 2001). In brief, it can be described as a structured program for reinforcement of fluent speech (i.e., operant conditioning), in a setting where the child should associate speech with positive experiences. From the viewpoint of stuttering as a basal ganglia motor disorder, operant conditioning of a functional speech motor pattern is theoretically very interesting.

Negative development of stuttering? Another question is whether stuttering in itself tends to generate more stuttering. The review in paper II indicates that long periods of repetitive movements may result in expansion and dedifferentiation of cortical sensorimotor representations, especially if the behavior is consciously attended to. This mechanism has been proposed to be involved in the development of dystonia. It is conceivable that stuttering in itself results in similar changes, possibly aggravating the stuttering and increasing superfluous muscular tension. If this is correct it may be important to try to break the stuttering pattern before it results in long-term changes of brain circuits.

However, reports that also severe stuttering in children may recover spontaneously speak against this model. It is clearly not generally the case that the severity of stuttering is correlated with the time since onset of stuttering. Maybe such plasticity is not a key factor in stuttering, though this has often been assumed. Might the symptoms of stuttering instead be more directly related for example to the neurochemical state? These questions indicate important tasks for future research.

Treatment of cases with attention deficits. As discussed in paper V, early neurological lesions resulting in stuttering seem to have a tendency to also result in deficits of attention. It seems likely that stuttering persons with attentional problems

will have difficulties in utilizing treatment methods requiring monitoring of speech. It would be important to investigate this hypothesis by comparing the result of fluency shaping programs to measures indicating the ability to maintain attention. If the hypothesis is correct, tests of attentional functions may be used as screening instruments before starting this type of therapy.

4.2.2. Speech-related anxiety

If the stuttering is aggravated by conditioned fear of certain speech situations, reduction of this fear may reduce the severity of stuttering. In such cases the reduction of anxiety might be regarded as improving the function of the medial system speech control.

4.2.3. Altered auditory feedback

The new type of miniaturized device for altered auditory feedback (Stuart et al., 2003), sold under the name SpeechEasy, has aroused considerable media interest recently. In principle, SpeechEasy is similar to a digital hearing aid fitted in the ear canal, but it is programmed to produce a slight delay and a frequency shift of the speaker's voice. It was introduced to the public in 2001, and 2548 devices had been sold by April 2004 (Rainmaker & Sun, 2004). The customers were entitled to return the device within one or two months if not satisfied, and to receive a 90% refund. The return rate has been 14% (Janus Development Group, Inc., personal communication, November 15, 2004).

Two studies of altered auditory feedback have been published in which the frequency of stuttering was measured at the initial use of the device and after some months of use, in groups of 8 and 9 persons (Stuart et al., 2003; Van Borsel et al., 2003). The study by Van Borsel et al. (2003) used a pocket DAF without FAF for an average of about 37 minutes per day. The result indicated that the fluency enhancing effect of DAF was reduced after 3 months, but also that the stuttering when not using the device had clearly improved. After 3 months the strongest remaining effect of the DAF was when reading aloud, and less during conversation. In the study by Stuart et al. (2003) the SpeechEasy device was used, with a combination of DAF and FAF. The fluency enhancing effect seemed to be somewhat stronger when reading aloud than during a monologue. The effect when reading aloud was unchanged after 4 months, while the effect in monologues had decreased slightly.

Both of these studies suggest a somewhat less stable effect for conversation or monologue than for reading aloud. It might be speculated whether this reduced effect during self-formulated speech may be related to an increased tendency to ignore the sound. When reading aloud it may be easier to attend to the auditory feedback, which therefore may result in a more stable effect.

Two surveys of the effects of SpeechEasy have also been reported. In the study by Kalinowski et al. (2004) a survey was sent to 250 customers, resulting in 105 replies (42%). A market research company (Rainmaker & Sun, 2004) sent a customer satisfaction survey to 2548 customers, yielding 489 responses (19%). The average time of use was 0.5 and 0.8 years for the two studies, respectively. In both studies the participants provided subjective self-ratings of their level of fluency,

suggesting that the use of SpeechEasy approximately halved the level of disfluency. The self-ratings in Kalinowski et al. (2004) indicate that avoidance of speech situations were clearly reduced. When asked about the impact on their quality of life, in the study by Rainmaker & Sun (2004), 19% answered that it had a very positive impact, whereas 57% reported a positive impact. This survey also supports the claims of a lasting effect of SpeechEasy in many cases: 50% considered that their current level of fluency when wearing the device was improved compared to when first starting to use it; 34% reported that the current level of fluency was the same, whereas 16% had found that their level of fluency when using the device had declined compared to the beginning.

It has been claimed that SpeechEasy works well for many stuttering children: *"Children seem especially susceptible to the beneficial effects of SpeechEasy. Almost every child tested to date has responded very well, showing very high levels of fluency while wearing SpeechEasy with almost no training.*" (SpeechEasy Device, Frequently Asked Questions, 2003) However, Skotko (2004) reported that she has had school age children who, after receiving the SpeechEasy device, had been put in purportedly unsuitable programs for stuttering in their schools. According to Skotko some of these children developed a more severe stuttering problem. She emphasize that it is important that the SpeechEasy device is administered by people knowledgeable in stuttering.

In summary, the studies reviewed above seem to support the claim that this type of device can be a valuable part of the arsenal in stuttering treatment. The effect seems to be fairly stable during long-term use, especially for reading aloud. There is one report of reduced stuttering when not using the device, but also one report of increased stuttering severity in school children if the device is not used correctly. Further studies are warranted, for example regarding the use of altered auditory feedback when reading aloud in schools.

A factor that may hinder widespread use of the SpeechEasy device is the relatively high cost, from $3600 to $4900 for the various models. This may be an especially important issue if using this technique for children, for short periods of time. The devices can be adapted for new users by changing the individual plastic shell. This means that it ought to be possible to develop administrative systems for leasing or recycling of devices, in order to keep down the cost for each user.

4.2.4. Pharmacological treatment, proposals for research

The discussion of the influence of neurotransmitters on stuttering naturally leads to questions about pharmacological treatment. There is still no established pharmacological therapy for stuttering, but several studies of the effect of various dopamine D2 receptor blockers have been published, for example recently regarding olanzapine (Maguire et al., 2004).

Dopaminergic drugs. In paper II of this thesis it was suggested that the stuttering population is heterogeneous regarding the effects of dopaminergic medications, with opposite effects of D2 blockers and dopamine stimulants. In order to test this hypothesis, and to characterize subgroups, there may be grounds for making an explorative short-term trial of stuttering adults with low doses of haloperidol and

amphetamine. It would also be interesting to include the new generation of dopamine modulators in such a trial, like aripiprazole (Abilify). (Haloperidol may not be suitable for longer periods, but in case of promising effects it may be changed to similar drugs with less risk of side effects after long-term use.)

Drugs for dystonia and spasms. In severe cases of stuttering with traits of dystonia, medications used for dystonia or spasms might be considered. Kiziltan and Akalin (1996) reported reduced stuttering in some cases under treatment with baclofen and biperiden (Akineton). Baclofen is a muscle relaxant and antispastic agent. According to Depue and Collins (1999), baclofen inhibits the dopamine transmission in the striatum, through inhibition of substance P. Biperiden is an anticholinergic drug and thus affect the functions of the basal ganglia. Another muscle relaxant, sometimes used in dystonia, is orphenadrine (Norflex).

GABA activation? In paper II the possibility that stuttering could be related to an overflow of speech-related signals to the basal ganglia was discussed. If this model is correct, strengthening the GABAergic inhibition of signal transmission would be expected to enhance speech fluency. Clonazepam increases the GABA transmission, and is used for treatment of epilepsy, but also of anxiety and twitching. A case reporting a good effect of clonazepam on stuttering is found on the Internet. This case used 2 mg daily, to be compared with the recommended dosage of 4 to 8 mg when used for epilepsy (Relieving stress to stop stuttering, 2004). However, it should be noticed that clonazepam may be addictive.

Calcium. As discussed in paper V, low calcium will result in increased excitability of both the central and peripheral nervous systems, with increased risk of tetany and anxiety. This is probably not a factor in most cases of stuttering, but it is conceivable that the combination of low calcium and stuttering will result in increased stuttering severity. Analysis of calcium is inexpensive and simple, thus it might be included as a screening procedure for stuttering persons.

4.2.5. "CM-stuttering"

In paper II, Section 4.3, four cases with stuttering related to pathology of the CM nucleus in the thalamus were reviewed. All of these cases showed repetitions of syllables or words, but none of them showed the reading adaptation effect (i.e. that the stuttering is reduced if the same text is read several times), and none developed concomitant symptoms such as facial grimaces, limb movements, or anxiety for speech. Furthermore, all of them had chronic neurogenic pain, leading to treatment by electrode implant in the left CM nucleus. During surgery it was shown that they had pathological electrical discharges in this structure. When these discharges were inactivated by the electrode, both the pain and the stuttering were relieved. Thus, if patients with this pattern of symptoms are observed, electrode implant could be considered.

4.2.6. Combination of methods?

In many cases a combination of different treatment methods may be advantageous, especially if the stuttering is severe. For example, the combination of fluency shaping and the electronic SpeechEasy device might have an additive effect. Possibly such a combination also could be tried in severe cases of stuttering in children, for example combining the Lidcombe program and the SpeechEasy device. Likewise, pharmacological treatment might be used as an adjunct to other therapy, especially for short periods.

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Paper I

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Stuttering, emotions, and heart rate during anticipatory anxiety: a critical review

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Abstract

Persons who stutter often report their stuttering is influenced by emotional reactions, yet the nature of such relation is still unclear. Psychophysiological studies of stuttering have failed to find any major association between stuttering and the activity of the sympathetic nervous system. A review of published studies of heart rate in relation to stressful speech situations indicate that adults who stutter tend to show a paradoxical reduction of heart rate compared with nonstuttering persons. Reduction of heart rate has also been observed in humans and mammals during anticipation of an unpleasant stimulus, and is proposed to be an indication of anticipatory anxiety resulting in a "freezing response" with parasympathetic inhibition of the heart rate. It is suggested that speech-related anticipatory anxiety in persons who stutter is likely to be a secondary, conditioned reaction based on previous experiences of stuttering.

Educational objectives: The reader will be able to: (1) describe how the autonomic nervous system is modulated by emotional responses; (2) explain how anticipatory fear often results in inhibition of heart rate due to parasympathetic activation; (3) discuss why emotional reactions in persons who stutter may be secondary to negative experiences of speech problems.

Keywords: Stuttering; Emotions; Heart rate; Parasympathetic nervous system; Freezing

The relation between stuttering and emotional factors has long been a matter of debate. Many people who stutter have the experience that stuttering is influenced by their emotional reactions, and this is also a common clinical experience. One way to investigate emotional aspects of stuttering is to measure physiological changes associated with activation of the

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sympathetic branch of the autonomic nervous system. Two of the most thorough studies in this field (Peters & Hulstijn, 1984; Weber & Smith, 1990) failed to find any significant overall group differences in sympathetic activation between the stuttering and the nonstuttering group, either at rest or in relation to speech or nonspeech tasks. However, speech was associated with relatively large increase in sympathetic activity for both groups. Weber and Smith (1990) showed significant correlations between measures of sympathetic activity and speech dysfluency in persons who stuttered, but the correlations only accounted for between 3 and 17% of the variance in fluency. In brief, this type of research has not been able to show any major association between sympathetic activity and stuttering.

If there is a close connection between stuttering and emotional factors, the nature of this connection is still unclear. Menzies, Onslow and Packman (1999) reviewed the existing research on stuttering and anxiety and came to the conclusion that the lack of evidence for a relationship between stuttering and anxiety may be a result of inadequate research designs regarding definitions and measures of anxiety, insufficient statistical power, or inappropriate speech tasks. They stated "It is our contention that the inadequate literature on anxiety and stuttering is not just an academic problem .... Until the precise nature of the relationship between anxiety and stuttering is understood, fully appropriate treatment of adult stuttering cannot be offered" (p. 8).

An assumption in psychophysiological research about stuttering has been that an increase in anxiety is related to increase in heart rate. In this article it will be argued that *reduction* of heart rate can indicate an emotional response of anticipatory anxiety, and that indications of this type of response have repeatedly been shown in the previous psychophysiological studies of stuttering. First, a brief overview of the functions of the autonomic nervous system (ANS) will be presented, and related to cardiovascular effects of different affective responses. Thereafter, studies of heart rate changes in persons who stutter will be reviewed and possible interpretations will be discussed.

1. The autonomic nervous system

The ANS controls the visceral functions of the body, such as the contractions of the heart, constriction of blood vessels, blood pressure, digestion, and sweating. The ANS consists of two major subdivisions, the *sympathetic* and the *parasympathetic systems*, which cooperate to adapt the bodily functions to different situations and demands (Guyton & Hall, 1996). In many autonomic functions, but not all, the sympathetic and parasympathetic systems have opposite effects, like acceleration versus deceleration of the heart rate, or dilation versus constriction of the pupil. The parasympathetic system is mainly passing through the two *vagus nerves* from the brain stem (Guyton & Hall, 1996). The vagus nerves send autonomic fibers to the heart, lungs, and digestive organs, but also non-autonomic fibers to organs involved in speech, like the larynx, pharynx, and soft palate (Porges, 1995).

The sympathetic system is often discussed in relation to stress and anxiety. Cannon (1915) found that fear, rage and pain tend to result in massive activation of the sympathetic system, a reaction known as the *fight or flight response* (also called the *alarm* or *stress response*). This is a catabolic reaction that prepares the body for action, with increased heart rate, blood pressure, blood sugar, and redirection of blood from the viscera and skin to the muscles

(Guyton & Hall, 1996). Porges (1997) argued that Cannon made a mistake in his focus on the sympathetic system in relation to emotions, neglecting parasympathetic contributions to emotionally induced cardiovascular reactions. Porges stated that this view still influences contemporary researchers. According to Porges also the parasympathetic innervation of the heart is modulated by affective responses in the brain.

1.1. Autonomic coactivation during anticipatory fear

The "traditional" view of the ANS is that the sympathetic and the parasympathetic branches work in a reciprocal manner, so that an increase of activity in one branch is accompanied by a decrease of activity in the other branch (Berntson, Cacioppo, & Quigley, 1991). In this model autonomic activation can be described by a single variable, like "arousal". However, this is not always the case. Berntson et al. (1991) claimed that the activity of the ANS must be described by two separate dimensions, for sympathetic and parasympathetic activation. In some situations the two branches of the ANS are *coactivated*. Coactivation means that an increase of sympathetic activity is paralleled by an increase of parasympathetic activity. In this case a large increase in ANS activity will have a small effect on the heart rate, since the accelerating sympathetic effect is inhibited by the parasympathetic system.

Autonomic coactivation in humans was shown by Obrist, Wood, and Perez-Reyes (1965) in a study of autonomic responses during anticipation of a painful stimulus. Tests with and without pharmacological blockade of the parasympathetic vagal nerve (with atropine) revealed autonomic coactivation starting before onset of the anticipated painful stimuli. The vagal activation resulted in bradycardia (reduction of heart rate) despite simultaneous sympathetic activation. The observation that anticipation of a painful stimulus tends to result in bradycardia was confirmed by a study of Santibanez-H and Schroeder (1988). They found that normal men and women as well as men with "anxiety neurosis" showed bradycardia during the anticipation period before the painful stimulus. (Women with anxiety neurosis tended to show the opposite response in this study, i.e. increase of heart rate.)

This type of reaction has been studied in more detail in rats. Iwata and LeDoux (1988) conditioned rats to associate a tone with an electric footshock. When exposed to the tone the rats showed a marked *freezing response* (see Section 2) with characteristic signs of anticipatory fear (piloerection, hunching of the back, etc.). In contrast, unconditioned rats that had been exposed to a random pattern of tones and footshocks rested quietly when exposed to the tone, showing no signs of fear. However, both groups showed the same increase of heart rate at the sound of the tone. Tests with drugs blocking the sympathetic or parasympathetic fibers revealed that the conditioned group, showing anticipatory fear, actually had a large sympathetic increase that was partly masked by a simultaneous parasympathetic increase. The unconditioned group displayed only sympathetic increase, with no change in the parasympathetic system. These results were confirmed in a similar study by Nijsen et al. (1998).

A relation between bradycardia and threatening stimuli has also been observed in other mammals. Mancia, Baccelli, and Zanchetti (1972) found that cats tend to react with immobility and slight bradycardia when approached by another hostile cat. Kalin, Shelton, Davidson, and Lynn (1996) reported bradycardia in rhesus monkeys during anticipation of

an unpleasant stimulus. In summary, it can be concluded that the widespread assumption of a direct relation between anxiety and increase of heart rate is not correct. Instead anticipatory fear often results in suppression of heart rate.

2. The freezing response: biological background

From an evolutionary perspective emotions can be seen as sets of genetically determined responses which are important to solve specific problems, like avoiding danger, finding food and reproducing. Each emotional state is associated with a specific way of reacting and behaving and the nervous system adapts the organism to the demands of the current situation. Both animals and humans show two contrasting behavioral expressions of fear. One is to freeze and become mute, and the other is to become active and for example scream and run away (Marks, 1987). These different defense mechanisms are also referred to as *freezing* versus *fighting and flight* (Fanselow, 1994). In the literature different terms are used for "freezing", such as "reactive immobility" (Carrive, 1993) and "vigilance reaction" (McCabe et al., 1994). The degree of freezing in an animal can vary gradually from total immobility to different degrees of movement inhibition (Marks, 1987; Blanchard & Blanchard, 1989). When the term "freezing" is used in the following discussion it does not imply that a person or animal is totally immobile. Instead it refers to a state of anxiety with varying degree of inhibition of movement and vocalization. A possible relation between the freezing response and stuttering was suggested by Peters and Guitar (1991).

2.1. The functional role of coactivation during freezing

If an animal notices a possible predator at some distance, the freezing response is activated to avoid being detected, while the animal becomes hyperreflexive and highly reactive to surrounding stimuli (Carrive, 1993). If the predator is coming close, the prey's behavior rapidly changes to either fight or flight, with facilitation of motor behavior. An important part of the freezing state is to prepare the organism for sudden motor activity if attacked. Increased sympathetic activity redirects blood to the muscles and the lungs and increases the blood sugar level. The simultaneous parasympathetic activation inhibits acceleration of the heart. The autonomic coactivation prepares the body for rapid acceleration of the heart, since the fastest way to increase heart rate is to withdraw the parasympathetic brake. Changes in the parasympathetic nerves to the heart reach maximum effect in about 0.5 s, compared with about 4 s for the sympathetic nerves (Berntson et al., 1997). Thus, autonomic coactivation during freezing may be seen as an important part of the defensive mechanisms in mammals.

2.2. Psychological aspects of freezing

Blanchard and Blanchard (1989) suggested that the freezing response is especially associated with situations involving potential or poorly understood threats, without clear information about the best way to act. This reasoning is in line with the proposition of Härtel (1987), that a combination of fear and the feeling of being helpless causes vagal

activation and bradycardia in humans. These types of situations, with potential and poorly understood threats and a feeling of being helpless, may parallel social situations for persons who stutter. The risk of not being able to speak because of stuttering can be regarded as a potential and poorly understood risk. The experience of being helpless in the moment of stuttering is often reported from persons who stutter. It would therefore not be surprising if persons with stuttering tend to react with a tendency for freezing and vagal activation during anticipation of stressful speech situations.

3. Autonomic activity in persons who stutter

Two of the most thorough studies of autonomic reactions in persons who stutter were made by Peters and Hulstijn (1984) and Weber and Smith (1990). Peters and Hulstijn measured skin conductance, pulse volume, and heart rate in 24 persons who stuttered and in 24 persons without speech problems. The measurements were taken before, during, and after tasks like mirror writing, intelligence test, reading aloud, and spontaneous speech. Contrary to what may have been expected, the stuttering group did not show significantly higher physiological responses, either during rest or during the different tasks. The only significant interaction effect between group and task was related to heart rate ($P < 0.01$). However, the largest group difference in heart rate was in the opposite direction to what was expected: During the anticipation period before spontaneous speech, the stuttering group only showed about 0.5 beats per minute (bpm) higher heart rate than during rest, while the corresponding result for the nonstuttering group was 5.2 bpm. That is, the stuttering group showed 4.7 bpm *less* increase of heart rate than the nonstuttering group during anticipation of the speech task. For the same period the measurements of skin conductance and pulse volume showed similar results for both groups.

The lower increase of heart rate in the stuttering group can hardly be explained by lower stress in this group. The stuttering participants reported significantly higher subjective anxiety during the speech tasks compared with nonstuttering participants and skin conductance and pulse volume did not indicate lower arousal in the stuttering group. Instead this result suggests that anticipation of a spontaneous speech task was associated with autonomic coactivation in the persons who stuttered.

Weber and Smith (1990) used similar procedures to those of Peters and Hulstijn (1984), with quite comparable results. During the anticipation period before the speech task, the heart rate of the stuttering group was *reduced* by 1.2%, while the nonstuttering group showed an *increase* of 1.3% (i.e. a group difference of 2.5%). During the same period, persons who stuttered and persons without speech problems showed approximately the same increase in indications of sympathetic activation, with somewhat higher mean increase for the stuttering group. (Figures for stuttering and control groups: reduction of pulse volume [indicates sympathetic activation] 10.9% versus 7.9%, increase of phasic skin conductance 0.15 versus 0.17, and increase of tonic skin conductance 1.04 versus 0.70.) During the speech task, the stuttering group showed 5.7% increase in heart rate compared with 10.4% increase in the nonstuttering group. The increase of the other measures, indicating sympathetic activation, was about the same for the two groups. (Figures for stuttering and control groups: reduction of pulse volume 51.0% versus 46.6%, increase of phasic skin conductance 0.26 versus

0.24, and increase of tonic skin conductance 1.51 versus 1.24.) These results confirm the indications of autonomic coactivation in relation to spontaneous speech in persons who stutter. Interestingly, in both studies the signs of parasympathetic activation were much weaker during anticipation of the reading task compared with anticipation of spontaneous speech. The difference between anticipation of reading and anticipation of spontaneous speech might be related to how the tasks were presented or to differences in level of fear for different speech tasks.

The tendency for persons who stutter to show suppression of the heart rate during speech-related stress is supported by the results from a study by Caruso, Chodzko-Zajko, Bidinger, and Sommers (1994). Changes in heart rate were registered in nine persons who stuttered and nine persons who did not stutter, under three different conditions designed to induce increasing levels of cognitive stress in combination with speech. The three conditions were (a) low stress, self paced reading aloud of the words RED, YELLOW, BLUE, and GREEN at a comfortable speech rate; (b) medium stress, to read the same words as rapidly as possible; (c) high stress, to name the screen color of the words as fast as possible, when the screen color and the word name were incongruent (i.e. if the word RED was shown in blue color, the correct verbal response would be "blue").

The mean heart rate, during the tasks, of the persons who stuttered was significantly *lower* than that of the persons who did not stutter ($P < 0.05$), with increasing difference as the task became more stressful. Stuttering subjects had 7.6 bpm lower heart rate in the low stress condition, 12.9 bpm lower in condition in the medium stress condition, and 20.5 bpm lower in the high stress condition. Increasing stress was related to increasing percentage of dysfluencies (see Fig. 1). In summary, the study indicates a relation between increased stress, increased dysfluency, and increased suppression of heart rate.

Also older psychophysiological studies of stuttering have found this type of "paradoxical" cardiovascular responses. Golub (1952) studied heart rate changes during reading in 26

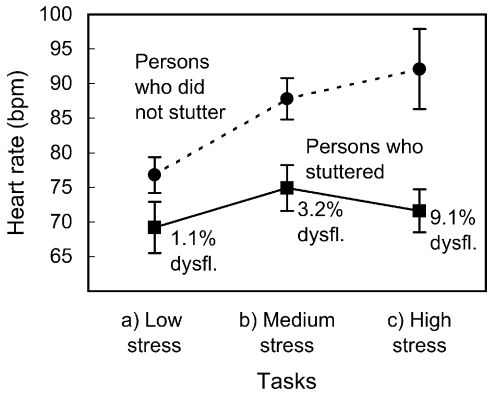

Fig. 1. Based on data from Caruso et al. (1994). Heart rate in beats per minute (bpm) for persons who stuttered (solid line) and persons without speech problems (dashed line), during reading in three conditions: (a) self-paced reading (low stress); (b) speed reading (medium stress); (c) speed reading + cognitive stress (high stress). The percentage of dysfluencies during reading is indicated for the stuttering group. The error bars represent standard errors of the mean.

persons who stuttered and 28 persons who did not stutter. It was found that the mean heart rate was significantly lower during passages with stuttering compared with passages with fluent speech. Berlinsky (1954) investigated changes in heart rate in 14 persons who stuttered and 14 persons who did not stutter, during anxiety inducing conditions with and without speech. The stuttering group showed lower heart rate in all conditions (with and without speech), but showed higher skin conductance compared with the nonstuttering group. It is interesting to note that the results of this study led the author to the conclusion that "stuttering acts as a cathartic activity relieving the anxiety of the stutterer"—a logical conclusion if regarding reduced heart rate as a sign of reduced anxiety. A similar interpretation was suggested by Dabul and Perkins (1973): They found that a difficult speech task involving stuttering reduced the mean systolic blood pressure in a group of persons who stuttered. Dabul and Perkins concluded that this result "is congruent with the psychodynamic implication that stuttering fulfills a need" (p. 590), but the authors did not exclude alternative explanations, like physiological effects.

4. Alternative explanations of reduced heart rate?

As mentioned above, Obrist et al. (1965) observed reduction of heart rate and increase of vagal activation during anticipation of conditioned unpleasant stimuli. Obrist et al. discussed how this observation could be interpreted, with the basic assumption that vagal responses are *not* related to emotions like anxiety. Suggested mechanisms like "conditioned pressor response", respiratory changes, or "orienting response" were found not to be congruent with the observations.

In persons who stutter it is conceivable that the heart rate is affected by effects of muscular tension. It is known that the so-called *Valsalva maneuver*, a forced expiration against a closed glottis, causes complex changes of heart rate and blood pressure (Ganong, Lange, & Lange, 1993). This may be relevant in stuttering, since a tense stuttering block could act as a Valsalva maneuver. The Valsalva maneuver results in increased abdominal pressure, which compresses the veins and thereby reduces the blood flow to the heart. The reduced flow leads to decreased arterial pressure and inhibition of baroreceptors, causing increased heart rate and constriction of peripheral vessels. When the Valsalva maneuver is released, the normal flow to the heart is restored but the peripheral vessels are still constricted, which leads to a rise of blood pressure above normal and a following reduction of heart rate below normal (Ganong et al., 1993). In summary, this mechanism could lead to an increase of heart rate during tense blocks or tense holding of breath, and a subsequent drop in heart rate during the periods after tense straining.

If this was the cause of the reduced heart rate seen in persons who stutter, then the reduction of heart rate should have been accompanied by signs of constricted peripheral vessels. The measurement of pulse volume in the finger is sensitive to constriction of peripheral vessels (Hugdahl, 1995) and should then be expected to covary with the reduction of heart rate. However, when looking at the data from Peters and Hulstijn (1984) and Weber and Smith (1990) this is not the case. During the anticipation period before spontaneous speech the pulse volume was almost exactly the same for persons who stuttered and persons who did not stutter. There are no indications in these studies that the reduction of heart rate in relation

to speech situations was an effect of peripheral vasoconstriction, and therefore, it seems unlikely that the reduction of heart rate was a result of frequent Valsalva maneuvers.

Another possibility could be that the findings of relatively reduced heart rate in relation to stuttering are part of a general reduction of heart rate. Available data give somewhat contradictory information about the "baseline" heart rate for persons who stutter, but in brief summary, they do not indicate generally low heart rate. For example, in the study by Peters and Hulstijn (1984), the mean heart rate during "rest" and during anticipation of the four different non-speech task was between 0.6 and 4.8 bpm *higher* for persons who stuttered compared with persons who did not stutter.

In summary, it seems to be difficult to find any non-emotional mechanism that could explain the observed reduction of heart rate. Autonomic coactivation during anticipatory anxiety appears to be a likely explanation.

5. Discussion

The reviewed psychophysiological studies of stuttering suggest that many adults who stutter tend to react with anticipatory anxiety and autonomic coactivation in stressful speech situations. This type of autonomic reaction is characteristic of a freezing response, which implies some degree of inhibition of motor activity and vocalisation. As mentioned above, a possible relation between the freezing response and stuttering was suggested by Peters and Guitar (1991). They proposed that observed co-contraction of antagonistic muscles in the larynx and in articulatory structures in persons who stutter could be part of a freezing response, with the function of silencing vocal output.

However, it is important to emphasize that emotional modulation of the severity of stuttering would not necessarily imply that emotional factors are the basic cause of stuttering. For example, it may be the case that certain types of instability in the speech system make the speech sensitive to quite normal emotional reactions. In such a case it would be reasonable to refer the cause of stuttering to the instability of the speech system and to regard the emotions as a modulating factor. Findings by Miller and Watson (1992) suggest that people who stutter do not have increased general anxiety. The increase in anxiety seems to be restricted to speech related situations and could be regarded as a rational response to negative experiences of communication. This view leads to the conclusion that the freezing reaction indicated in the reviewed studies of stuttering is likely to be a secondary, conditioned reaction, based on previous negative experiences of stuttering. It is also important to note that the reviewed indications of autonomic coactivation are based on group means for adults and may be limited to a subgroup of persons who stutter. Clinical experience suggests that anxiety is an issue for some but not all adults who stutter.

The distinction between two contrasting behavioral expressions of fear (Marks, 1987) with inhibition versus activation of motor activity (freezing versus fight/flight) might explain some paradoxical reports regarding the relation between stuttering and stress. For example, Bloodstein (1995) mentioned two cases from World War II. Two stuttering persons reported that they could only manage oral communication fluently when the situation was very dangerous. This is an extreme example, but similar experiences seem fairly common among persons who stutter. It is possible that acute danger, when the necessary course of action is

clear, may result in a fight/flight-reaction with facilitation of motor activity and vocalisation, and that this reaction ameliorates stuttering.

If emotional reactions like freezing and fight/flight affect the severity of stuttering, what would be the mediating mechanism? It seems likely that emotional states can affect the speech fluency through pathways in the central nervous system. Limbic structures like the amygdala and hypothalamus may exert strong influence on several levels of the nervous system, such as the brain stem, the basal ganglia and the cortical level. However, a detailed discussion of possible mechanisms for emotional influence on speech is beyond the scope of this article.

For future studies of emotional reactions in persons who stutter it is important to consider autonomic coactivation as a possible sign of anxiety. One way to get an indication of coactivation may be to measure the PQ interval in the electrocardiogram. Nijsen et al. (1998) found that the duration of the PQ interval (in rats) is mainly influenced by parasympathetic activity, which has a prolonging effect. During conditioned fear and freezing, rats showed a slight increase in heart rate combined with prolongation of the PQ interval. The authors claim that this combination of increased heart rate and increased PQ interval can only be explained by autonomic coactivation.

In summary, the main conclusions of this review is that (a) anticipatory anxiety can result in coactivation of the sympathetic and the parasympathetic systems, with parasympathetic suppression of the heart rate; (b) many adults who stutter tend to react with anticipatory anxiety in stressful speech situations, with a relative decrease of heart rate; and (c) there are indications that this increase of anxiety usually is limited to speech related situations, and may reflect negative experiences of previous stuttering.

CONTINUING EDUCATION

Stuttering, emotions, and heart rate during anticipatory anxiety: a critical review

QUESTIONS

1. What are the functions of the autonomic nervous system?
   a. To control the muscles of the speech organs
   b. To regulate the visceral functions of the body, such as heart rate, blood pressure, and digestion
   c. To support automatic control of speech articulation
2. How is activation of the sympathetic nervous system related to activation of the parasympathetic nervous system?
   a. The sympathetic and the parasympathetic systems are always reciprocal, so that a sympathetic increase will result in a parasympathetic decrease
   b. The two systems are always co-activated, working together
   c. The activation of the two systems may vary independently
3. Which are the basic behavioral expressions of fear, in human and other mammals?
   a. To freeze and become mute, or to become active and for example scream, run, or fight
   b. To fight or to run away
   c. To play dead and become mute

4. What has been a common conclusion from psychophysiological studies of speech-related anxiety and stuttering (the studies by Peters and Hulstijn (1984) and Weber and Smith (1990))?
   a. That stuttering is likely to be caused by emotional reactions, resulting in strong autonomic activation
   b. That persons who stutter do not show stronger autonomic reactions than non-stuttering persons
   c. That persons who stutter show a paradoxical reduction of sympathetic activation, resulting in reduced heart rate
   d. That persons who stutter tend to show a strong reduction of parasympathetic activation, resulting in increased heart rate
5. How should existing studies of heart rate in persons who stutter be interpreted according to this paper?
   a. That they tend to show a relative reduction of heart rate in relation to stressful speech situations, which is likely to be an indication of anticipatory anxiety
   b. That there is no relation between heart rate and anxiety in persons who stutter
   c. That they tend to show reduction of heart rate in relation to stressful speech situations, which indicates a paradoxical reduction of anxiety

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Paper II

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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*.

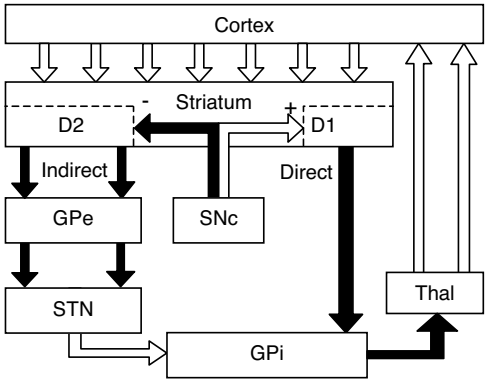

Fig. 1. Simplified diagram of basal ganglia-thalamocortical circuitry (motor circuit). White arrows are excitatory, black are inhibitory. GPe = external segment of globus pallidus; GPi = internal segment of globus pallidus; STN = subthalamic nucleus; SNc = substantia nigra pars compacta; Thal = thalamus. 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

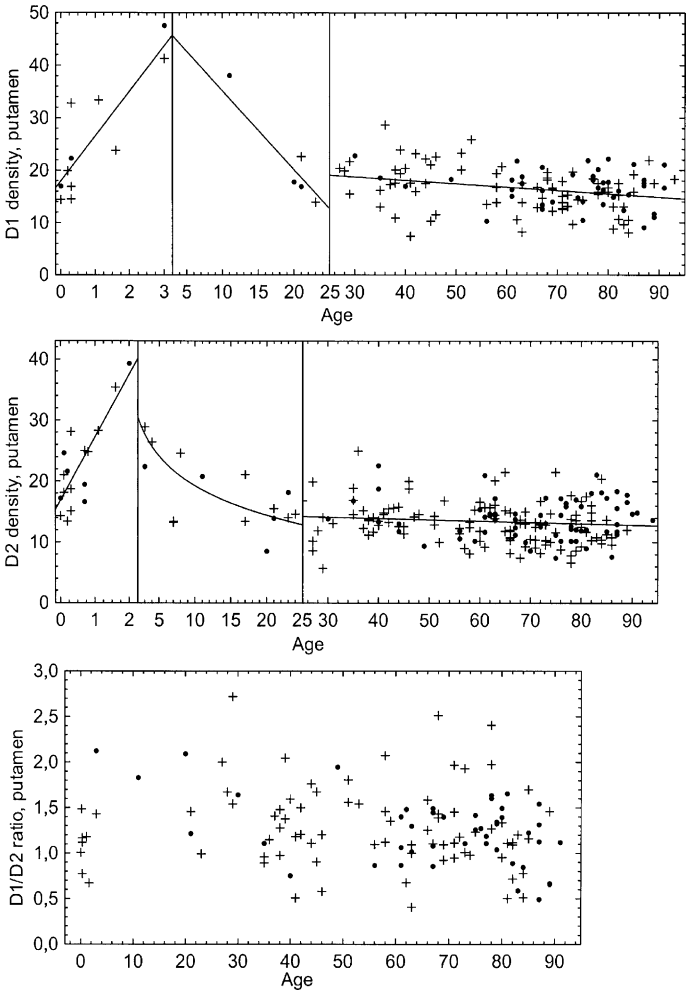

Fig. 2. Density of D1- and D2-receptors in the putamen, and D1/D2 ratio, based on postmortem data published by Seeman et al. (1987), from 244 cases in the general population. The sign ● marks females and + marks males. The regression lines are calculated for the rise, decline, and adult periods. The 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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Paper III

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Copper in developmental stuttering:
a study of plasma copper, ceruloplasmin, and estimated free copper

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Abstract

It has previously been reported that men with developmental stuttering showed reduced concentration of copper in the blood, and a negative correlation between the copper level and the severity of stuttering. Disorders of copper metabolism may result in dysfunction of the basal ganglia system and dystonia, a motor disorder sharing some traits of stuttering. It has been shown that copper ions affect the dopamine and the GABA systems. With this background we investigated the plasma level of copper, the copper binding protein ceruloplasmin, and the estimated level of free copper in stuttering adults. Sixteen men with developmental stuttering were compared with 16 men without speech problems. The samples were assayed in one batch in a pseudo-random and counterbalanced order. No significant differences were found between stuttering men and the control group in any of the biological variables, and no relation between copper and the severity of stuttering was shown. This result indicates that there is no relation between developmental stuttering and copper in the main population of stuttering adults.

Keywords: Stuttering, copper, ceruloplasmin

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1. INTRODUCTION

Stuttering is a frequent speech motor disorder of unclear etiology. A relation to basal ganglia dysfunction has been suggested [1–3]. The existence of aberrations of the dopamine system is supported by an FDOPA-PET study indicating increased dopamine synthesis in stuttering adults [4], and by improvement of some cases of stuttering with pharmacological treatment using D2 receptor antagonists [5].

There are several parallels between stuttering and *task specific dystonia* like writer's cramp [2,3,6]: excessive muscular contraction limited to specific automated sequential movements (for example writing or playing an instrument), blocking or altering the sensory feedback often improves the condition, some cases are responsive to drugs affecting the dopamine system, and lesions causing dystonia or stuttering are often located in the lentiform nucleus.

A possible relation between copper (Cu) and developmental stuttering is suggested by a study by Pesak and Opavsky [7,8]. A group of 16 male persons with developmental stuttering had significantly lower serum Cu levels than controls ($p < 0.001$): 14.1 μmol/l serum Cu (SD 2.1 μmol/l) in the stuttering group and 17.2 in the control group (SD 2.3 μmol/l) [8], making a difference in means of 3.1 μmol/l. Furthermore, the level of Cu showed a negative correlation ($r = –0.57$) with a measurement of the severity of stuttering (uncertain phonation starts). This report of low serum level of Cu in stuttering is interesting in relation to the suggestions of stuttering as a basal ganglia disorder with traits of dystonia. It is well known that disorders of Cu metabolism can result in basal ganglia dysfunction. In Wilson's disease the binding of Cu to the protein ceruloplasmin (Cp) is impaired, resulting in deposition of Cu in the liver and in the basal ganglia while the blood level of Cu and Cp is lower than normal. The neurological symptoms of Wilson's disease are predominantly movement related, like slurred speech, dystonia, and tremor [9]. A relation between Cu and dystonia has also been suggested in patients without Wilson's disease [10].

Cu ions have been shown to have a potent inhibitory effect on GABA(A) receptors [11], and to have pronounced effects on the dopamine system [12]. GABA and dopamine are of critical importance for the functions of the basal ganglia [2]. Thus, anomalies in the exact regulation of Cu might theoretically be related to different types of behavioral disorders, for example stuttering. Excess tissue Cu has been suggested to be involved in schizophrenia. Bowman and Lewis [13] concluded that the hypothesis of a relation between Cu and schizophrenia has neither been compellingly demonstrated nor convincingly refuted.

Normally about 95% of the total Cu in serum is bound to Cp. Each Cp molecule binds six to eight Cu atoms. Cp not containing Cu has a much shorter half-life than Cp with Cu. As a result, the blood levels of Cu and Cp normally show high correlation. Estrogens increase the level of serum Cp and Cu, and these levels are normally higher in women than in men, with larger difference when using estrogenic contraceptives or during pregnancy. When binding of Cu to Cp is impaired, as in Wilson's disease, the amount of "free" Cu in the blood is increased, while the total blood Cu is reduced [14]. The level of free Cu can be estimated by comparing the

levels of total serum (or plasma) Cu and Cp. The amount of free Cu ions in the blood might be an interesting factor when discussing possible effects of Cu on neural systems.

Are the levels of Cu and Cp influenced by stress? Cu is reported to be increased by physical stress, like inflammation and infections [15]. A test of 24 hours intermittent speed driving resulted in 37% increase of Cp [16]. However, the effect of emotional stress does not seem clear. It might be theoretically possible that emotional and physical stress caused by stuttering could increase the level of Cp and Cu, but there are no indications of such effect.

The result from Pesak and Opavsky [8] of low serum Cu in stuttering men was supported by a pilot study of stuttering men in our laboratory, without control group (n = 23, plasma Cu = 14 μmol/L to be compared with 14.1 μmol/L Cu in the study by Pesak and Opavsky [8]). The pilot study also indicated a low level of ceruloplasmin and a high level of estimated free copper. Therefore we conducted the controlled study reported in this paper.

The general purpose of the present study was to investigate possible differences regarding Cu and Cu-related measures in persons who stutter. The primary purpose was to replicate the study by Pesak and Opavsky [8] of Cu in men with stuttering, and to expand it by estimation of the level of free Cu based on analysis of Cp. In the present study also females were included, but the statistical analysis was limited to men, because of difficulties in achieving a sufficient number of female participants who stutter, especially since the level of Cu is affected by estrogenic contraceptives.

2. METHOD

2.1. Estimation of Stuttering Severity

The severity of stuttering was estimated as a global severity score based on rating of video recordings of speech samples, ranging from 0 (no stuttering) to 7 (very severe). The global rating was determined by first estimating scores for superfluous muscular activity and scores for the proportion of speech time with symptoms of stuttering, during spontaneous speech and during reading aloud. Thereafter the global score was set as an approximate composite of the sub-scores. Scoring was done independently by two raters, with rater agreement indicated by Pearson correlation coefficient r = 0.92 and rater bias = 0.84 (i.e., the difference of the mean scores of the raters). The mean of the two ratings was used for the final analysis. In 5 of the 20 cases the video recordings were judged to be clearly not representative of the stuttering in these cases, for example because of situational variations or use of fluency techniques. To increase to validity of the severity ratings the global scores for these 5 cases were adjusted based on additional information (from observations and interviews).

2.2. Participants

The participants were 16 males (age 22–48, mean 39.2) and 4 females (age 19–43, mean 34.2) with developmental stuttering, and 16 males (age 25–59, mean 37.6) and 12 females (age 24–50, mean 37.7) without speech problems. Persons with active inflammatory disease, diabetes, liver disorder, estrogenic drugs, corticosteroids, or diuretic medication were excluded, as well as control persons with a history of stuttering or cluttering in the family, or with neurological or psychiatric disorders. The mean stuttering severity score for males was 3.2 (range 0.5–7) and for females 4.1 (range 1.5–5.5). The study was performed as part of a larger study of stuttering, approved by the Lund University Research Ethics Committee.

2.3. Biochemical Methods

Blood samples were collected between 12:20 and 4:00 p.m., centrifuged, and stored at –70°C. The analyses were performed in one batch, with stuttering persons and controls intermingled in a pseudo-random and counterbalanced order. Plasma Cu was assayed using an atomic absorption spectrophotometer (Perkin-Elmer 1100B). Plasma Cp was analyzed by immunologic method (Hitachi 917) using rabbit anti-human ceruloplasmin antibodies (Dakopatts, Denmark, Cat. No. A031) and the calibrator BCR Reference Material CRM 470 (Dakopatts). An estimation of the concentration of "free" Cu unbound to Cp was calculated with the assumption that 1 mg Cp binds 3.2 μg Cu [17], resulting in the formula: estimated free Cu = Cu – Cp * 50.4.

2.4. Statistics

Group differences relating to Cu and Cp levels for men were evaluated by independent samples t tests, with the software Statistica 6.0 (StatSoft, Inc). Alpha was set at 0.05 for all statistical tests. One-tailed tests were used for plasma Cu and Cp, based on the result of Pesak and Opavsky [8]. Two-tailed test was used for estimated free Cu. Statistical power was calculated using PS software version 2.1.31 [18].

3. RESULTS

No differences were found between stuttering men and the control group in any of the biological variables. No relation between the levels of plasma Cu, or estimated free Cu, and the severity of stuttering was found. Also the group of women (N = 4) with stuttering showed results similar to the controls. The correlation between plasma levels of Cu and Cp was r = 0.95 (based on all available cases, including females using estrogenic contraceptives). Table 1 summarizes the means and standard deviations of the participants.

Independent samples t test showed no statistical difference in the level of plasma Cu between stuttering men and controls ($t(30) = 0.16$, $p = 0.56$, one-tailed).

Likewise, t tests of levels of Cp ($t(30) = 1.10$, $p = 0.86$, one-tailed) and estimated free Cu ($t(30) = 0.78$, $p = 0.44$, two-tailed) showed no difference between stuttering men and controls. The level of plasma Cu or estimated free Cu showed no significant correlation with measures of stuttering severity. The non-significant tendency was towards a positive correlation, with $r = 0.33$ between plasma Cu and the severity score.

Table 1. Means and standard deviations for plasma Cu, plasma ceruloplasmin, and estimated level of free Cu in plasma, in participants with and without stuttering.

		P-Cu (μmol/L)			P-Cp (g/L)		Free Cu (μmol/L)	
Group	*n*	*M*	*SD*	*range*	*M*	*SD*	*M*	*SD*
Males								
Stuttering	16	15.49	1.9	11.4–18.7	0.219	0.030	4.4	1.5
Control	16	15.35	2.9	9.1–20.7	0.207	0.034	4.9	2.0
All	32	15.42	2.4	9.1–20.7	0.213	0.032	4.7	1.8
Reference interval [14]				11.0–22.0	0.18–0.45			
Females								
Stuttering	4	15.25	2.5	13.0–17.8	0.225	0.021	3.9	1.8
Control	12	17.14	2.9	13.0–22.2	0.245	0.043	4.8	1.7
All	16	16.67	2.7	13.0–22.2	0.240	0.039	4.6	1.7
Reference interval [14]				12.6–24.3	0.18–0.45			

4. DISCUSSION

The result of this study points clearly against any relation between developmental stuttering in adults and plasma levels of Cu. Pesak and Opavsky [7] found lower Cu in stuttering men and a negative correlation between Cu and the severity of stuttering but this was not seen in the present study. On the contrary, the mean Cu level of the stuttering group of men was slightly higher than in the controls, and the non-significant correlation between Cu and the severity of stuttering was in the opposite direction than what was reported by Pesak and Opavsky. In the study by Pesak and Opavsky [8] the group of stuttering men showed a 3.1 μmol/L lower level of Cu than the control group. The present study had a power of 0.97 to detect a population difference of this magnitude, or a power of 0.80 to detect a difference in population means of 2.1 μmol/L (one-tailed tests). Jones et al. [19] argued for the importance of accumulation of null results with adequate power in research on

stuttering, in order to rule out the possibility of causal relations. A minimum power of 0.80 was recommended.

For all groups the estimated levels of free Cu were higher than expected, corresponding to about 70% binding of Cu to Cp according to the calculation, to be compared with the expected level of about 95% binding [14]. The level of Cp was lower than expected in all groups, for example about 30% lower than the levels in healthy individuals reported by Varela et al. [20]. It is possible that differences in method have resulted in relatively low levels of Cp in the present study, with increased level of estimated free Cu as a consequence. This does not, however, affect the comparisons between the groups since the levels of Cu and Cp showed a high correlation, $r = 0.95$, implying good consistency of the measurements.

Also the levels of plasma Cu were generally lower in the present study compared with published studies of healthy individuals. The pooled mean for men in this study was 15.4 μmol/L, to be compared with published mean levels of 18.6 [21], and 17.2 (age 18–60) [22]. The same tendency is shown for females. However, the high levels of estimated free Cu in the present study points against a bias towards low measurements of total plasma Cu. At all events, the mean level of plasma Cu for stuttering men was higher in this study than in the study of Pesak and Opavsky [8], 15.5 vs. 14.1 μmol/L. A possible cause of differing results may be heterogeneity in the stuttering population, but in the present study there is no indication of any subgroup with especially low plasma Cu.

It can be noted that Pesak and Opavsky [8] reported that the Cp levels were within normal limits in the group of stuttering men with reduced level of serum Cu. If these measurements were correct this would point to a *reduced* concentration of free Cu in these stuttering men. The assumed normal concentration of free Cu is about 1 μmol/L, to be compared with the 3.1 μmol/L reduction of mean Cu level in this group of stuttering men. The finding of normal level of Cp raises the question of a possible bias in the analysis of Cu in this stuttering group. In Pesak and Opavsky [7] it is mentioned that the control group was analyzed subsequently, which implies a risk for differences in the analysis of the two groups.

In summary, the results of the present study indicate that there is no relation between developmental stuttering and copper in the main population of stuttering adults.

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