The Role of the Corpus Callosum and Interhemispheric Connectivity in Tourette Syndrome

Kerstin Jessica von Plessen

Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2006

The Role of the Corpus Callosum and Interhemispheric Connectivity in Tourette Syndrome

Kerstin Jessica von Plessen

Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

The research was conducted at the

Regional Center for Child and Adolescent Mental Health and the

Department for Biological and Medical Psychology

ACKNOWLEDGEMENTS

LIST OF ARTICLES

The present thesis is based on the following papers:

I. Plessen K.J., Wentzel-Larsen T., Hugdahl K., Feineigle P., Klein J., Staib L., Leckman JF., Bansal R., Peterson B.S. (2004) **Altered interhemispheral connectivity in individuals with Tourette syndrome.** American Journal of Psychiatry 161:2028-2037

II. Plessen K.J., Lundervold A., Grüner R., Hammar Å., Lundervold A.J., Peterson B.S., Hugdahl K. **Functional brain asymmetry, attentional modulation and interhemispheric transfer in boys with Tourette syndrome.** In Press. Neuropsychologia

III. Plessen K.J., Grüner R., Lundervold A., Xu D., Hirsch J., Hammar Å., Lundervold A.J., Wentzel-Larsen T., Lie S.A., Bansal R., Gass A., Peterson B.S., Hugdahl K. (2006) **Reduced white matter connectivity in the Corpus Callosum of children with Tourette syndrome.** Journal of Child Psychology and Psychiatry 47:1013-1022

ABBREVIATIONS

ADHD   Attention Deficit Hyperactivity Disorder
ANOVA   Analysis of variance
CC   Corpus callosum
CSTC   Cortico striato thalamo cortical
DTI   Diffusion Tensor Imaging
EF   Executive Functions
FA   Fractional Anisotropy
HC   Healthy Control
IQ   Intelligence Quotient
MRI   Magnetic Resonance Imaging
OCD   Obsessive Compulsive Disorder
TS   Tourette Syndrome
WBV   Whole Brain Volume

I. INTRODUCTION

1. Tourette syndrome

1.1. Symptoms

Tourette syndrome (TS) is a developmental neuropsychiatric disorder with a peak onset around 3 - 8 years of age (Leckman, 2002), and with a prevalence between 0.6 % (Khalifa & von Knorring, 2003) and 3 % (Mason, Banerjee, Eapen, Zeitlin, & Robertson, 1998) in European populations of school-age children. TS is characterized by both multiple motor tics and one or more vocal tics that have been present, although not necessarily concurrently. Tics should occur many times a day throughout a period of more than one year, as defined in the diagnostic classifications DSM IV (Association, 1994) and ICD-10 (WHO, 1992). During this time period, there should not have been a tic–free period of more than three consecutive months (Association, 1994) (two months in the ICD-10 classification (WHO, 1992)). Motor tics are sudden semi-voluntary movements, which often start in the facial region, but which can involve other regions of the body as well and may present in a variety of movement intensities and motor patterns. Vocal tics have their peak onset later than motor tics, often around the age of 11 years (Leckman et al., 1998). Vocal tics frequently present initially by coughing, throat clearing or by the production of short and meaningless sounds. In the course of the disease, though, vocal sounds frequently worsen and extend into pronounced symptoms, such as iterating words or the more seldom symptom of involuntary cursing (coprolalia), the symptom for which the condition seems to have become predominantly known. Individuals with TS usually repeat movements and sounds in set patterns over a period of time. The symptoms are waxing and waning over weeks or months, but the condition often deteriorates until puberty. Vocal symptoms in particular can disturb social and academic activities. Many individuals with TS experience their tics as voluntary responses to sensory phenomena that frequently precede tic activity (Leckman, Walker, & Cohen, 1993). These phenomena have been termed "premonitory urges" and a lag of three years between the onset of tics and the initial awareness of these sensory phenomena has been reported in a large sample of children and adults with TS (Leckman et al., 1993). In many cases, symptoms attenuate during or after puberty (Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003) and more than 40 % of individuals with TS lose their symptoms until the age of 18 (Leckman et al., 1998). The typical course of the condition with an improvement during

puberty may even suggest that the basis of the condition could be regarded as a developmental variant rather than a progressive disorder (Singer & Minzer, 2003).

Treatment options for patients with TS can be improved by studying the nature of biological and environmental factors which influence the course of TS and which may lead to the decline of tics during youth. In particular, it is crucial to understand the mechanisms of how these factors specifically act on brain development in individuals with TS. Furthermore, understanding the governing principles during the neural development of individuals with TS may potentially also help to learn about general rules of brain development. The topics of this dissertation include measures of brain-morphometry and function in both children and adults with TS. Although this is no longitudinal study, certain implications of the characteristics of children versus adult populations still can be drawn from these cross-sectional data.

1.2. Comorbidity

Even though core TS symptoms, as listed in the classifications, appear to be of neurologic character, and the origin of the condition is assumed to be neuro-biological, individuals with TS often experience emotional and behavioral problems as well as high rates of psychiatric comorbidity. Due to these accompanying symptoms and the high rate of comorbidity with psychiatric conditions, treatment is usually provided in psychiatry, most frequently in child- and adolescent psychiatry. A gold-standard work-up for individuals with TS should involve a standardized diagnostic procedure in order to detect co-existing conditions such as Obsessive Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD) or Depression. A genetically mediated relation between TS and Obsessive-Compulsive Disorder (OCD) has been established through population (Pauls, Raymond, Stevenson, & Leckman, 1991) and molecular genetic (State et al., 2003) studies. Moreover, complex tics and obsessive-compulsive symptoms are often difficult to distinguish. It has been suggested to term these typical motor or vocal patterns "obsessive-compulsive behavior" (OCB), referring to typical compulsive behaviors which often involve the "just-right" perceptions and which could be an intrinsic part of the TS symptomatology (Leckman, Walker, Goodman, Pauls, & Cohen, 1994). Rates of comorbidity with OCD (meeting the formal diagnostic criteria of OCD) in TS patients exceed 40 % in clinical samples of adults (King, Leckman, Scahill, & Cohen, 1999) and children (Termine et al., 2005). A recent prospective study reported that OCD symptom onset is significantly later than the onset of tics and that the manifestation of OCD symptoms correlates positively with IQ measures (Bloch et

al., 2006). Detecting manifest OCD is crucial for families and patients, as this condition often remains undetected and over years may disturb family interactions and child self-esteem. The education about potential OCD symptoms should thus be obligatory in the consultations of individuals with a new onset TS (Bloch et al., 2006).

Comorbidity with ADHD is observed in 60 % of children with TS in clinical samples (Robertson, Banerjee, Eapen, & Fox-Hiley, 2002), yet the etiologic relationship between TS and ADHD remains controversial (Spencer et al., 2001). Patients with TS, striving with impulsivity control, as shown in American soap operas, may rather imply a comorbid ADHD condition than representing typical cases of TS. Several cross-sectional studies show that problems of social adjustment and externalizing symptoms are significantly higher in children with TS and a comorbid ADHD condition as compared to children with TS alone (Carter et al., 2000; Sukhodolsky et al., 2003), who rather exhibit internalizing symptoms (Carter et al., 2000). Moreover, failure in academic settings could be attributable to problems primarily derived from the ADHD symptoms, such as distractibility and problems with executive functions (EF). Individuals with TS alone may not lack executive control and it has been suggested that early reports showing EF deficits in TS (as reviewed in (Como, 2001)) did not control sufficiently for comorbid ADHD condition (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005).

Other comorbid conditions involve Autistic Spectrum Disorders (ASD) and Depression (Robertson et al., 2002). Comorbid depressive symptoms can present as a biological condition independent of the TS condition, or in other individuals, the depression may be a consequence of the psychosocial disadvantages that TS children may experience in school or peer-settings. It should, however, also be noted that depression can be a side-effect of treatment with neuroleptic medication used to control tics behavior.

1.3 Clinical diagnostics

The diagnostic criteria for TS are clearly described in the current diagnostic manuals, and the diagnosis is clinically based on both the observation of the child and on information concerning the child's symptoms as described by the child her/himself or her/his caregivers. However, parents often describe the startling absence of tic symptoms during medical consultations. This absence of symptoms in consultations may be due to the child's excitement and concentration upon an unfamiliar situation which could trigger tic suppression

abilities in line with enhanced attention. Children with tics often are recognized in primary health care settings and should already early receive an assessment of their general psycho-social situation and tic severity. The physician in charge should strive to get a complete picture as to which degree the child and her/his family suffer from tics. Another important aim of the first medical consultations is the exclusion of concurrent comorbid conditions.

Tic severity can be assessed directly by a semi-structured interview (researcher dependent), e.g. by using the Yale Global Tic Severity Scale (Leckman et al., 1989) which since its first publication consistently has been used in major research studies. The YGTSS has been proven to be an appropriate instrument for assessing symptom changes and the impact of tic symptoms on other relevant variables. Tic symptoms may also be reported by patients themselves or by caregivers, using tables of registration for different specified tics e.g. the Tourette Symptom Self-Report (Cohen, Leckman, & Shaywitz, 1984) (sometimes referred to as the Tourette's Syndrome Symptom list) .

Patients and parents may need education in order to recognize recurrent behaviors as tic symptoms (Leckman 2002). Due to the high frequency of co-occurring compulsive-obsessive symptoms in children with TS and the nature of these disturbing symptoms that often lead to severe isolation and family problems (Thomsen, 2000), the physician should assure herself/himself specifically of the absence of OCD symptoms. A questionnaire e.g. the Child Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989) can be used for adequately covering this topic. Another frequent problem that may require attention is the occurrence of sleep disturbances (Rothenberger et al., 2001). Depending on the setting (primary care or specialist service), the diagnostic interview will often convey characteristics of a short or more thorough clinical medical history. The gold-standard, however, for the assessment of patients with tics is a mental health assessment with a structured clinical psychiatric interview (Coffey et al., 2000) ensuring that potentially important symptoms and conditions have been explored. Examples for these interviews are semi-structured interviews, such as the Kiddie-SADS (Kaufman et al., 1997)(used in the present study), or the CAS (Hodges, McKnew, Cytryn, Stern, & Kline, 1982), or structured other interviews, as e.g. the DAWBA (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). Beyond the importance of a comprehensive clinical evaluation on an individual basis for every patient, the recent focus on genetic psychiatric research into mental disorders additionally increases the need for precise and standardized descriptions of symptoms or "phenotypes" and even "endophenotypes" (Gottesman & Gould, 2003).

1.4. Genetics

The role of genetic factors that predispose individuals to develop TS has been confirmed during the last decades, mostly in twin and population based genetic studies (Pauls, 2003). Originally, heritability was assumed to be a rare, autosomal dominant trait (Pauls & Leckman, 1986), yet more recently, the genetic influence is thought to be mediated through poly-or oligogenetic inheritance (Walkup et al., 1996). Genome-wide screening analysis efforts have implicated intervals on chromosomes (4, 5, 8, 11, 17), yet without identifying disease related mutations (The TSA International Consortium for Genetics, 1999; Merette et al., 2000; Paschou et al., 2004; Zhang et al., 2002). A recent and promising study (Abelson et al., 2005), however, could identify one frameshift mutation and sequence variants in Slit and Trk-like 1 (SLITRK1) gene on chromosome 13q31.1. in three of 174 unrelated probands, but in none of 3600 controls.

1.5. Pathophysiology: Neural mechanisms for the generation of tics and suppression of tics

The generation and suppression of tics can be regarded as continuous interplay in the brain of patients with tics and with TS.

The generation of tics is thought to arise from cortico-striato-thalamo cortical circuits (CSTC) and especially from the basal ganglia portion. This follows the symptom presentation of the condition as a movement disorder. The basal ganglia constitute the "fine-tuning station" of the brain for movements and consist of five nuclei: the striatum (caudate nucleus + putamen), the subthalamic nucleus (STN), the globus pallidus (devided into the interna portion (GPi) and the externa portion (GPe)) and the substantia nigra (substantia nigra compacta (SNc) and reticulata (SNr)). The different portions of the basal ganglia interplay intricately with the cortical regions in cortical-subcortical circuits.

All afferent fibres to the basal ganglia terminate in the caudate and the putamen, whereas all efferent fibers originate in the GPi (terminate in thalamic nuclei, which in turn project to the motor cortex, supplementary motor area, and prefrontal cortex) and the SNr (terminate mostly at the colliculi superior for eye-movement initiation). CSTC circuits include several largely parallel organized circuits that interconnect cortical and subcortical areas by directing information from specific cortical regions to the basal ganglia and the thalamus, and back again to the specific cortical regions (Alexander, DeLong, & Strick, 1986).

13

Although the number of cortical-subcortical circuits remains controversial, at least four circuits are recognized as critical: the motor, the oculomotor, the prefrontal (including the dorsolateral prefrontal and lateral orbitofrontal cortex), and the anterior cingulate circuits (Alexander, Crutcher, & DeLong, 1990). These frontostriatal circuits are implicated in self-regulatory control in normal cognitive function (Marsh et al., 2006) as well as in the pathophysiology of several neuropsychiatric disorders (Sowell, Thompson et al., 2003; Spessot & Peterson, In Press). Each of the cortical-subcortical pathways has two different striato-thalamic pathways (Mink, 2001): first, a **direct** pathway passing from striatum to globus pallidus, pars **interna** to thalamus, with an overall **excitatory** effect and second, an **indirect** pathway that proceeds from the striatum to the globus pallidus pars **externa** to the subthalamic nucleus to globus pallidus interna to thalamus, with an overall **inhibitory** effect. The indirect pathway is thought to act as an intrinsic modulator on the direct pathway. The inhibitory output of the basal ganglia acts as a "brake" on motor pattern generators in the cerebral cortex and brainstem (Mink, 2001).

Nevertheless, evidence converges on cortical regions being heavily involved in the pathophysiology of TS (Singer, 2005), particular in the suppression of tics (Gerard & Peterson, 2003). The prefrontal region is thought to mediate performance on tasks that require decisions of whether, when, and how to act across a time delay, as needed in working memory, behavioral inhibition, and go/no-go tasks (Fuster, 2002). In the case of tic symptoms, prefrontal cortices may inhibit across time a behavioral response to the somatosensory urge to tic, and they determine at the same time when to release the tic behavior from controlled suppression (Spessot, Plessen, & Peterson, 2004). Dysfunction of prefrontal regions in TS patients is therefore likely to impair their ability to inhibit tic symptoms (Peterson, Staib et al., 2001).

1.6. Observations from neuroimaging

Although other brain mapping and imaging modalities have also been successfully used in exploring biological correlates of Tourette syndrome, due to the topic of the thesis this overview is restricted to MR studies.

1.6.1. Functional Magnetic Resonance Imaging

The first functional Magnetic Resonance Imaging (fMRI) study of 22 adult individuals with TS examined how CSTC circuits contribute to the voluntary suppression of tic behaviors

(Peterson et al., 1998) by comparing neuronal activation in cortical and subcortical structures during tic suppression with a rest condition, when subjects were allowed to tic spontaneously. The magnitudes of signal change in the MR images were correlated with measures of tic severity. Significant increases in signal intensity were detected in both the prefrontal area and the caudate nucleus during tic suppression and correlated positively with each other. This was expected due to excitatory connections between cortical regions and nucleus caudate. At the same time, significant decreases in activity were observed in the putamen, globus pallidus, and thalamus. Increased activity in the caudate nucleus was in turn associated with greater decreases in activity of the putamen, globus pallidus, and thalamus, consistent with the known inhibitory projections from the caudate to these other subcortical nuclei. Moreover, the magnitudes of the decreases in signal intensity in the caudate, putamen, globus pallidus, and thalamus correlated inversely with the severity of tic symptoms outside the scanner. The clinical picture and the course of the condition suggest that there is a smooth transition between voluntary and involuntary tic suppression. The findings from this study could be assumed to be a demonstration of the tic suppression process, continuously taking place in the brain of patients with TS, even though the process remains unconscious most of the time.

1.6.2. Anatomical MR-studies of basal ganglia regions

Due to the hypothesized origin of tic generation in the basal ganglia, this region has been in focus since the early days of MR brain morphometry. The first volumetric imaging study of the basal ganglia in TS examined 14 adult patients with TS (Peterson et al., 1993) and 14 healthy controls and found the volume of the left lenticular nucleus (putamen and globus pallidus combined) decreased in the TS group compared to the HC group. The unilateral character of this finding raised the question, whether individuals with TS could exhibit an affection of lateralized parts of the CNS, since in normal right handed individuals the lenticular nucleus usually is larger on the left compared to the right side.

The findings of a reduced size of the lenticular nucleus and a deviation of the physiological asymmetry were confirmed in a MR volumetric study in 37 children with TS and 18 control children (Singer et al., 1993), where boys with TS showed a trend towards a smaller lenticular nucleus and in both males and females the lenticular asymmetry was either reduced or reversed (right larger than left lenticular nucleus). In another study (Hyde et al., 1995) basal ganglia were measured in 10 monozygotic twin pairs with discordance for tic severity (aged 9-31). Lenticular nucleus volumes did not differ between co-twins, but the

caudate nuclei of the more affected co-twin were smaller (on average 6%). The absence of a control group in this study design did not allow for a statement whether both identical twins may also have had a genetically determined reduction of caudate size, since the observed difference in size was due to non-shared environmental factors.

Lastly, the so far largest anatomical MRI study of basal ganglia volumes in 154 children and adults with TS and 130 healthy control subjects (Peterson et al., 2003), indicated that volumetric abnormalities did not affect all basal ganglia structures in the TS group, but that the abnormalities were specific to the caudate nucleus in both children and adults. Smaller volumes of the putamen and globus pallidus were found in adults but not in children with TS. The results of this anatomical imaging study have several implications for the understanding of the role of the basal ganglia in the pathophysiology of TS. First, the presence of significantly smaller caudate nuclei in both children and adults suggests that hypoplasia of the caudate nucleus may represent a trait morphological abnormality in persons with TS. Second, decreased caudate nucleus volumes that persist into adulthood imply that the caudate nucleus is not a prime target for plastic changes in response to the presence of tics, nor is it a likely the candidate for the cause of the normal attenuation of tic symptoms during adolescence. Moreover, in a subpopulation of this sample the size of the caudate nucleus in child age predicted significantly tic severity in adult age (Bloch, 2005), with a smaller caudate predicting more severe tic and OCD symptoms.

1.6.3. Anatomical MR-studies of cortical regions

Whereas anatomical and functional studies suggest that the caudate nucleus may be the locus of trait abnormalities in children and adults with TS, cortical portions of CSTC circuits are thought to be involved in the modulation of tic symptoms in individuals with tics. In a sample of 155 children and adults with TS and 131 normal control subjects, cortical regions were determined by cortical parcellation and larger dorsal prefrontal volumes were detected in children with TS whilst smaller volumes were observed in adults with TS (Peterson, Staib et al., 2001). In addition, a higher proportion of white matter was found in the right frontal lobe in 11 boys with TS as opposed to 14 boys with comorbid TS-ADHD and 12 with ADHD-only compared to 26 HC subjects (Fredericksen et al., 2002). Larger cortical volumes were significantly associated with fewer tic symptoms in both the orbitofrontal and parieto-occipital regions (Peterson, Staib et al., 2001).

These inverse correlations of prefrontal volumes with tic severity suggest that the larger volumes in children with TS could in some way be due to a compensatory or adaptive process in the brains of these children that helps to attenuate the severity of tics. This possibility gains further credence from the findings of the fMRI study of effortful tic suppression, previously described, in which broad expanses of prefrontal cortices activated robustly during the suppression of tics. The need to suppress tics at school and in other social settings would activate these prefrontal regions repeatedly (and frequently). This repeated activation could then induce activity-dependent, plastic hypertrophy of prefrontal cortices in children and adolescents with TS.

Activity-dependent plasticity and hypertrophy within prefrontal regions would in turn help to attenuate the severity of tic symptoms by increasing inhibitory reserve and the capacity for self-regulatory control. This interpretation of the anatomical and fMRI findings in prefrontal cortices is consistent with the known role of the dorsoprefrontal region in subserving self-regulatory functions (Spessot et al., 2004).

1.6.4. Antomical MR-studies of corpus callosum

Ever since the early reports of abnormal brain lateralization in individuals with TS, the corpus callosum (CC) has been one of the brain areas of focus in the exploration of biological correlates of TS. The CC is thought to mirror brain asymmetry and hemispheral specialization (Banich, 2003b). The first study in 14 young adults with TS and 14 control subjects revealed a smaller CC area size in the TS group compared to the controls (Peterson et al., 1994), with a reduction of all callosal subregions. In a second study, the CC area size in 16 TS children was compared with the size in 21 children who had TS-ADHD and with 13 children who had ADHD-only as well as with 21 control children (Baumgardner et al., 1996). In this study the group with TS alone had on average a larger CC area size, the group with comorbid TS-ADHD had an intermediate CC area size and finally the ADHD group had a reduced CC area size. In another study (Moriarty et al., 1997), CC area size of 17 adults with TS and 8 controls was compared, and an increased CC area size was found in the TS group.

In order to evaluate the gender effect on CC area size on TS, one study included 10 girls with TS, 9 girls with a comorbid TS-ADHD and a control-group of 22 girls (Mostofsky, Wendlandt, Cutting, Denckla, & Singer, 1999). The absence of differences in CC size across the diagnostic groups in this study was interpreted as a sign that CC differences in TS were

restricted to boys. All of these studies share the disadvantage of not having re-aligned midsagittal MR images prior to measuring the CC (Rauch & Jinkins, 1996). This may have lead to inter-individual differences in measurement due to differences in midline positioning of the subjects in the scanner.

A survey of MRI studies thus suggests that anatomical and functional abnormalities in the caudate nucleus may predispose an individual to tics, while abnormal functioning of neural regulatory systems based largely within prefrontal cortices both may unmask this predisposition in individuals with TS and on the other side also may contribute to successful tic suppression in the greater majority of individuals with TS.

1.7. Treatment

In milder cases, information concerning the benign nature of tic symptoms to the child, the parents and the teachers is most important and often proves a sufficient intervention. Parents and children might, however, need help to get hold of the available information. Families may appreciate written information, e.g. handouts from the National Tourette Association (Norsk Tourette Forening: www.touretteforeningen.no) or information distributed by the National Competence Center for TS, ADHD and Narkolepsi in Oslo (Nasjonalt Kompetansesenter for AD/HD, Tourettes Syndrom og Narkolepsi: http://www.nasjkomp.no). Both are important sources for parents and individuals with TS, who wish to keep updated about research advances in the field or who wish to get into contact with other families in a similar situation. Also parents and children should be encouraged to educate their wider family, friends and peers about the condition, as this may help the child to feel more at ease in social situations.

Since the condition usually is diagnosed in childhood already, the following paragraph predominantly deals with children, yet also adult individuals with TS may need help in adapting their professional life to the condition. For children with TS, it is desirable to assess the overall school situation by establishing contact to the teacher/s and even observing the child in a regular school situation, as parents often do not possess sufficient information concerning the every day life their child experiences at school. Children with TS have a higher percentage of learning difficulties, although, as mentioned earlier, this may partly be attributed to a comorbid ADHD condition (Abwender et al., 1996; Erenberg, Cruse, & Rothner, 1987). Children with TS should thus undergo neuropsychological testing, including

an evaluation of reading and writing skills, if there is any uncertainty concerning the child's scholastic skills. Another domain that should be assessed at school is the interaction with peers, in order to detect any signs for mobbing at an early stage.

Many parents and children with tics, however, have experienced major problems with school teachers, particularly if the teachers themselves do not regard the child's tic symptoms as involuntary. Especially vocal tics easily can attract attention of the whole class and thus disturb the working atmosphere. Parents and therapists can help the child in the school situation by educating teachers and classmates concerning the involuntary nature of tics.

Children with comorbid conditions, however, should be referred to a specialist, and the treatment of comorbid conditions should follow the usual international guidelines and should be prioritized, as tics may diminish after successfully treating comorbid conditions (Leckman, 2002).

The treatment e.g. of a diagnosed comorbid OCD may even lead to an alleviation of tics, since the distinction of compulsive symptoms and complex and repetitive tic patterns can be difficult. The guidelines for the pharmacological treatment of a comorbid ADHD condition have, however, been object of controversy, since in several studies stimulants have been shown to increase the rate of tics (as reviewed in (Robertson, 2000)). This has resulted in a recommendation to avoid treatment with stimulants in TS patients with comorbid ADHD during the last two decades of the 20th century. A more recent understanding of the complex interaction between TS and ADHD suggests that stimulants, possibly in combination with an α 2 adrenergic agent, should be given whenever a child meets the formal criteria for an ADHD diagnosis and needs pharmacological treatment (Leckman, 2002). It is assumed that stimulant medication, by decreasing the stress level in both the child and the family, even may improve tic symptom severity.

The importance of developing more standardized and validated methods for behavioral treatment of tics is acknowledged by all involved parties. This is particularly relevant as knowledge concerning the ability of self-regulation and tic suppression advances. In addition, the ability of older children with TS to monitor their "premonitory urges", and thus being conscious about their physical signs preceding the tics could be an ideal onset for introducing behavioral treatment. It was, however, found, that the ability to suppress tics is not dependent on the awareness of premonitory urges (Banaschewski, Woerner, & Rothenberger, 2003),

which is important for younger children, who may not yet be aware of the specific sensory phenomena (Leckman et al., 1993). In general, individuals with TS tend to be aware of their ability to suppress tics for a certain period of time, the length of which may vary individually. While focusing on behavioral measures or encouraging the children to further develop their ability to suppress tics, it is important to find the right balance in conveying the children the feeling of mastering tic behaviour. The impression should be avoided that exhibiting tics is ostracised, which would attribute a form of stigmatization to the tics. Several specific behavioural techniques have been described in order to decrease tic severity such as relaxation, biofeedback techniques and habit reversal. Unfortunately, systematically collected evidence concerning the effectiveness of behavioural intervention is scarce (Leckman, 2002).

As yet pharmacological treatment of tics is purely symptomatic. Moreover, the assessment of any therapeutic intervention proves difficult due to the waxing and waning nature of the tic symptoms. A close follow-up of every patient receiving therapy is thus crucial. The decision to treat children with TS with pharmacological agents should be based on the child's own psychological strain as opposed to the environment's concerns for the patient or as a result of insufficient resources in the academic system. If, however, tics are so severe that the child is not able to concentrate at school or if tics cause physical pain (as e.g. seldom may be the case in severe motor tics) or if the child itself experiences the tics as extremely disturbing in social settings, pharmacological treatment should be considered.

In a recent overview (Singer, 2005), it has been recommended to start pharmacological treatment by using non-neuroleptic medications, especially in case of milder tics and rather reserve neuroleptic medications to suppress severe tic behavior. Typical non-neuroleptic drugs used in the treatment of tics are clonidine, guanfacine, baclofen and clonazepam. Neuroleptic drugs, such as D2 dopamine receptor antagonists, are effective tic-suppressing agents, yet may have numerous side-effects, which patients and families should receive information about. Newer, so- called atypical neuroleptics (as e.g. olanzapine, risperidone and quetiapine), in addition to being weaker D2 receptor antagonists have a greater affinity to 5-HT2 receptors, which result in an improved profile of side-effects for the patients usually with less extra-pyramidal symptoms. Due to the side-effect profile and the dynamic symptom patterns in TS, pharmacotherapy should be evaluated closely and drug holidays for patients receiving medication may be an easy way to re-evaluate the indication of the drug.

2. Brain lateralization and the corpus callosum

2.1 Brain asymmetry

Structures of the humans' physical body exhibit a high degree of symmetry, with an almost congruent mirror organization of the limbs and trunk. An even more salient feature is the gross anatomical surface similarity of the cortex of the right and left hemisphere, especially when taking into account the distinct differences in functional tasking (Hugdahl, 2005). Although simplified, in most persons the left hemisphere is specialized for the processing of language stimuli, whereas the right side is specialized for processing stimuli dealing with spatial orientation and stimuli with emotional contents (Gazzaniga, 2000). The two hemispheres engage in a continuous dialogue that is mediated through the CC as well as through ipsilateral non-crossed cortico-spinal facilitating and inhibitory projections that e.g. accompany motor activity. Knowledge concerning the functional differentiation of brain asymmetry has been gained through experiments involving persons without a functional CC due to surgically splitting the callosal bundle of fibers in order to improve intractable epileptic seizures (Sperry, Gazzaniga, & Bogen, 1969) or due to congenital agenesis/dysgenesis (Lassonde, 2003). A congenital CC agenesis, however, results in remarkably few symptoms, probably due to compensatory pathways. Even though, the CC is the main and largest axonal cortical interhemispheric connection, other subcortical commisures have been described, such as the anterior commisure or the hippocampal commisure (Lassonde, 2003).

Although the human body in general exhibits a symmetrical organization, several cortical and subcortical regions have an asymmetrical pattern. The right frontal lobe has e.g. been shown larger than the left, whereas the left temporal lobe is generally larger than the right (Crow, 1997). Asymmetry in the temporal lobe is closely related to another brain region that has been extensively studied, namely the planum temporale region located in the superior temporal gyrus including Wernicke's classical speech area. This temporal brain region is larger in the left hemisphere (corresponding to its crucial role in processing language) (Geschwind & Levitsky, 1968), whereas it is not entirely clear whether such asymmetry exists in the primates (Gannon, Holloway, Broadfield, & Braun, 1998; Hopkins, Marino, Rilling, & MacGregor, 1998), and whether primates also may possess a differentiated form of language (Peters & Ploog, 1973). Moreover, a proof for the behaviour-function correlate in the planum temporale region is found in the smaller left-sided region in children with dyslexia as compared to age-matched literate controls (Heiervang et al., 2000; Hugdahl, Heiervang et al., 2003).

2.2. The Dichotic Listening paradigm

The functional significance of this asymmetry in the temporal lobe is tested by the WADA test (Wada & Rasmussen, 1960). The WADA test is applied prior to neurosurgical interventions in order to ensure the location of the the individual patient's language center by examining in which hemisphere the patient processes language stimuli. A non-invasive test for language lateralization, however, is the dichotic listening task (DL). During the DL situation, subjects are presented with two different consonant-vowel combinations, one in each ear and are asked to report the syllable they hear. Numerous studies have shown a consistent right ear advantage (REA) in more than 70 % of healthy adult individuals (Hugdahl, 2003). The classic structural model (Kimura, 1967) assumes that the REA is the result of several interacting factors: first, that the auditory input to the contralateral hemisphere is more strongly represented in the brain. Second, that the left hemisphere is specialized for language in most individuals. Third, auditory information sent along the ipsilateral pathways seems to be suppressed or blocked by contralateral information. Finally, the REA may be the result of the fact that information reaching the contralateral right hemisphere has to be transferred across the corpus callosum to the language processing area in the left temporal lobe.

The REA can be modified by instructing the individual to attend either to the right or left ear stimulus (Bryden, Munhall, & Allard, 1983; Hugdahl & Andersson, 1986), thus adding a "top-down" component in this originally "bottom-up" stimulus laterality effect. When focusing on the right ear stimulus (forced right condition), the REA is even increased, whereas it is less prominent or even absent when probands focus their attention on the left ear (forced left condition), thus creating a left ear advantage (LEA). Thus, DL can be regarded as both a measure of temporal lobe function (Spreen & Strauss, 1991) and, by adding the "forced attention" condition as an attentional measure of prefrontal executive function (Hugdahl, Rund et al., 2003). Moreover, the forced left condition also tests functionality of the CC. The correct report of syllables heard by the left ear is dependent on callosal transfer to the language center and has been shown to correlate positively with CC size (Reinvang, Bakke, Hugdahl, Karlsen, & Sundet, 1994). This has been confirmed in experiments with patients who have undergone commisurotomy and who subsequently have a complete or near-complete extinction in the left ear channel (Milner, Taylor, & Sperry, 1968). DL thus is a relatively simple experimental test, which is easy to administer and which allows testing of different cognitive functions, that in turn can be correlated with specific brain regions in both

anatomic and functional MR scans or other brain mapping modalities (Hugdahl, 2005). The left hemispheric dominance for language processing is matched by a predominantly right hemispheric processing for musical stimuli (Hugdahl et al., 1999; Peretz & Morais, 1988) as well as a right hemisphere visuo-spatial processing (Thomsen et al., 2000), although hemispheral asymmetry in these tasks is present to a lesser degree than in tasks involving processing of language.

2.3 The corpus callosum

2.3.1 Morphology and function

The CC is the main white fiber commisure in the brain that connects the two hemispheres and plays a key role for integration and segregation of interhemispheric information. It consists of more than 300 000 000 neuronal fibers that mature through myelination in line with cortical maturation. Generally, the callosal axons are thought to exhibit a topographical distribution with different CC regions serving different cortical regions (Pandya & Seltzer, 1986). Recent DTI investigations, however, show that cortical fibers spread widely into the CC , e.g. fibers originating in the frontal lobe nearly occupy 100% of the genu and the anterior body of the CC (Huang et al., 2005). From studies of patients with partial callosal lesions it is known that the posterior regions of the CC rather transfer sensory information related to vision, audition and somatosensory information, whereas anterior regions of the CC transfer information concerning attentional and higher cognitive functions (Gazzaniga, 2005). The axons of the CC develop prenatally following a general anterior to posterior rule with a growth peak between the 19th and 21th week of gestation (Achiron & Achiron, 2001). Postnatally there is no evidence for the development of new axons, yet myelination and pruning of the CC axons take place parallel to the maturation of the cortical regions (Thompson, Narr, Blanton, & Toga, 2003). During the first month of postnatal life the CC is uniformly thin, but appears in its typical form around 8 months of age (Barkovich & Kjos, 1988). Further myelination of the CC takes a cranio-caudal growth, as has been demonstrated by age correlations in cross-sectional (Giedd et al., 1996) and partly in longitudinal studies by means of MR examinations (Giedd, Blumenthal, Jeffries, Rajapakse et al., 1999; Thompson et al., 2000). The CC continues to increase in size due to myelination until the early adult years (Giedd, Blumenthal, Jeffries, Rajapakse et al., 1999; Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993; Thompson et al., 2000). In animal models, cortical damage has been shown to result in a degeneration of callosal axons (Rosen,

Galaburda, & Sherman, 1989; Skoff et al., 2001). In humans, cortical damage has been proven to correlate with CC atrophy (Pantel et al., 1999; Yamauchi et al., 1996).

2.3.2. Measuring the size of the corpus callosum

The midsagittal area of the CC represents the bulk of crossing axons, and thus constitutes an indicator of the amount of cortical neurons that connect interhemispherally through crossing axons (Aboitiz, Scheibel, Fisher, & Zaidel, 1992) (see Fig. 1). Differences in the cross-sagittal size of the CC may have functional significance, as a larger total or partial callosal size reflects a higher number of crossing fibers (Aboitiz, Ide, & Olivares, 2003).

Fig1.: Midsagittal T1 weighted antomical image with CC in midsagittal position.
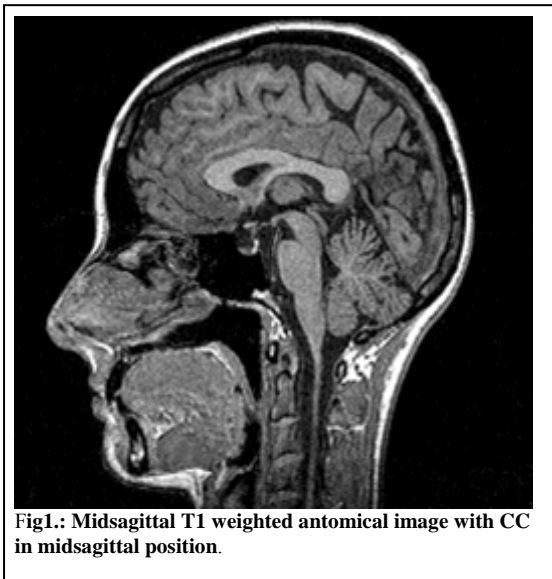
When studying CC area size in vivo in MR images, it is important to remember that the CC can vary considerably in shape and size in healthy individuals. Thus it is essential that studies aiming at assessing differences in CC size across diagnostic groups utilize precise techniques. In order to avoid statistical Type II errors, one should also strive to recruit a high number of subjects. CC size as measured on T1 weighted midsagittal MR images is dependent on the phenomenon of the CC fibers fanning out parasagitally. A recent study, however, revealed a transitional constriction some millimeters parasagitally in the anterior portions of the CC bundle of fibers (all portions with exception of the splenium) before fanning out to the sides (Luders et al., 2005). Local parasagittal changes thus may lead to measuring intra-individual changes of CC size that spuriously can be attributed to true changes of area, yet they may be the result of an oblique placement in the scanner. Hence, MR images should be re-aligned in the true midsagittal axis, in addition to following a reliable procedure of positioning the subject in the scanner. Midsagittal re-alignment consists of reslicing the MR images by orientation towards prominent midsagittal landmarks (Rauch & Jinkins, 1996).

Moreover, it has been shown that CC size varies dependent on the size of the whole brain (Holloway, Anderson, Defendini, & Harper, 1993). Hence, the importance of scaling factors, which are recognized for numerous regions of the brain, also applies for the structure of the CC (Gould, 1981). In statistical analyses that include measures of CC size, the variable

should therefore be controlled for whole brain volume (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991; Peterson, 2003).

Fig. 2: Midsagittal and parasagittal slices showing databasis for the DTI analyses in a healthy control child. Red color codes left-right crossing fiber direction, green color codes anterior-posterior fiber direction and blue color codes the rostral-caudal direction (and vice versa).
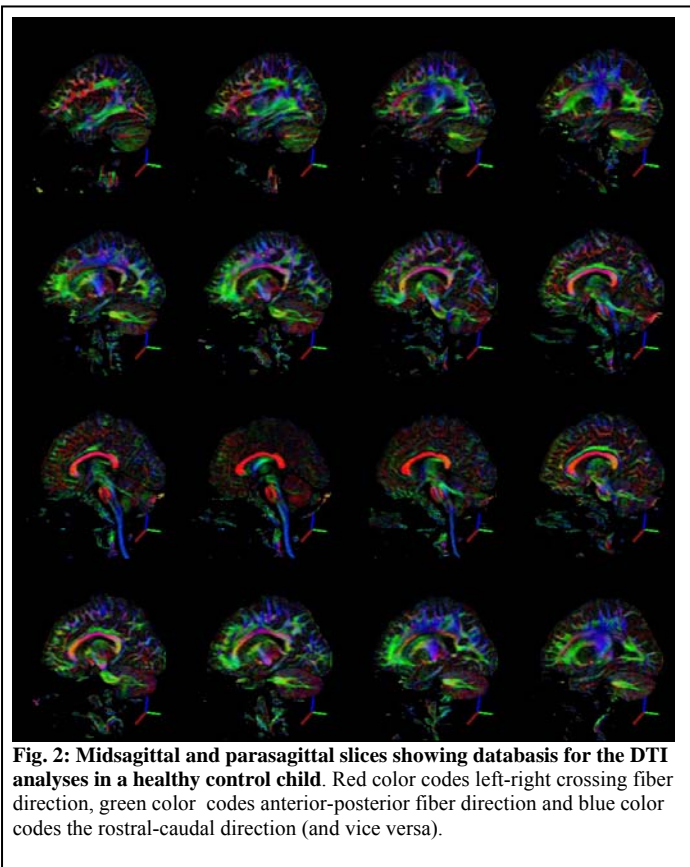
Another method of exploring the characteristics of the CC is the measurement by Diffusion Tensor Imaging (DTI), which is a non-invasive method to investigate white matter fiber organization (see Fig.2). DTI is an MRI based technique to visualize white matter connectivity, with the aim to enhance the understanding of how information "flows" in neuronal networks that constitute the connectional brain anatomy (Ramnani, Behrens, Penny, & Matthews, 2004). DTI is based on visualizing the diffusion of water molecules, and is expressed as a measure of anisotropy that mainly reflects the organization and integrity of white matter substance. DTI differs from conventional MRI in that additional magnetic fields (gradients) are applied to the main magnetic fields (Basser, Mattiello, & LeBihan, 1994). The parameters of DTI differ between types of tissue, e.g. in the cerebro-spinal fluid, water molecules can move around relatively freely (isotropic) as compared to white matter tissue, with a preferential molecular diffusion along the longitudinal axis of fibers and myelin sheaths (anisotropic diffusion). It has been shown that DTI reliably detects white matter tracts and therefore can be used as a tool to map connectivity between cortical regions (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Pierpaoli et al., 2001). DTI reflects the tissue architecture on a microscopic level and can be expressed mathematically as a tensor. The parameter that has been used most widely, especially in clinical applications of DTI, is the "Fractional Anisotropy" (FA) index that ranges from 0 (total isotropic diffusion) to 1 (total anisotropic diffusion) (Pierpaoli & Basser, 1996). FA is a measure for the magnitude of the tensor that can be ascribed to the anisotropic diffusion, and thus gives an equivalent to the directionality of the measured diffusity in a tissue on a voxel basis. FA seems to be less affected by noise than other anisotropy measures

(Hasan, Alexander, & Narayana, 2004). FA has been shown to correlate with histological markers of myelination (Wimberger et al., 1995) in newborns and adults (Huppi et al., 1998), and with myelination in infants and toddlers (Hermoye et al., 2006; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999). Neural myelination is part of the neuroanatomical process of maturation contributing to the development of the brain by speeding up the exchange of neuronal impulses (Paus et al., 1999).

In future investigations, the true midsagittal slice in DTI images could also be determined by a midsagittal re-alignment to ensure that FA values stem from the same midsagittal localization. In the majority of the present DTI studies, however, slice thickness still has produced gaps that do not allow for this procedure. Nevertheless re-alignment seems less crucial in the respect that the FA is measured voxel by voxel independently. Due to the FA being a measure on a single voxel level, it is not recommended to covary the anisotropy index measure with whole brain size (Schulte, Sullivan, Muller-Oehring, Adalsteinsson, & Pfefferbaum, 2005). Thus, a more direct measure of interhemispheric connectivity is applied by using DTI in addition to anatomical MR.

2.3.3. Inhibitory and excitatory functions of the corpus callosum

It has been discussed whether the CC executes a predominantly excitatory or inhibitory function on the respective contralateral hemispheres (Bloom & Hynd, 2005). Even though axons of the CC mainly act glutamatergic on a synaptic level, net inhibitory effects are thought to emerge through axonal CC endings on GABAergic interneurons (For a review on the cellular basis of callosally mediated inhibition (Saron, Foxe, Simpson, & Vaughan, 2003).

A primarily excitatory function of the CC suggests that the CC takes an active part in integrating information between the two hemispheres, by e.g. updating and facilitating the contralateral hemisphere on ipsilateral activity. This observation is the basis for the benefit of callosotomy in patients with intractable epileptic seizures, where the surgical splitting of the hemispheres prevents spreading of excitatory epileptic activity (Roberts, 1999).

A primary inhibitory function of the CC, on the other hand, means that the CC contributes to the inhibition of contralateral activity in order to allow for a more efficient intracortical processing. Hence, attention modulation may rely on callosal inhibition of the contralateral hemisphere that is assumed to be mediated through the small-diameter fibers (Hugdahl, 1998). Another example proving the inhibitory aspects of the CC is the observation

of physiological mirror movements in children during development. Mirror movements arise when one limb is moved deliberately and the contralateral limb starts to mimic the same movement (mirroring). Mirror movements are predominantly observed in small children and their persistence beyond the age of 9 years is regarded as a sign of a retarded maturation of the nervous system (Cohen, Taft, Mahadeviah, & Birch, 1967). The decrease in mirror movement activity during development has been described to correlate with the myelinisation of the CC and hence may give another clue to the importance of transcallosal inhibition (Mayston, Harrison, & Stephens, 1999).

The microscopic composition of the CC, however, with different types of fibers, ranging from small diameter (mostly in the genu) to large diameter fibers (predominantly in the body) (Aboitiz et al., 2003) suggests distinctive functional specifications of the various callosal regions. Or, in other words, "rather than conceptualizing the callosum as a single cable, we might better consider it as a network of connection – multiple channels, if you will" (Banich, 2003a).

3. Brain development and neuronal plasticity

3.1. Development of the human brain

Before touching upon general principles of neural plasticity it might be useful to shortly outline the general rules of brain development in humans, although the two processes are greatly overlapping. The first part of neural development takes place before birth and consists of predominantly genetically determined and precisely timed processes that involve both gross anatomical and cellular changes. The main principles involve *neurulation* (embryonic formation of the neural tube) and on the cellular level the *proliferation, migration* and *differentiation* of neurons – All of these histogenetic events that take place in utero (Webb, Monk, & Nelson, 2001).

Neurons proliferate from early precursor cells that migrate radially from the ventricular zone perpendicular to the surface to establish the six-layered cellular architecture of the cerebral cortex. Migration is initiated from the deepest cortical layer and advances in a typical outward movement, during which the neurons "climb up" the radial glia cells. Once dendrites and axons have reached their target destination (about 16th fetal week), they arborize massively and form initial intercellular communications and synapses (Andersen, 2003). The vast overproduction of neurons is followed by selective and massive apoptosis (programmed

cell death), during which approximately 50% of neurons are eliminated shortly before birth (Monk, Webb, & Nelson, 2001).

Huttenlocher suggested that postnatal cortical development could be divided into two phases: Phase 1 includes the first 12 postnatal months and is characterized by a decline in neuronal density, increase in synaptic density, increase in number of synapses per neuron, dendritic growth, and increasing cerebral volume. The second phase extends from the first year into adolescence and is characterized by a slow decline in both synaptic and neuronal density, increases in dendritic growth, and the decrease of synaptic density along dendrites (Huttenlocher, 1979).

During late gestation and early postnatal brain development, synaptic density increases dramatically in all cortical layers and reaches its peak approximately two months after birth (Bougeois, 2001). Intra-uterine synaptogenesis is largely under genetic control, whereas the rapid pre- and postnatal synaptogenesis is modulated increasingly by experience. Timing of synaptic production and elimination of the postnatal human brain varies across various regions of the cortex, with the frontal cortex reaching the peak density of neurons at a later stage than e.g. the visual cortex (Huttenlocher, 1979). The amount of synapses remains stable on a high level between 2 to 3 years of age and until puberty, where about 40% of the existing synapses are eliminated (Huttenlocher & de Courten, 1987). This elimination is also termed "pruning" and refers to the largely environmentally regulated elimination of synapses per dendritic unit, however, without loss of the whole neuron. The peak in synaptogenesis between 2 and 3 years of age is concurrent with the peak production of pyramidal neuron dendrites and a massive axonal growth during this critical time period (Webb et al., 2001). Other prominent mechanisms during postnatal development include the modulation of neuronal activity through neurotransmission (Herlenius & Lagercrantz, 2004).
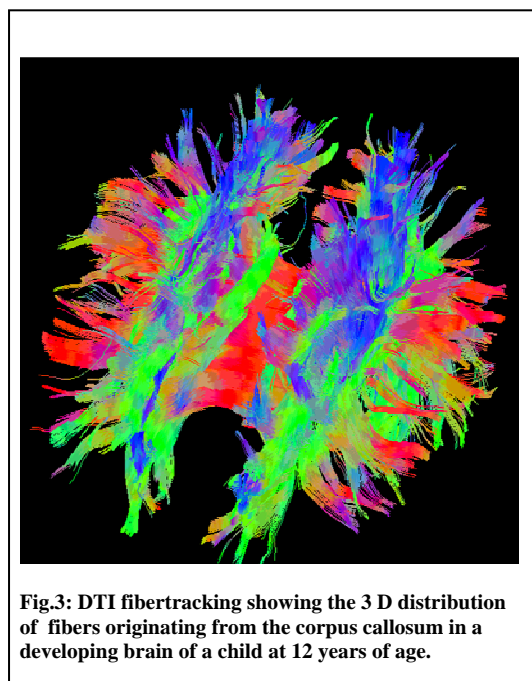
Fig.3: DTI fibertracking showing the 3 D distribution of fibers originating from the corpus callosum in a developing brain of a child at 12 years of age.

Lastly, the enhanced axonal neural transmission through myelination is a process that coincides with cortical maturation (see Fig.3). In the CNS myelin consists of

oligodendrocytes, which are increasingly recognized as active participants in neural development (Bullock et al., 2005). This is opposed to the prior premise that regarded oligodendrocytes as merely ancillary cells (Bullock et al., 2005). Coincident with myelination, white matter structure of the developing brain increases in childhood, whereas gray matter volume decreases coincident with prominent neural pruning and elimination processes during childhood and adolescence (Sowell, Peterson et al., 2003). This pattern of white matter generation in the early years of childhood is congruent with a recent description of maturation of human neural circuits in infants and toddlers by DTI measures (Hermoye et al., 2006). Neuroimaging data of children support the brain development as outlined above and reveal that at the age of 6 years the brain has reached approximately 90 % of adult brain size (Giedd, 2004). Macroscopic re-organization, however, continues throughout adolescence as confirmed by MRI studies (Giedd, Blumenthal, Jeffries, Castellanos et al., 1999; Sowell, Peterson et al., 2003).

Brain development thus is characterized of a largely genetically determined overproduction of neurons, axons and synapses with subsequent processes of elimination that partly underlie genetic control. As the child grows older, however, re-organization of the nervous system underlies sensory environmental input and other epigenetic factors. The genetic determination of early development is appreciated as a general rule; yet, the developing brain is highly susceptible to adverse environmental events or developmental pathologies at every stage of development, and the fascinating timeline and precision of maturation can easily be disturbed at every stage of the process.

3.2. Plasticity in the developing brain

The initial overproduction of synapses may be related to the functional property of the immature brain to allow for recovery and adaptation after focal injury or malformation and thus may impart plasticity (Huttenlocher, 1984). The view on plasticity has, however, been extended in recent years. Observations from animal research and basic sciences show that neurogenesis is not restricted to young organisms, but that neurogenesis is even observed in adult organisms (Gould, Reeves, Graziano, & Gross, 1999). Furthermore, an enriched environment augments the rate of neurogenesis in adult mammalian organisms (as reviewed by Kempermann (2002)). To date it is not yet sufficiently clear how hippocampal neurogenesis is related to learning processes and memory. The assumption that plastic recovery to neuronal damage is much more efficient in childhood (Kennard, 1938) still holds

true (Payne & Lomber, 2001), but needs modification in recognizing that prominent functional and structural alterations take place in the nervous system throughout life which may represent the basis for learning, memory and adaptation.

Several factors mentioned above as mechanisms of action in the developing brain are not distinguishable from general principles of neural plasticity, such as the pruning of synapses and of axons. Experience helps to sculpture the brain, and thus development and plasticity may be viewed as two widely overlapping processes or rather as one single process.

The basis for the "use it or lose it" hypothesis (Giedd, 2004), has been postulated half a century ago. This hypothesis regards activity dependent synaptic strengthening or elimination in childhood and adolescence as a main factor for guiding brain maturation. In 1949 Hebb proposed the rule that coincident activity in two connected neurons leads to strengthening of their connection (Hebb, 1949). This observation was verified years later by the observation of long- term potentiation in the dentate area of the hippocampus in rabbits (Bliss & Lomo, 1973). Even though a simplification of the complex mechanisms involved in the development of brain circuits, Hebb's principle is still appreciated as a general framework for relating behavior to synaptic organization (Seung, 2000).

In order to distinguish various interactions between brain development and environmental factors, two distinct mechanisms have been described (Greenough, Black, & Wallace, 1987). "Experience-expectancy" characterizes the kind of experiences that are expected to occur in all humans, and which involve basic perceptions (e.g. development of the visual system is dependent on eye-function, in order to develop the neural basis for vision as such) (Hubel & Wiesel, 1965). "Experience-dependency", on the other hand, refers to individual experiences which help to sculpture each particular central nervous system (e.g. training of specific muscles will lead to a broader region relating to the muscle group in the motor cortex) (Ungerleider, Doyon, & Karni, 2002).

3.3. Plasticity in the Corpus Callosum

The perinatal exuberance of axons in the CC and the presence of "transient callosal axons" are recognized in different species. The final shape and size of the adult CC structure is thought to be achieved through a combination of competitive elimination, of axonal pruning, and of the ongoing axonal myelination in postnatal life (Innocenti, Aggoun-Zouaoui, & Lehmann, 1995). In rhesus monkeys, CC fibers of the infant outnumber the CC fibers of

the adult animal by at least 3.5 times (LaMantia & Rakic, 1990). The selection of callosal axons in strabismic cats during pruning is dependent on incoming sensory stimuli (Milleret & Houzel, 2001). The development of the human callosum through axonal pruning and myelination coincides with the attainment of cognitive prowess and cortical maturation, suggesting that development of the CC and the cerebral cortex mutually influence each other (Klingberg et al., 1999). Experience-dependent plasticity of the CC has been supported by positive correlations of CC size with duration of training in professional musicians (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). Moreover, abnormalities of the CC in conditions that are directly dependent and influenced by the quality of perceptual experience during sensitive periods of development such as illiteracy (Castro-Caldas et al., 1999) and dyslexia (von Plessen et al., 2002) support the neuronal plasticity of the CC observed in animal studies. This assumption conflicts with a study that showed a high genetic influence on the midsagittal CC size (Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003). Yet in the future studies will further elucidate the interaction between underlying genetic factors and the influence of environmental factors (Sur & Rubenstein, 2005).

II Objective of the study

We aimed to explore the contributing effects of lateralization, attentional modulation, as well as structural and functional characteristics of the corpus callosum and interhemispheric connectivity for the understanding of the pathophysiology of TS.

It was hypothesized that:

1. the area of the corpus callosum would differ between the TS and Healthy Control (HC) group (Report I)

2. the TS group would exhibit an absence of a normal functional brain asymmetry, the presence of the ability to actively shift attention towards the right ear stimulus and an impaired callosal transfer of information (Report II)

3. the TS group would show reduced interhemispheral connectivity as measured by Diffusion Tensor Imaging (DTI) (Report III)

III Methods

Data collection in this thesis was based on two separate substudies. The core instruments and applied techniques, however, were similar in both data collections and are thus described jointly.

1. Subjects

The TS subjects were recruited from the Yale Child Study Center in the US (Report I), the Department of Child-and Adolescent Psychiatry, Haukeland University Hospital, and from outpatient clinics in the greater Bergen area in the Hordaland County in Norway (Report II and III). Healthy controls (HC) were recruited by randomly contacting individuals from a telemarketing list with the same ZIP codes as subjects with TS (Report I) or by randomly contacting local schools in the same geographic areas as the subjects with TS (Report II and III).

Individuals that were included in the TS groups all met DSM-IV criteria (Association, 1994) for the condition. Healthy controls (HC) were matched for age and gender. Exclusion criteria for the control group were a lifetime history of Tic disorder, Obsessive Compulsive disorder (OCD), Attention-Deficit/-Hyperactivity Disorder (ADHD), or a current DSM-IV Axis I disorder. Additional exclusion criteria for both groups were epilepsy, head trauma with loss of consciousness, former or present substance abuse, or an IQ below 80 (Report I) or 70 (Report II and III), as measured by WISC-III, WAIS or the Kaufmann-Brief Intelligence Test.

Diagnoses were established by using the Kiddie-SADS (Kaufman et al., 1997) or the "Schedule for Tourette Syndrome and Other Behavioural Disorders" (which includes the Kiddie-SADS) (Pauls & Hurst, 1996) and a "best estimate consensus procedure" using all available information (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982). OCD symptoms were quantified using the Yale Brown Obsessive Compulsive Scale (Goodman et al., 1989), and the severity of tics was rated by Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) (Report I) or in a Norwegian translation (Strand & Plessen, 2004) (report II and III). Handedness was measured by the Edinburgh handedness inventory (Oldfield, 1971).

Use of medication was registered for all TS subjects. Healthy Controls did not use psychotropic agents. Socio-economic status (SES) was estimated in all participants either by using the Hollingshead Four-Factor Index (Hollingshead, 1975), or by using guidelines for estimation of SES as indicated in the Journal of the American Society for Child and Adolescent Psychiatry ((Journal of the American Academy of Child and Adolescent Psychiatry), 2005) (Report II and III).

2. MR Scanning Procedure

The MR scanning for the data reported in Report I was conducted by the staff at the Yale Child Study Center, USA. For Report II and II, MR data were collected by staff at the Department of Radiology, Haukeland University Hospital (including the doctoral candidate). For the data in Report II and III, the children and their families received thorough information concerning the MRI examination in the letter of invitation. During MR scanning, a situation as comfortable as possible was created for children and their families by first showing the MR scanner and briefly explaining scanner characteristics before starting the actual examination. During image acquisition the children were accompanied in the MR scanner room by the doctoral candidate. In addition, the use of mental techniques of relaxation helped to acquire high quality data in both groups. Series with movement artifacts were replaced. Several children with severe tics agreed to repeat the MR scanning in order to enhance data quality. The participants met the same examiner during MR examination as in the clinical examination (Report II and III). Two individuals had to be excluded from the study due to motion artifacts in the MR imaging. The MR pre- and post processing procedures for DTI and for anatomical images are described in detail in the Method sections of Report I-III.

3. Statistics

For the description and for the testing of possible differences in demographical characteristics between the groups, a t-test or chi square test were used when applicable. Statistical analyses were performed using SPSS v. 13 (SPSS, 1999), R software (R DC Team, 2003), SAS v. 8.2 (SAS Institute Inc., Cary NC) or Statistica (StatSoft, 2003). All p-values were of the two-sided type, and thresholded at p < .05.

3.1 Report I

General linear regression was used to test group- and age-specific abnormalities in overall size of the CC in individuals with TS. Moreover, the effect of a TS diagnosis on the different regions of the CC was tested by using a repeated-measures analysis of variance (ANOVA), mixed-effects model.

3.2. Report II

In Report II, analyses of variance were performed to test the experimental hypotheses. A three-way ANOVA (Ear x Group x Attentional instruction) was used, since the groups were matched for age, gender and handedness. To follow-up the group effect, a separate two-way ANOVA (Group x Ear) was performed for the forced-left condition.

3.3. Report III

The influence of group specific changes on the FA values of the CC was tested by using a mixed-model regression analysis (PROC MIXED in SAS) with repeated measures, over a spatial domain (the five regions of the CC), with a first order autoregressive (AR1) model of the covariance structure.

3.4. Controlling for potential confounding factors

In order to control for comorbidity, statistical analyses were repeated by subsequently excluding individuals with a comorbid ADHD or OCD condition, while keeping the HC sample at the same size. In addition, the presence of ADHD and OCD was included in the main analyses as a covariate if estimated reasonable from a statistical point of view and the influence of the comorbid condition was tested statistically (Report I). A similar strategy was used for individuals who received medication for their tics. Eventual effects of WBV on CC size were accounted for by covarying morphometrical measures of CC size with WBV, either by including the measure in the main analyses and or by controlling for WBV in analyses of correlation. IQ was controlled for by either using a conservative exclusion criterion (Report I), or by including IQ scores as covariates in the main analyses (Report III), or by testing correlations of IQ with measures of function (Report II). Age was controlled for by including age as a covariate. In addition, by including the square of age, we controlled for a possible curvilinear relationship of CC size with age (Giedd, Blumenthal, Jeffries, Castellanos et al., 1999; Peterson, Feineigle, Staib, & Gore, 2001) in the study that included elderly individuals (Report I).

4. Ethical Considerations

A written letter of invitation was sent to the parents of eligible children and further information was presented during the first interview. All MR images were evaluated by a neuro-radiologist in order to rule out pathologic conditions. If a condition that would require treatment was detected, the individual and her/his family were followed-up until in specialist care. Written informed consent was obtained from the parents and/or the participants and the study was approved by the human investigation committee at the Yale School of Medicine, New Haven, Connecticut in the US (Report I) or clarified in accordance with the Regional Committee for Medical Research Ethics, West-Norway and the Norwegian Social Science Services (NSD) (Report I and II; Number 8686 NSD).

IV Summary of papers

Report I

The corpus callosum is the major commissure connecting the cerebral hemispheres. Prior evidence suggests its involvement in the pathophysiology of Tourette syndrome (TS).

The size of the corpus callosum was determined on the true midsagittal slices of reformatted, high-resolution MRI scans and compared across diagnostic groups in a cross-sectional case control study of 158 subjects with TS and 121 controls, 5 to 65 years of age. In the context of increasing midsagittal corpus callosum area from childhood to age 30, children with TS overall had smaller overall corpus callosum size, whereas adults with TS on average had larger corpus callosum size, yielding a prominent interaction of diagnosis with age. Corpus callosum size correlated positively with tic severity. Corpus callosum size also correlated inversely with dorsolateral prefrontal and orbitofrontal cortical volumes in both the subjects with TS and the comparison subjects, but the magnitudes of the correlations were significantly greater in the TS group. The effects of medication and comorbid illnesses had no appreciable influence on the findings. Given prior evidence for the role of prefrontal hypertrophy in the regulation of tic symptoms, the current findings suggest that neural plasticity may contribute to the smaller corpus callosum size in persons with TS, which thereby limits neuronal trafficking across the cerebral hemispheres and reduces input to cortical inhibitory interneurons within prefrontal cortices. Reduced inhibitory input may in turn enhance prefrontal excitation, thus helping to control tics and possibly contributing to the cortical hyperexcitatibility reported previously in patients with TS.

Report II

We tested the hypothesis that children with Tourette Syndrome (TS) would exhibit aberrant brain lateralization compared to a healthy control (HC) group, and used an attentional modulation version of a verbal dichotic listening task with consonant-vowel syllables. The modulation of attention to focus on the right ear stimulus in the dichotic listening situation is thought to involve the same prefrontal attentional and executive functions that are involved in the suppression of tics, whereas performance when focusing attention on the left ear stimulus additionally involves a callosal transfer of information. In

light of presumed disturbances in transfer of information across the corpus callosum, we hypothesized that children with TS would, however, have difficulty modulating the functional lateralization that ensues through a shift of attention to the left side. This hypothesis was tested by exploring the correlations between CC size and left ear score in the forced- left condition.

Twenty boys with TS were compared with 20 age - and handedness matched healthy boys. Results indicated similar performance in the TS and HC groups for lateralization of hemispheric function. TS subjects were also able to shift attention normally when instructed to focus on the right ear stimulus. When instructed to focus attention on the left ear stimulus, however, performance deteriorated in the TS group. Correlations with CC area further supported the hypothesized presence of deviant callosal functioning in the TS group.

Report III

Brain imaging studies have revealed anatomical deviations in the brains of individuals with Tourette syndrome (TS). Prefrontal regions have been found to be larger and the corpus callosum (CC) area has been found smaller in children and young adults with TS compared with healthy control subjects, and these anatomical features have been understood to reflect neural plasticity that helps to attenuate the severity of tics. CC white matter connectivity, as measured by the Fractional Anisotropy (FA) index from diffusion tensor images, was assessed in twenty clinically well-defined boys with Tourette syndrome and twenty age- and gender matched controls. The hypothesis that children with TS would show reduced measures of connectivity in CC fibers was confirmed for all subregions of the CC. There was no significant interaction of TS and region. Reductions in FA in CC regions may reflect either fewer crossing fibers or reduced axonal myelination. FA values did not correlate significantly with the severity of tic symptoms. Group differences in measures of connectivity did not seem to be attributable to the presence of comorbid ADHD or OCD, to medication exposure, or group differences in IQ.
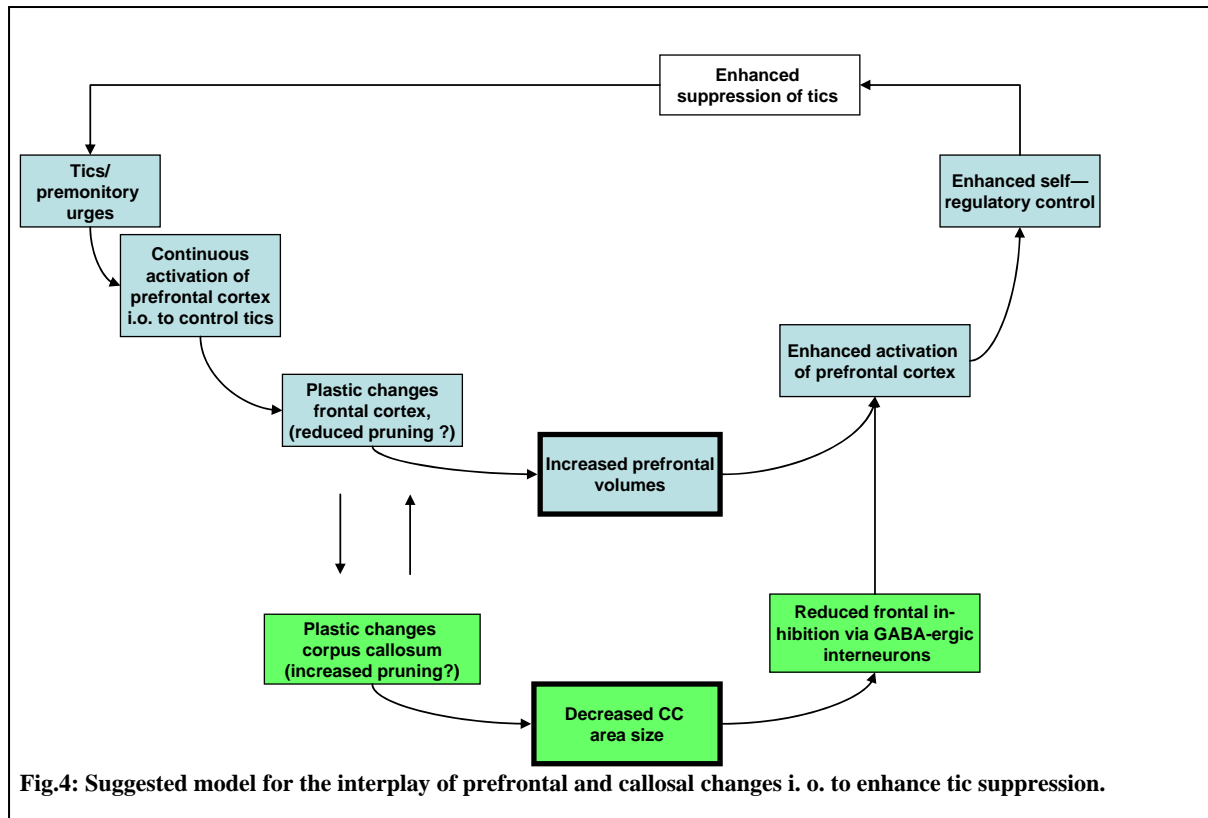
Our findings of reduced interhemispheral white matter connectivity add to the understanding of neural connectivity and plasticity in the brains of children with TS.

V Discussion

The outset for the present thesis were previous reports of reduced structural brain asymmetry of the basal ganglia in TS patients, and the subsequent postulation by Sandra Witelson that the CC may be involved in TS (Witelson, 1993). The hypothesis of abnormal functional brain lateralization was not confirmed in this empirical study, since children with TS did not differ from the HC group on the DL measure of brain laterality. The reported findings of morphometric and functional deviations of callosal measures are, however, consistent with other reports of tic suppression in TS (Peterson et al., 1998; Peterson, Staib et al., 2001). Thus, the present findings can be interpreted in a new perspective, emphasizing the ability of TS patients to control tics.

1. Neuronal plasticity in the CC involved in tic suppression

The neuronal mechanisms thought to be involved in tic suppression are assumed to be located primarily in prefrontal cortical regions. Findings of prefrontal neuronal activation during tic suppression (Peterson et al., 1998), larger dorsoprefrontal volumes (Peterson, Staib et al., 2001), as well as increased white matter volume prefrontally (Fredericksen et al., 2002) in children with TS support this hypothesis. Positive correlations of CC size with tic severity suggest that the smaller CC area in children (Report I) could be a result of the TS brain's continuous attempt to suppress tic severity. Stronger correlations of CC area with prefrontal volume in the TS group as compared to the control group (Report I) additionally suggest a relation between a deviation of the CC area and prefrontal self-regulatory control in tic suppression. However, continuous tic suppression usually takes place unconsciously and is most of the time not dependent on the individual's own volition to suppress motor or phonic activity. The main finding in Report I thus provides evidence that the CC is smaller in children with TS. A deviation of the microstructural white matter interhemispheric connectivity was then found (Report III) in another sample of TS children who on average did not have a smaller CC area size. The absence of the prior described findings of a smaller CC area size could, however, be the result of the relatively small sample size. Finally (Report II), findings from anatomical and diffusion tensor MR imaging were confirmed in a functional task by revealing altered callosal transfer in the TS group as compared to the HC group. A finding of smaller CC size in the sample in Report II and III would have been desirable in

Fig.4: Suggested model for the interplay of prefrontal and callosal changes i. o. to enhance tic suppression.

order to confirm the initial results. Nevertheless, the studies in Report II and III showed that interhemispheric deviations in individuals with TS are not solely dependent on CC size.

Report II and III thus validated the findings in report I in a broader sense by extending the results to microstructural measures of interhemispheric connectivity and to CC function.

Based on the findings presented in this thesis, a smaller CC area (as reported in Report I) corresponds to reduced structural and functional interhemispheric connectivity (Report I, II and III). Furthermore, based on correlations with tic severity it is assumed that reduced interhemispheric connectivity leads to reduced inhibition of prefrontal neurons, and thus facilitates tic suppression. The facilitation of tic suppression is most likely mediated through prefrontal cortical fibers that ultimately control motor activity through CSTC circuits. As reviewed in Part I, the CC has inhibitory functions and the reduction of such inhibitory influences may result in increased cortical excitation (Ziemann, Paulus, & Rothenberger, 1997). In children, the inhibitory influence of the CC may be best observed in the disappearance of mirror movements in childhood that parallels the maturation of the CC

(Mayston et al., 1999). The inhibition of contralateral limb movements has been confirmed neurophysiologically to depend on transcallosal inhibition (Duque et al., 2005), which is mediated via GABAergic interneurons (Carr & Sesack, 1998). We suggest that the neurophysiological mechanisms of experience-dependent axonal and synaptic pruning are more pronounced in the CC of those individuals in the TS population who successfully have developed the ability to suppress their tics (see Fig.4).

2. Children versus adults with TS

As described in the Introduction, children with TS experience a considerable decrease of symptom severity during and after puberty. Adults with persistent tic symptoms, who have stayed in touch with a specialty clinic over the years (Report I) may thus be regarded as a selection of individuals with TS who either from the onset of the condition may have suffered from a serious form of the condition, or alternatively who may not have been able to sufficiently adapt to successful tic suppression strategies. The latter interpretation was supported by Report I, showing that subjects with TS in adult age had significantly higher scores for tic severity, and in addition that adults with TS on average had larger CC area size compared to the age-matched HC group. This is also in concordance with another study reporting interaction with age in samples including an age-spectrum from childhood to late adulthood, indicating opposing findings in children and adults for prefrontal cortical regions (Peterson, Staib et al., 2001). Moreover, the observation that adults with persistent tics could be a selected subgroup of all individuals with TS, is relevant with respect to functional (fMRI and PET) neuroimaging studies, that typically only included adult subjects with TS. Restricting neuroimaging studies to adult populations leads to deriving results that stem from a subgroup which does not show the phenomenologically and clinically well documented adaptation to tic behavior and increasing ability for tic suppression with age (Bloch et al., 2006; Leckman et al., 1998; Pappert et al., 2003). Thus results concerning adults alone, cannot be applicable to the general population of children with tics in clinical care; nevertheless they still are important for the understanding of the pathophysiology in TS (Stern et al., 2000).

3. Gender

TS occurs more frequently in boys than in girls. Hence most studies strive to include girls in order to achieve representative samples. In the first Report, girls were included in the

sample and the results showed that girls with TS on the average also had smaller CC area size, in line with the findings from the male group. This is different from a prior report (Mostofsky et al., 1999), which did not find deviant CC areas in girls with TS compared to controls. The mentioned study suffered, however, from small sample size which could be the reason for not detecting underlying differences (increased probability for a Type-II statistical error). Such an outcome would be in line with what may be proposed based on the findings of CC size in Report II and III. In addition, in the mentioned study a simplified measurement of brain size (intracranial area on the midsagittal slice) (Witelson, 1993) was used to control for scaling effects, and midsagittal slices were not realigned before measurement.

As a consequence of fewer girls with TS in the general and in clinical populations, it was not possible to recruit enough girls for the studies in Report II and III. In addition, the two girls that were recruited had such severe tics that their MR images were of inferior quality and could not be used for further morphometric purposes. An increase of movement in one subgroup could of course be of interest in itself and a topic for future studies. Hence it was not possible to examine gender aspects in the two studies in Report II and III.

4. Correlations of CC with cortical volumes

Prefrontal function was not the primary topic of this thesis, but several of our findings touch upon self-regulatory control that emerges during childhood and which is closely related to fronto-striatal pathways (Marsh et al., 2006), as large parts of the anterior CC connect prefrontal and frontal cortical regions (Huang et al., 2005). Changes in callosal size seem thus closely connected to changes in frontal brain regions. An earlier study, reported larger dorsoprefrontal cortical volumes in children with TS (Peterson, Staib et al., 2001) (that were a subsample of the present study in Report I). Given the larger prefrontal volumes, a larger CC size could have been expected in children with TS, if following scaling effects in the brain. Yet, on average a smaller CC area size was found in the TS children. In addition, dorsoprefrontal cortical volume correlated inversely with CC area size, whereas motor cortical volume correlated positively with CC area size and the volume of the orbitofrontal cortex correlated inversely with callosal size in the TS group. The stronger inverse correlations of prefrontal (gray and white matter) volumes with CC area size in the TS group suggest a deviant callosal connectivity in the TS group, which was further confirmed in the DTI study (Report III).

5. IQ

As previously mentioned, the findings in Report I were based on data acquired at the Yale Child Study Center, USA, which has special expertise for tic disorders. On the basis of a large data collection, individuals with an IQ lower than 80 were excluded. Such a conservative exclusion criterion for IQ was chosen to ascertain that the groups did not differ significantly in IQ. For the samples in Report II and III a less conservative IQ criterion was adopted (excluding all individuals with full IQ score < 70) in order to maintain a reasonable sample size. This resulted in a significant difference of IQ for the TS and HC group. Thus, by covarying (Report II) and correlating (Report III) with IQ measures, the potential confounding influence of IQ in the statistical analyses was controlled for.

6. Comorbidity and medication

Comorbidity of TS with ADHD and OCD is well documented and described in part I. In the samples presented in this thesis, comorbidity with both ADHD and OCD was present in a sub-set of the subjects. In consequence of having three diagnostic groups (TS only, TS + ADHD, TS + OCD), comorbidity was controlled for in the statistical analyses. When exploring underlying factors in TS. It thus arises the question whether to examine "pure" groups and "lose" statistical power, or to include patients with and without comorbidities in the statistical analyses. By including all subjects, statistical power will be gained, but for the prize that findings may be obscured by combining concurrent pathologies. This could be critical when exploring several regions of the brain, e.g. the prefrontal regions. Children with TS have larger prefrontal volumes (Peterson, Staib et al., 2001) whereas children with ADHD have smaller volumes (Sowell, Thompson et al., 2003). Such opposing effects may seriously confound results, when including individuals that suffer from several comorbid conditions. Comorbidity was controlled for by retesting the stability of the findings when excluding subjects with comorbid ADHD and OCD symptoms (Report I-III). In Report I the sample was large enough to additionally include comorbid diagnoses as covariates in the statistical analyses. Medication is another potentially confounding factor and was controlled for in the same way as outlined for comorbid diagnoses.

7. Clinical Implications

Neural plasticity in brain development could contribute to the understanding of the typical course of TS, with an attenuation of tic-symptoms during puberty and early adult age. For the clinician it is important to emphasize the possible positive outcome of TS in the sense that the brain of children is able to self-regulate and to adapt to adverse conditions. The present thesis attempts to further unravel the complex mechanisms that accompany the clinical observation of an attenuation of tics during and after puberty. It could be more helpful for families and clinicians to emphasize the dynamics of brain plasticity and self-regulatory control than focussing on pathological findings, such as the disturbed interhemispheric transfer. A consequence of the present findings is that physicians, therapists and caregivers should try to facilitate the child's own capacity of self-regulatory control. We describe compensatory processes in the brains of children with TS, yet without approaching the important question of the factors, which could contribute to facilitate such positive effects and which factors impede such development (as assumed in the adult group in Report I). This has not been the object of the present thesis and the formal testing of these factors would require a longitudinal study design. Individuals with TS often experience the tics as ego-synton (Sacks, 1992) and estimate the tics to be semi-voluntary responses to preceding sensory phenomena (Leckman et al., 1993). Emphasizing the individual's own capacity of self-regulation will further strengthen the ability of children with TS to cope with unwanted tic behaviour.

8. Future outlook

In the extension of this thesis, it should be tested how medication and other forms of treatment influence the development of self-regulatory control and ultimately the development of compensatory neuronal pathways in individuals with TS. Longitudinal studies that include children with TS from population based samples could enhance the understanding of the biological bases for tics. Moreover, designing clinical studies i.o. to test, whether children with tics could profit of interventions that have the potential to enhance plasticity in the context of other neurological conditions (Hummel & Cohen, 2005) could potentially improve treatment options.

VI References

Abelson, J. F., Kwan, K. Y., O'Roak, B. J., Baek, D. Y., Stillman, A. A., Morgan, T. M., Mathews, C. A., Pauls, D. L., Rasin, M. R., Gunel, M., Davis, N. R., Ercan-Sencicek, A. G., Guez, D. H., Spertus, J. A., Leckman, J. F., Dure, L. S., Kurlan, R., Singer, H. S., Gilbert, D. L., Farhi, A., Louvi, A., Lifton, R. P., Sestan, N., & State, M. W. (2005). Sequence variants in SLITRK1 are associated with Tourette's syndrome. *Science, 310*(5746), 317-320.

Aboitiz, F., Ide, A., & Olivares, R. (2003). Corpus Callosum Morphology in Relation to Cerebral Asymmetries in the Postmortem Human Brain. In E. Zaidel & M. Iacoboni (Eds.), *The Parallel Brain* (pp. 33-46). Cambridge, Massachusetts: MIT Press.

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Fiber composition of the human corpus callosum. *Brain Res, 598*, 143-153.

Abwender, D. A., Como, P. G., Kurlan, R., Parry, K., Fett, K. A., Cui, L., Plumb, S., & Deeley, C. (1996). School problems in Tourette's syndrome. *Arch Neurol, 53*(6), 509-511.

Achiron, R., & Achiron, A. (2001). Development of the human fetal corpus callosum: a high-resolution, cross-sectional sonographic study. *18*(4), 343-347.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res, 85*, 119-146.

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

Andersen, S. L. (2003). Trajectories of brain development: point of vulnerability or window of opportunity? *Neuroscience and biobehavioral review, 27*, 3-18.

Arndt, S., Cohen, G., Alliger, R. J., Swayze, V. W., 2nd, & Andreasen, N. C. (1991). Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Res, 40*(1), 79-89.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders, 4*th *ed.* Washington, DC

Banaschewski, T., Woerner, W., & Rothenberger, A. (2003). Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. *Dev Med Child Neurol, 45*(10), 700-703.

Banich, M. (2003a). Interacting Hemispheres: A Means of modulating Attention. In E. Zaidel & M. Iacoboni (Eds.), *The parallel brain* (pp. 267-270). Cambridge, Massachusetts: MIT Press.

Banich, M. (2003b). Interaction between the Hemispheres and its Implications for the Processing Capacity of the Brain. In K. Hugdahl & R. J. Davidson (Eds.), *The Asymmetrical Brain* (pp. 261-302). Cambridge, Massachusetts: MIT Press.

Barkovich, A. J., & Kjos, B. O. (1988). Normal postnatal development of the corpus callosum as demonstrated by MR imaging. *Am J Neuroradiol, 9*(3), 487-491.

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophys J, 66*(1), 259-267.

Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magn Reson Med, 44*(4), 625-632.

Baumgardner, T. L., Singer, H. S., Denckla, M. B., Rubin, M. A., Abrams, M. T., Colli, M. J., & Reiss, A. L. (1996). Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology, 47*(2), 477-482.

Bliss, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol, 232*(2), 331-356.

Bloch, M.H, Leckman, J. F., Zhu, H., Peterson, B.S. (2005). Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology, 65*(8), 1253-1258.

Bloch, M. H., Peterson, B. S., Scahill, L., Otka, J., Katsovich, L., Zhang, H., & Leckman, J. F. (2006). Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med, 160*(1), 65-69.

Bloom, J. S., & Hynd, G. W. (2005). The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychol Rev, 15*(2), 59-71.

Bougeois, J.-P. (2001). Synaptogenesis in the Neocortex of the Newborn: The Ultimate Frontier for Individuation. In C. A. Nelson & M. Luciana (Eds.), *Developmental Cognitive Neuroscience* (pp. 23-34). Cambridge, Massachusetts, London, England: Bradford Book, MIT press.

Bryden, M. P., Munhall, K., & Allard, F. (1983). Attentional biases and the right-ear effect in dichotic listening. *Brain Lang, 18*(2), 236-248.

Bullock, T. H., Bennett, M. V., Johnston, D., Josephson, R., Marder, E., & Fields, R. D. (2005). Neuroscience. The neuron doctrine, redux. *Science, 310*(5749), 791-793.

Carr, D. B., & Sesack, S. R. (1998). Callosal terminals in the rat prefrontal cortex: synaptic targets and association with GABA-immunoreactive structures. *Synapse, 29*(3), 193-205.

Carter, A. S., O'Donnell, D. A., Schultz, R. T., Scahill, L., Leckman, J. F., & Pauls, D. L. (2000). Social and emotional adjustment in children affected with Gilles de la Tourette's syndrome: associations with ADHD and family functioning. Attention Deficit Hyperactivity Disorder. *J Child Psychol Psychiatry, 41*(2), 215-223.

Castro-Caldas, A., Miranda, P. C., Carmo, I., Reis, A., Leote, F., Ribeiro, C., & Ducla-Soares, E. (1999). Influence of learning to read and write on the morphology of the corpus callosum. *Eur J Neurol 6*(1), 23-28.

Coffey, B. J., Biederman, J., Spencer, T., Geller, D. A., Faraone, S. V., & Bellordre, C. A. (2000). Informativeness of structured diagnostic interviews in the identification of Tourette's disorder in referred youth. *J Nerv Ment Dis, 188*(9), 583-588.

Cohen, D. J., Leckman, J. F., & Shaywitz, B. A. (1984). The Tourette's syndrome and other tics. In D. Shaffer, A. A. Ehrhardt & L. L. Greenhill (Eds.), *Diagnosis and treatment in pediatric psychiatry* (pp. 3-28). New York: Macmillan Free Press.

Cohen, H. J., Taft, L. T., Mahadeviah, M. S., & Birch, H. G. (1967). Developmental changes in overflow in normal and aberrantly functioning children. *J Pediatr, 71*(1), 39-47.

Como, P. G. (2001). Neuropsychological function in Tourette syndrome. *Adv Neurol, 85*, 103-111.

Crow, T. J. (1997). Schizophrenia as failure of hemispheric dominance for language. *Trends Neurosci, 20*, 339-343.

Duque, J., Mazzocchio, R., Dambrosia, J., Murase, N., Olivier, E., & Cohen, L. G. (2005). Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. *Cereb Cortex, 15*(5), 588-593.

Erenberg, G., Cruse, R. P., & Rothner, A. D. (1987). The natural history of Tourette syndrome: a follow-up study. *Ann Neurol, 22*(3), 383-385.

Fredericksen, K., Cutting, L., Kates, W., Mostofsky, S., Singer, H., Cooper, K., Lanham, D., Denckla, M., & Kaufmann, W. (2002). Disproportionate increases of white matter in right frontal lobe in Tourette syndrome. *Neurology, 58*, 85-89.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *J Neurocytol, 31*(3-5), 373-385.

Gannon, P. J., Holloway, R. L., Broadfield, D. C., & Braun, A. R. (1998). Asymmetry of chimpanzee planum temporale: humanlike pattern of Wernicke's brain language area homolog. *Science, 279*(5348), 220-222.

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? *Brain, 123*, 1293-1326.

Gazzaniga, M. S. (2005). Forty-five years of split-brain research and still going strong. *Nat Rev Neurosci, 6*(8), 653-659.

Gerard, E., & Peterson, B. S. (2003). Developmental processes and brain imaging studies in Tourette syndrome. *J Psychosomat Res, 55*(1), 13-22.

Geschwind, N., & Levitsky, W. (1968). Human brain: left-right asymmetries in temporal speech region. *Science, 161*(837), 186-187.

Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci, 1021*, 77-85.

Giedd, J. N., Blumenthal, J., Jeffries, N., Castellanos, F., Liu, H., Zijdenbos, A., Paus, T., Evans, A., & Rapoport, J. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci, 2*, 861-863.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Rajapakse, J. C., Vaituzis, A. C., Liu, H., Berry, Y. C., Tobin, M., Nelson, J., & Castellanos, F. X. (1999). Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry 23*(4), 571-588.

Giedd, J. N., Rumsey, J. M., Castellanos, F. X., Rajapakse, J. C., Kaysen, D., Vaituzis, A. C., Vauss, Y. C., Hamburger, S. D., & Rapoport, J. L. (1996). A quantitative MRI study of the corpus callosum in children and adolescents. *Brain Res Dev Brain Res 91*(2), 274-280.

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry, 41*(5), 645-655.

Goodman, W., Price, L., Rasmussen, S., Mazure, C., Fleischmann, R., Hill, C., Heninger, G., & Charney, D. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry, 46*(11), 1006-1011.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry, 160*(4), 636-645.

Gould, E., Reeves, A. J., Graziano, M. S., & Gross, C. G. (1999). Neurogenesis in the neocortex of adult primates. *Science, 286*(5439), 548-552.

Gould, S. J. (1981). *The mismeasure of man*. New York: W.W. Norton.

Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Dev, 58*(3), 539-559.

Hasan, K. M., Alexander, A. L., & Narayana, P. A. (2004). Does fractional anisotropy have better noise immunity characteristics than relative anisotropy in diffusion tensor MRI? An analytical approach. *Magn Reson Med, 51*(2), 413-417.

Hebb, D. (1949). *The Organization of Behavior: A Neuropsychological Theory*. New York: Wiley.

Heiervang, E., Hugdahl, K., Steinmetz, H., Inge Smievoll, A., Stevenson, J., Lund, A., Ersland, L., & Lundervold, A. (2000). Planum temporale, planum parietale and dichotic listening in dyslexia. *Neuropsychologia, 38*(13), 1704-1713.

Herlenius, E., & Lagercrantz, H. (2004). Development of neurotransmitter systems during critical periods. *Exp Neurol, 190 Suppl 1*, S8-21.

Hermoye, L., Saint-Martin, C., Cosnard, G., Lee, S. K., Kim, J., Nassogne, M. C., Menten, R., Clapuyt, P., Donohue, P. K., Hua, K., Wakana, S., Jiang, H., van Zijl, P. C., & Mori, S. (2006). Pediatric diffusion tensor imaging: Normal database and observation of the white matter maturation in early childhood. *Neuroimage, 29*(2), 493-504.

Hodges, K., McKnew, D., Cytryn, L., Stern, L., & Kline, J. (1982). The Child Assessment Schedule (CAS) diagnostic interview: a report on reliability and validity. *J Am Acad Child Psychiatry, 21*(5), 468-473.

Hollingshead, A. (1975). *Four-Factor Index of Social Status*. New Haven, Conneticut: Yale University Press.

Holloway, R. L., Anderson, P. J., Defendini, R., & Harper, C. (1993). Sexual dimorphism of the human corpus callosum from three independent samples: relative size of the corpus callosum. *Am J Phys Anthropol, 92*(4), 481-498.

Hopkins, W. D., Marino, L., Rilling, J. K., & MacGregor, L. A. (1998). Planum temporale asymmetries in great apes as revealed by magnetic resonance imaging (MRI). *Neuroreport, 9*(12), 2913-2918.

Huang, H., Zhang, J., Jiang, H., Wakana, S., Poetscher, L., Miller, M. I., van Zijl, P. C., Hillis, A. E., Wytik, R., & Mori, S. (2005). DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. *Neuroimage, 26*(1), 195-205.

Hubel, D., & Wiesel, T. (1965). Binocular interaction in striate cortex of kittens reared with artificial squint. *J Neurophysiol, 28*, 1041-1059.

Hugdahl, K. (1998). The Corpus Callosum: more than a passive "corpus". *Behavioral and Brain Sciences, 21*(3), 335.

Hugdahl, K. (2003). Dichotic Listening in the Study of Auditory Laterality. In K. Hugdahl & R. J. Davidson (Eds.), *The Asymmetrical Brain* (pp. 441-475). Cambridge: MIT press.

Hugdahl, K. (2005). Symmetry and Asymmetry. *European Review, 13*, 119-133.

Hugdahl, K., & Andersson, L. (1986). The "forced-attention paradigm" in dichotic listening to CV-syllables: a comparison between adults and children. *Cortex, 22*(3), 417-432.

Hugdahl, K., Bronnick, K., Kyllingsbaek, S., Law, I., Gade, A., & Paulson, O. B. (1999). Brain activation during dichotic presentations of consonant-vowel and musical instrument stimuli: a 15O-PET study. *Neuropsychologia, 37*(4), 431-440.

Hugdahl, K., Heiervang, E., Ersland, L., Lundervold, A., Steinmetz, H., & Smievoll, A. I. (2003). Significant relation between MR measures of planum temporale area and dichotic processing of syllables in dyslexic children. *Neuropsychologia, 41*(6), 666-675.

Hugdahl, K., Rund, B. R., Lund, A., Asbjornsen, A., Egeland, J., Landro, N. I., Roness, A., Stordal, K. I., & Sundet, K. (2003). Attentional and executive dysfunctions in schizophrenia and depression: evidence from dichotic listening performance. *Biol Psychiatry, 53*(7), 609-616.

Hummel, F. C., & Cohen, L. G. (2005). Drivers of brain plasticity. *Curr Opin Neurol, 18*(6), 667-674.

Huppi, P. S., Maier, S. E., Peled, S., Zientara, G. P., Barnes, P. D., Jolesz, F. A., & Volpe, J. J. (1998). Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res 44*(4), 584-590.

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res, 163*(2), 195-205.

Huttenlocher, P. R. (1984). Synapse elimination and plasticity in developing human cerebral cortex. *Am J Ment Defic, 88*(5), 488-496.

Huttenlocher, P. R., & de Courten, C. (1987). The development of synapses in striate cortex of man. *Hum Neurobiol, 6*(1), 1-9.

Hyde, T., Stacey, M., Coppola, R., Handel, S., Rickler, K., & Weinberger, D. (1995). Cerebral morphometric abnormalities in Tourette's syndrome: a quantitative MRI study of monozygotic twins. *Neurology, 45*, 1176-1182.

Innocenti, G. M., Aggoun-Zouaoui, D., & Lehmann, P. (1995). Cellular aspects of callosal connections and their development. *Neuropsychologia, 33*(8), 961-987.

Journal of the American Academy of Child and Adolescent Psychiatry (2005). *Instructions for the authors*, from http://www.jaacap.com

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry, 36*(7), 980-988.

Kempermann, G. (2002). Why New Neurons? Possible Functions for Adult Hippocampal Neurogenesis. *J Neurosci, 22*(3), 635-638.

Kennard, M. (1938). Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *Journal of Neurophysiology 1* 477-496.

Khalifa, N., & von Knorring, A. L. (2003). Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol, 45*(5), 315-319.

King, R. A., Leckman, J. F., Scahill, L., & Cohen, D. J. (1999). Obsessive-compulsive disorder, anxiety, and depression. In J. F. Leckman & D. J. Cohen (Eds.), *Tourette Syndrome - Tics, obsessions, compulsions: Developmental psychopathology and clinical care* (pp. 43-62). New York: Wiley.

Kimura, D. (1967). Functional asymmetry of the brain in dichotic listening. *Cortex, 3*, 163-168.

Klingberg, T., Vaidya, C. J., Gabrieli, J. D., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport 10*(13), 2817-2821.

LaMantia, A. S., & Rakic, P. (1990). Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. *J Neurosci, 10*(7), 2156-2175.

Lassonde, M. (2003). Agenesis of the Corpus Callosum. In E. Zaidel & M. Iacoboni (Eds.), *The Parallel Brain* (pp. 357-369). Cambridge, Massachusetts: MIT Press.

Leckman, J. F., Riddle, M., Hardin, M., Ort, S., Swartz, K., Stevenson, J., & Cohen, D. (1989). The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry, 28*(4), 566-573.

Leckman, J. F., Sholomskas, D., Thompson, W., Belanger, A., & Weissman, M. (1982). Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry, 39*(8), 879-883.

Leckman, J. F. (2002). Tourette's syndrome. *Lancet, 360*(9345), 1577-1586.

Leckman, J. F., Walker, D. E., & Cohen, D. J. (1993). Premonitory urges in Tourette's syndrome. *Am J Psychiatry, 150*(1), 98-102.

Leckman, J. F., Walker, D. E., Goodman, W. K., Pauls, D. L., & Cohen, D. J. (1994). "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. *Am J Psychiatry, 151*(5), 675-680.

Leckman, J. F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., Kim, Y. S., & Peterson, B. S. (1998). Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics, 102*, 14-19.

Luders, E., Narr, K. L., Zaidel, E., Thompson, P. M., Jancke, L., & Toga, A. W. (2005). Parasagittal Asymmetries of the Corpus Callosum. *Cereb Cortex*.

Marsh, R., Zhu, H., Schultz, R. T., Quackenbush, G., Royal, J., Skudlarski, P., & Peterson, B. S. (2006). A developmental fMRI study of self-regulatory control. *Hum Brain Mapp*.In Press.

Mason, A., Banerjee, S., Eapen, V., Zeitlin, H., & Robertson, M. (1998). The prevalence of Tourette syndrome in a mainstream school population. *Dev Med Child Neurol, 40*, 292-296.

Mayston, M. J., Harrison, L. M., & Stephens, J. A. (1999). A neurophysiological study of mirror movements in adults and children. *Ann Neurol 45*(5), 583-594.

Merette, C., Brassard, A., Potvin, A., Bouvier, H., Rousseau, F., Emond, C., Bissonnette, L., Roy, M. A., Maziade, M., Ott, J., & Caron, C. (2000). Significant linkage for Tourette syndrome in a large French Canadian family. *Am J Hum Genet, 67*(4), 1008-1013.

Milleret, C., & Houzel, J. C. (2001). Visual interhemispheric transfer to areas 17 and 18 in cats with convergent strabismus. *Eur J Neurosci 13*(1), 137-152.

Milner, B., Taylor, L., & Sperry, R. W. (1968). Lateralized suppression of dichotically presented digits after commissural section in man. *Science, 161*(837), 184-186.

Mink, J. W. (2001). Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns. *Adv Neurol, 85*, 113-122.

Monk, C. S., Webb, S. J., & Nelson, C. A. (2001). Prenatal neurobiological development: molecular mechanisms and anatomical change. *Dev Neuropsychol, 19*(2), 211-236.

Moriarty, J., Varma, A., Stevens, J., Fish, M., Trimble, M., & Robertson, M. (1997). A volumetric MRI study of Gilles de la Tourette's syndrome. *Neurology, 49*(2), 410-415.

Mostofsky, S., Wendlandt, J., Cutting, L., Denckla, M., & Singer, H. (1999). Corpus callosum measurements in girls with Tourette syndrome. *Neurology, 53*(6), 1345-1347.

Oldfield, R. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Pandya, D. N., & Seltzer, B. (1986). The Topography of Commissural Fibers. In F. Lepore, M. Ptito & H. H. Jasper (Eds.), *Two Hemispheres-One Brain: Functions of the Corpus Callosum* (pp. 47-73): Alan R. Liss.

Pantel, J., Schroder, J., Jauss, M., Essig, M., Minakaran, R., Schonknecht, P., Schneider, G., Schad, L. R., & Knopp, M. V. (1999). Topography of callosal atrophy reflects distribution of regional cerebral volume reduction in Alzheimer's disease. *Psychiatry Res 90*(3), 181-192.

Pappert, E. J., Goetz, C. G., Louis, E. D., Blasucci, L., & Leurgans, S. (2003). Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology, 61*(7), 936-940.

Paschou, P., Feng, Y., Pakstis, A. J., Speed, W. C., DeMille, M. M., Kidd, J. R., Jaghori, B., Kurlan, R., Pauls, D. L., Sandor, P., Barr, C. L., & Kidd, K. K. (2004). Indications of linkage and association of Gilles de la Tourette syndrome in two independent family samples: 17q25 is a putative susceptibility region. *Am J Hum Genet, 75*(4), 545-560.

Pauls, D., & Hurst, C. (1996). *Schedule for Tourette and Other Behavioral Syndromes*. New Haven, Conneticut: Yale University Child Study Center.

Pauls, D. L. (2003). An update on the genetics of Gilles de la Tourette syndrome. *J Psychosom Res, 55*(1), 7-12.

Pauls, D. L., & Leckman, J. F. (1986). The inheritance of Gilles de la Tourette's syndrome and associated behaviors. Evidence for autosomal dominant transmission. *N Engl J Med, 315*(16), 993-997.

Pauls, D. L., Raymond, C. L., Stevenson, J. M., & Leckman, J. F. (1991). A family study of Gilles de la Tourette syndrome. *Am J Hum Genet, 48*(1), 154-163.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., Rapoport, J. L., & Evans, A. C. (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science, 283*(5409), 1908-1911.

Payne, B. R., & Lomber, S. G. (2001). Reconstructing functional systems after lesions of cerebral cortex. *Nat Rev Neurosci, 2*(12), 911-919.

Peretz, I., & Morais, J. (1988). Determinants of laterality for music: towards an information processing account. In K. Hugdahl (Ed.), *Handbook of Dichotic Listening:Theories, Methods and Research* (pp. 323-358). Chichester: Wiley.

Peters, M., & Ploog, D. (1973). Communication among primates. *Annu Rev Physiol, 35*, 221-242.

Peterson, B. S. (2003). Conceptual, methodological, and statistical challenges in brain imaging studies of developmentally based psychopathologies. *Dev Psychopathol 15*(3), 811-832.

Peterson, B. S., Feineigle, P., Staib, L., & Gore, J. (2001). Automated measurement of latent morphological features in the human corpus callosum. *Hum Brain Mapp, 12*(4), 232-245.

Peterson, B. S., Leckman, J., Duncan, J., Wetzles, R., Riddle, M., Hardin, M., & Cohen, D. (1994). Corpus callosum morphology from magnetic resonance images in Tourette's syndrome. *Psychiatry Res, 55*(2), 85-99.

Peterson, B. S., Riddle, M. A., Cohen, D. J., Katz, L. D., Smith, J. C., Hardin, M. T., & Leckman, J. F. (1993). Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology, 43*(5), 941-949.

Peterson, B. S., Skudlarski, P., Anderson, A. W., Zhang, H., Gatenby, J. C., Lacadie, C. M., Leckman, J. F., & Gore, J. C. (1998). A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. *Arch Gen Psychiatry, 55*(4), 326-333.

Peterson, B. S., Staib, L., Scahill, L., Zhang, H., Anderson, C., Leckman, J. F., Cohen, D. J., Gore, J. C., Albert, J., & Webster, R. (2001). Regional brain and ventricular volumes in Tourette syndrome. *Arch Gen Psychiatry, 58*(5), 427-440.

Peterson, B. S., Thomas, P., Kane, M. J., Scahill, L., Zhang, H., Bronen, R., King, R. A., Leckman, J. F., & Staib, L. (2003). Basal Ganglia volumes in patients with Gilles de la Tourette Syndrome. *Arch Gen Psychiatry, 60*(4), 415-424.

Pierpaoli, C., Barnett, A., Pajevic, S., Chen, R., Penix, L. R., Virta, A., & Basser, P. (2001). Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage, 13*(6 Pt 1), 1174-1185.

Pierpaoli, C., & Basser, P. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine, 36*(6), 893-906.

Pujol, J., Vendrell, P., Junque, C., Marti-Vilalta, J. L., & Capdevila, A. (1993). When does human brain development end? Evidence of corpus callosum growth up to adulthood. *Ann Neurol 34*(1), 71-75.

R Development Core Team (2003): *R: A language and and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria.

Ramnani, N., Behrens, T. E., Penny, W., & Matthews, P. M. (2004). New approaches for exploring anatomical and functional connectivity in the human brain. *Biol Psychiatry, 56*(9), 613-619.

Rauch, R., & Jinkins, J. (1996). Variability of corpus callosal area measurements from midsagittal MR images: effect of subject placement within the scanner. *AJNR Am J Neuroradiol, 17*(1), 27-28.

Reinvang, I., Bakke, S., Hugdahl, K., Karlsen, N. R., & Sundet, K. (1994). Dichotic listening performance in relation to callosal area on the MRI scan. *Neuropsychology, 8*, 445-450.

Roberts, D. W. (1999). Corpus Callosotomy in the treatment of neuronal migration disorders. In P. Kotagal & H. O. Luders (Eds.), *The Epilepsies:Etiologies and Prevention* (pp. 103-112). San Diego, CA: Academic Press.

Robertson, M. M. (2000). Tourette syndrome, associated conditions and the complexities of treatment. *Brain, 123*, 425-462.

Robertson, M. M., Banerjee, S., Eapen, V., & Fox-Hiley, P. (2002). Obsessive compulsive behaviour and depressive symptoms in young people with Tourette syndrome. A controlled study. *Eur Child Adolesc Psychiatry, 11*(6), 261-265.

Rosen, G. D., Galaburda, A. M., & Sherman, G. F. (1989). Cerebrocortical microdysgenesis with anomalous callosal connections: a case study in the rat. *Int J Neurosci 47*(3-4), 237-247.

Rothenberger, A., Kostanecka, T., Kinkelbur, J., Cohrs, S., Woerner, W., & Hajak, G. (2001). Sleep and Tourette syndrome. *Adv Neurol, 85*, 245-259.

Sacks, O. (1992). A neurologist's notebook: A surgeon's life. *The New Yorker*(March), 85-94.

Saron, C. D., Foxe, J. J., Simpson, G. V., & Vaughan, H. G. (2003). Interhemispheric Visuomotor Activation:Spatiotemporal Electrophysiology Related to Reaction Time. In E. Zaidel & M. Iacoboni (Eds.), *The Parallel Brain* (pp. 171-219). Cambridge, Massachusetts: MIT PRess.

Scamvougeras, A., Kigar, D. L., Jones, D., Weinberger, D. R., & Witelson, S. F. (2003). Size of the human corpus callosum is genetically determined: an MRI study in mono and dizygotic twins. *Neurosci Lett 338*(2), 91-94.

Schlaug, G., Jancke, L., Huang, Y., Staiger, J. F., & Steinmetz, H. (1995). Increased corpus callosum size in musicians. *Neuropsychologia, 33*(8), 1047-1055.

Schulte, T., Sullivan, E. V., Muller-Oehring, E. M., Adalsteinsson, E., & Pfefferbaum, A. (2005). Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb Cortex, 15*(9), 1384-1392.

Seung, H. S. (2000). Half a century of Hebb. *Nat Neurosci, 3 Suppl*, 1166.

Singer, H., Reiss, A., Brown, J., Aylward, E., Shih, B., Chee, E., Harris, E., Reader, M., Chase, G., Bryan, R., & al, e. (1993). Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. *Neurology, 43*(5), 950-956.

Singer, H. S. (2005). Tourette's syndrome: from behaviour to biology. *Lancet Neurol, 4*(3), 149-159.

Singer, H. S., & Minzer, K. (2003). Neurobiology of Tourette's syndrome: concepts of neuroanatomic localization and neurochemical abnormalities. *Brain Dev, 25 Suppl 1*, S70-84.

Skoff, R. P., Bessert, D. A., Barks, J. D., Song, D., Cerghet, M., & Silverstein, F. S. (2001). Hypoxic-ischemic injury results in acute disruption of myelin gene expression and death of oligodendroglial precursors in neonatal mice. *Int J Dev Neurosci 19*(2), 197-208.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nat Neurosci, 6*(3), 309-315.

Sowell, E. R., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., & Peterson, B. S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet, 362*(9397), 1699-1707.

Spencer, T., Biederman, J., Coffey, B., Geller, D., Faraone, S., & Wilens, T. (2001). Tourette disorder and ADHD. *Adv Neurol, 85*, 57-77.

Sperry, R. W., Gazzaniga, M. S., & Bogen, J. E. (1969). Interhemispheric relationships:The neocortical commisures; syndromes of hemisphere disconnection. In P. J. Vinken & G. W. Bruyn (Eds.), *Handbook of clinical neurology* (Vol. 4, pp. 273-290). Amsterdam: North-Holland.

Spessot, A. L., & Peterson, B. S. (2006). Tourette Syndrome: A Multifactorial, Developmental Pychopathology. In D. Cicchetti & D. J. Cohen (Eds.), *Manual of Developmental Psychopathology* (pp 436-469). New York: John Wiley.

Spessot, A. L., Plessen, K. J., & Peterson, B. S. (2004). Neuroimaging of developmental psychopathologies: the importance of self-regulatory and neuroplastic processes in adolescence. *Ann N Y Acad Sci, 1021*, 86-104.

Spreen, O., & Strauss, E. (1991). *A compendium of neuropsychological tests*. New York: Oxford University Press.

SPSS, I. (1999). SPSS Base 10.0 for Windows User's Guide Chicago IL: SPSS Inc.

State, M. W., Greally, J. M., Cuker, A., Bowers, P. N., Henegariu, O., Morgan, T. M., Gunel, M., DiLuna, M., King, R. A., Nelson, C., Donovan, A., Anderson, G. M., Leckman, J. F., Hawkins, T., Pauls, D. L., Lifton, R. P., & Ward, D. C. (2003). Epigenetic abnormalities associated with a chromosome 18(q21-q22) inversion and a Gilles de la Tourette syndrome phenotype. *Proc Natl Acad Sci U S A, 100*(8), 4684-4689.

StatSoft. (2003). Inc. (2001). STATISTICA (data analysis software system), version 6. www.statsoft.com.

Stern, E., Silbersweig, D. A., Chee, K. Y., Holmes, A., Robertson, M. M., Trimble, M., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (2000). A functional neuroanatomy of tics in Tourette syndrome. *Arch Gen Psychiatry, 57*(8), 741-748.

Strand, G., & Plessen, K. J. (2004). *Norwegian translation of the YGTSS*. National Competence Center for ADHD, TS and narkolepsia, Oslo.

Sukhodolsky, D. G., Scahill, L., Zhang, H., Peterson, B. S., King, R. A., Lombroso, P. J., Katsovich, L., Findley, D., & Leckman, J. F. (2003). Disruptive behavior in children with Tourette's syndrome: association with ADHD comorbidity, tic severity, and functional impairment. *J Am Acad Child Adolesc Psychiatry, 42*(1), 98-105.

Sur, M., & Rubenstein, J. L. (2005). Patterning and plasticity of the cerebral cortex. *Science, 310*(5749), 805-810.

Termine, C., Balottin, U., Rossi, G., Maisano, F., Salini, S., Nardo, R. D., & Lanzi, G. (2006). Psychopathology in children and adolescents with Tourette's syndrome: A controlled study. *Brain Dev* 28(2):69-75.

The Tourette Syndrome Association International Consortium for Genetics (1999). A complete genome screen in sib pairs affected by Gilles de la Tourette syndrome. *Am J Hum Genet, 65*(5), 1428-1436.

Thompson, P. M., Giedd, J. N., Woods, R. P., MacDonald, D., Evans, A. C., & Toga, A. W. (2000). Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature, 404*(6774), 190-193.

Thompson, P. M., Narr, K. L., Blanton, R. E., & Toga, A. W. (2003). Mapping Structural Alterations of the Corpus Callosum During Brain Development and Degeneration. In E. Zaidel & M. Iacoboni (Eds.), *The Parallel Brain*. Cambridge, Massachusetts: MIT Press.

Thomsen, P. H. (2000). Obsessions:the impact and treatment of obsessive-compulsive disorder in children and adolescents. *J Psychopharmacol, 14*(2 Suppl 1), 31-37.

Thomsen, T., Hugdahl, K., Ersland, L., Barndon, R., Lundervold, A., Smievoll, A. I., Roscher, B. E., & Sundberg, H. (2000). Functional magnetic resonance imaging (fMRI) study of sex differences in a mental rotation task. *Med Sci Monit, 6*(6), 1186-1196.

Ungerleider, L. G., Doyon, J., & Karni, A. (2002). Imaging Brain Plasticity during Motor Skill Learning. *Neurobiol Learn Mem 78*(3), 553-564.

Verte, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2005). Executive functioning in children with autism and Tourette syndrome. *Development and Psychopathology, 17*, 415-445.

von Plessen, K., Lundervold, A., Duta, N., Heiervang, E., Klauschen, F., Smievoll, A. I., Ersland, L., & Hugdahl, K. (2002). Less developed corpus callosum in dyslexic subjects--a structural MRI study. *Neuropsychologia, 40*(7), 1035-1044.

Wada, J., & Rasmussen, T. (1960). Intracarotid injections of sodium amytal for the lateralization of cerebral speech dominance. *J. Neurosurgery, 17*, 266-282.

Walkup, J. T., LaBuda, M. C., Singer, H. S., Brown, J., Riddle, M. A., & Hurko, O. (1996). Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. *Am J Hum Genet, 59*(3), 684-693.

Webb, S. J., Monk, C. S., & Nelson, C. A. (2001). Mechanisms of postnatal neurobiological development: implications for human development. *Dev Neuropsychol, 19*(2), 147-171.

WHO. (1992). *ICD-10: The ICD-10 Classification of Mental and Behavioural Disorders:Clinical Descriptions and Diagnostical Guideline*. Geneva: World Health Organization.

Wimberger, D. M., Roberts, T. P., Barkovich, A. J., Prayer, L. M., Moseley, M. E., & Kucharczyk, J. (1995). Identification of "premyelination" by diffusion-weighted MRI. *J Comput Assist Tomogr, 19*(1), 28-33.

Witelson, S. F. (1993). Clinical neurology as data for basic neuroscience: Tourette's syndrome and the human motor system. *Neurology, 43*(5), 859-861.

Yamauchi, H., Fukuyama, H., Nagahama, Y., Katsumi, Y., Dong, Y., Konishi, J., & Kimura, J. (1996). Atrophy of the corpus callosum associated with cognitive impairment and widespread cortical hypometabolism in carotid artery occlusive disease. *Arch Neurol 53*(11), 1103-1109.

Zhang, H., Leckman, J. F., Pauls, D. L., Tsai, C. P., Kidd, K. K., & Campos, M. R. (2002). Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette syndrome. *Am J Hum Genet, 70*(4), 896-904.

Ziemann, U., Paulus, W., & Rothenberger, A. (1997). Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. *Am J Psychiatry 154*(9), 1277-1284.