# MRI measures of brain volume and cortical complexity in clinical groups and during development

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# Contents

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# Abstract

The complex structure of the surface of the brain might elude classical magnetic resonance imaging (MRI) methods of characterization, when it comes to measures of surface irregularities. Such measures may be important when studying brain structural abnormalities in various clinical groups. By combining volumetric measures of grey (GM) and white matter (WM) with the characterization of the complexity of the border between them by the calculation of fractal dimension (FD), new information can be retrieved about structural modifications in development, clinical impairments and diseases. These measures were used in the present thesis when studying brain development and differences between males and females, and when comparing brain structural abnormalities in clinical groups.

The first study in the current thesis was done on patients with schizophrenia, comparing our results with previous findings and testing the reliability of the fractal dimension measurement by use of validation procedures. The results confirmed previous research and found significantly larger abnormalities in the schizophrenia patients compared to healthy control subjects, in the complexity of the cortical foldings.

The second study was focused on dyslexia, comparing boys and girls. MRI structural differences were found in GM and WM volume, the GM/WM ratio and the FD measurement, revealing differences between the groups in complexity of the border between GM and WM. Of particular importance was the finding that changes were more marked for the dyslexia girls, indicating more serious effects in girls once they show signs of dyslexia. Structural changes also occur during maturation and development, as found in the third study, which compared adolescents with young adults. Structural brain differences were more pronounced in the right hemisphere, and in the young females.

It is concluded that the results of the present thesis show the importance of using volumetric measures together with shape characterization techniques, like the fractal dimension, when studying brain structural development and maturation and in clinical groups.

# List of papers

Anca-Larisa Sandu, Inge-Andre Rasmussen jr., Arvid Lundervold, Frank Kreuder, Gesche Neckelmann, Kenneth Hugdahl, Karsten Specht - "Fractal dimension analysis of MR images reveals grey matter structure irregularities in schizophrenia", Computerized Medical Imaging and Graphics 32 (2008) 150–158.

Anca-Larisa Sandu, Karsten Specht, Harald Beneventi, Arvid Lundervold, Kenneth Hugdahl - "Sex-differences in grey-white matter structure in normal-reading and dyslexic adolescents", Neuroscience Letters 438 (2008) 80-84.

Anca-Larisa Sandu, Karsten Specht, Harald Beneventi, Kenneth Hugdahl - "Post-adolescent developmental changes in grey-white matter brain structure: Effects of gender", manuscript.

# 1. Introduction

## 1.1 Cerebrum

The human brain (cerebrum) is the most complex organ of the body and has attracted the interest of researchers and philosophers from the early times. Already in ancient times, the father of Western medicine Hippocrates (460-379 B.C.) identified the brain as the organ where thinking occur and sensations are centralized (Bear et al, 2001).

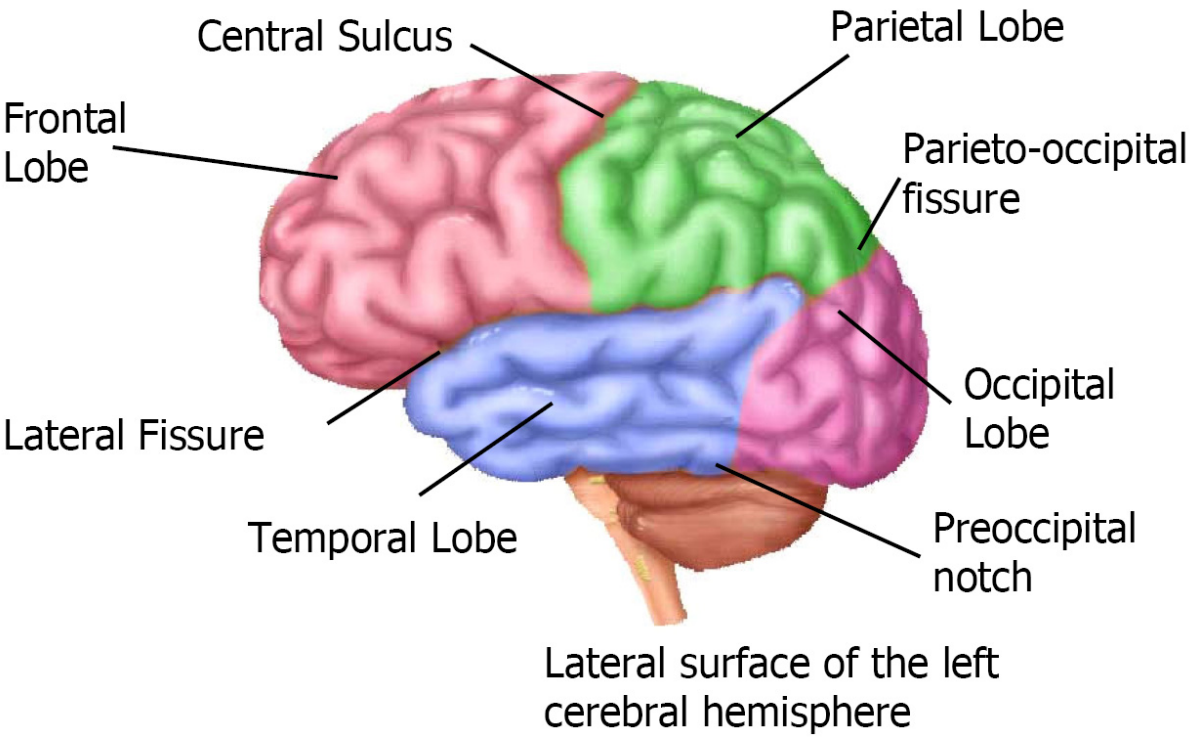
Around 100 billions ($10^{11}$) neurons are located in the cerebrum, namely 80% of the total, and while representing only 2% of the total body weight, the cerebrum accounts for 20% of the total oxygen consumption.

The neurons are usually arranged in six layers, and they communicate through electrical impulses; there are $6x10^{13}$ synapses (60 trillions) making the brain the largest "computer" ever. The cerebral cortex consists of convoluted neuronal layers and its architecture is not uniform; for example instead of six layers, the hippocampus, which is the phylogenetically oldest structure, has at most three cellular layers. Other factors contributing to the differences that exist between neocortical architectonic fields are the variation in thickness or cell type and the anatomy of the cortical folds; for example the thickness of a given layer can vary from region to region (White et al, 2003).

In this context it may be worth mentioning that while the cerebral cortex thickness measures only 1.5-4.5 mm, its surface is around 1600 $cm^2$ (Hilgetag & Barbas, 2006).

## 1.2 Structure of the cortex

The "substance" of the brain, i.e. the brain tissue, is divided into two parts, the grey matter (GM) and white matter (WM). In the early history of neuroanatomy, it was correctly assumed that WM, composed mainly of myelinated axons and which continues with the nerves of the body is responsible for information transfer to the GM (Bear et al, 2001). GM on the other hand predominates in the cortex, is distributed at the surface of the cerebral hemispheres and consists of neurons, glial cells (astroglia and oligodendrocytes), capillaries, and short nerve cell extensions (axons and dendrites).



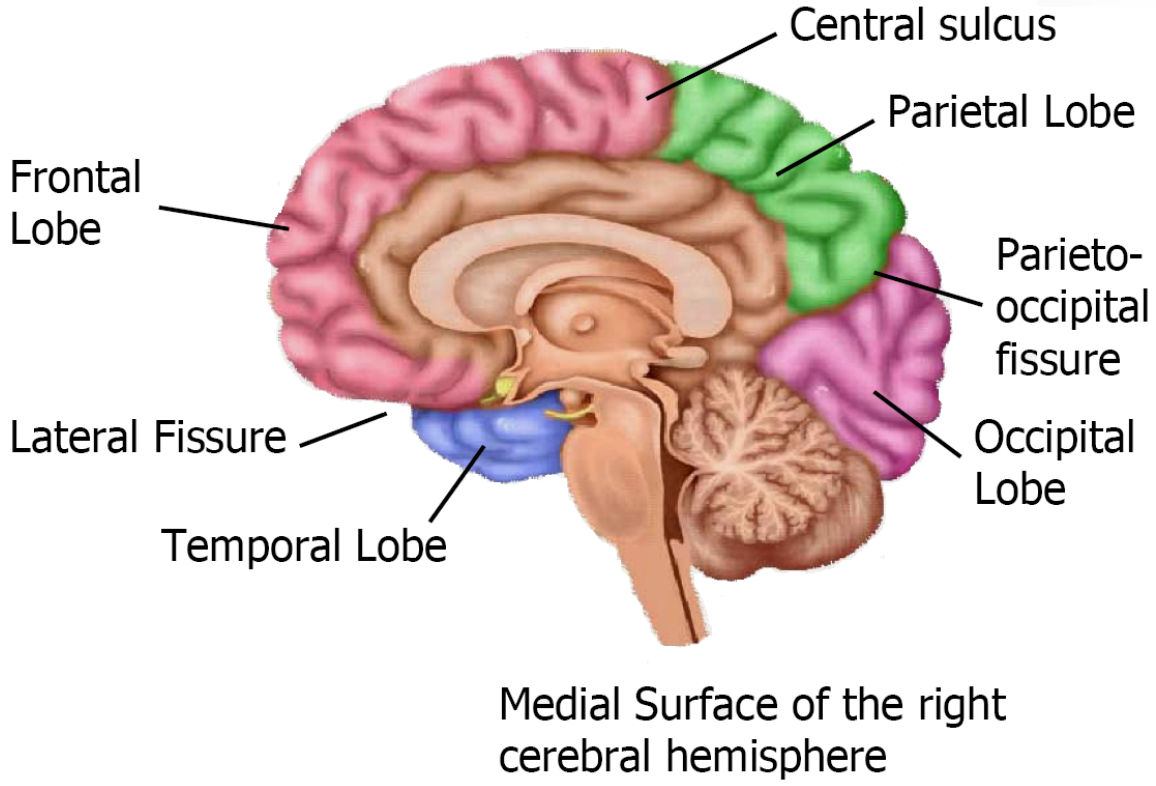




Fig.1 Major divisions of cerebrum for the left and right hemispheres adapted from Stewart (http ://home.oise.utoronto.ca/~mlewis/cerebrum_1.pdf)

By the end of the eighteenth century, another neuroanatomical observation was that the cortical surface consists of ridges, named gyri, and furrows named sulci or if they extend below the cortical folding, they are named fissures. The deepest of the fissures, the longitudinal fissure separates the two cerebral hemispheres. The main sulci on the lateral surface of each of the hemisphere are the Rolandic (central) fissure and the Sylvian (lateral) fissure. The cerebrum is further parcelled into lobes that take their names from the cranial bones under which they are situated. The frontal lobe is separated from the parietal lobe by the central sulcus, the temporal lobe is found anterior to the Sylvian fissure. At the very back of the cerebrum is situated the occipital lobe, surrounded by the parietal and temporal lobes. Deep inside the cerebral cortex is a structure named insula, which borders are separated by the temporal and the frontal lobes.

As much as two thirds of the cerebral cortex is situated inside the cortical sulci (Kuperberg et al, 2003). Thus, an increase of the cerebral cortex surface occurs due to the convolutions without increasing the overall volume of the brain.

A more advanced view that emerged in the eighteenth century was that the complex surface structure created by the sulci and gyri differs not only between individuals but also between the hemispheres of the same individual, especially in the frontal and parieto-occipital regions (Ono et al, 1990). A more recent observation is that areas defined by macroscopical landmarks do not coincide exactly with those defined using cytoarchitectonical criteria (Zilles et al, 2004).

## 1.3 Mapping brain function to structure

The above described pattern of the parcelling of the brain and the underlying similarities in the brain surface between individuals led the scientists of the eighteenth century to the idea that different functions might be localized in different areas of the brain. It was the emergence of a new and very important concept, relating function to structure, i.e. cerebral localization.

With the work of Brodmann in the beginning of the twentieth century, a functional correspondence to structural characteristics saw its beginning. Brodmann observed that packing, size and shape of neurons varied from one region to another and based on this he defined 52 cytoarchitectonically areas which are assumed to act as functional entities (Bear et al, 2001).

A further refinement of the concept of functional localization occurred with the introduction of modern functional imaging techniques, which allow researchers to "see" the brain in working. It seems however that also the classic architectonic mapping approach is not without problems where one also has to take into account other factors such as the regional distribution of various neurotransmitter receptors (Zilles et al, 2004).

The implication for neuroscientists is that there is a strong link between structure and function, which are assumed to interact and remodel each other. Important are both the number of neurons, which are consistently reflected in the structural aspect, and the network of their connections, reflected in the functional aspect, where from the interest of analyzing GM together with WM.

Cytoarchitectural anomalies are also reflected at a macroanatomic level. During the last decades neuroscience has had a great impact where development, impairments and mental and neurological illnesses are recognized to be intertwined with brain pathology. An open issue is whether psychotic disorders like schizophrenia have a neurodevelopmental or neurodegenerative course.

## 1.4 MRI-based in vivo morphometry

Direct observation of the processes that take place in the brain has become possible during the last half of the 20th century due to non-invasive techniques such as structural and functional MRI, which can be used to obtain structural images and for studying the metabolism in vivo.

MRI is a technology based on the physical phenomenon of nuclear magnetic resonance. The nucleus of elements with odd number of protons and neutrons (such as the hydrogen) possesses a magnetic moment $\boldsymbol{\mu}$. Hydrogen is omnipresent in soft tissue in the human body, for example in water, which is abundant in the brain.

Without an external magnetic field the magnetic moments are randomly oriented, thus the total magnetization is zero. In the presence of a strong magnetic field, ranging in the order of 1-10 Tesla the individual magnetic moments start to precess around their own axis along the direction of the magnetic field and create a net magnetization $\boldsymbol{M}$. The frequency of the precession is dependent on the external magnetic field given by the formula $\boldsymbol{\omega = \gamma B,}$ called Lamor frequency. Thereby is $\boldsymbol{\gamma}$ the gyromagnetic ratio (a value specific to each element) and $\boldsymbol{B}$ is the external magnetic field.

If an oscillatory external magnetic field is applied, perpendicular to the initial magnetic field and with a frequency equal to the Larmor frequency resonant energy transfer occurs and the individual magnetic moments $\boldsymbol{\mu}$ are tilted to a direction perpendicular to the initial magnetic field. Once the perturbation is removed, the magnetic moments will return to the initial position emitting an electromagnetic signal, which is captured by the receiving coil.

There are a number of physical processes involved which allow the retrieval of meaningful information. First of all, by means of a magnetic field gradient, each slice has a slightly different Larmor frequency, thus information about the origin of the signal is available. Another parameter involved is the $\boldsymbol{T_1}$ (longitudinal) relaxation time, which describes how fast the tilted magnetic moments return to their initial orientation (around 1s). It is also important that immediately after the application of the RF pulse, there is coherence between the individual magnetic moments and this coherence is lost after the $\boldsymbol{T_2}$ (transverse) relaxation time. The order of magnitude of $\boldsymbol{T_2}$ relaxation time is of the order of ten milliseconds. However, both, the $\boldsymbol{T_1}$ and $\boldsymbol{T_2}$ times are tissue dependent. For the brain, this means that $\boldsymbol{T_1}$ and $\boldsymbol{T_2}$ are different for the main compartments, i.e. GM, WM, and cerebro-spinal fluid (CSF). Depending on which of the two characteristic times are taken into account, there are $\boldsymbol{T_1}$-weighted images, giving for example high contrast in fat containing tissues or $\boldsymbol{T_2}$-weighted images where water provides a strong signal.

The spatial resolution of the MR technique being very good, of the order of mm, MR images provide detailed information about the volumes of GM and WM, the structure of the brain. However, classic MR approaches to structural brain imaging do typically not provide adequate measures of surface complexity or irregularity. For this reason, the fractal dimension was introduced in the present thesis.

## 1.5 A measure of shape complexity - the fractal dimension (FD)

The concept of fractal geometry was introduced by the French mathematician Mandelbrot, who has a Polish origin. He introduced the term of fractal in the 1970ies to describe rough geometrical shapes, which could not be characterized mathematically (Mandelbrot, 1977). The term itself comes from the Latin “fractus” which means “broken”. Mandelbrot argued that in nature smooth surfaces are the exception and not the rule. One has to think only about fjords, mountains, clouds. Indeed, most of the shapes we see around us in daily life have a complex shape, which cannot be fully characterized using only Euclidean geometry.

The simplest description of a fractal is an object that can be divided in smaller parts, where each part is similar to the whole. This is the most important property of the fractal, called self-similarity.

Interestingly, the best known examples of fractals; the Koch curve, the Sierpinski gasket or the Cantor set, were constructed as mathematical artefacts already at the beginning of the twentieth century (Mandelbrot, 1977).

Some of the basic concepts of fractality can be exemplified with the Koch curve, named after the Swedish mathematician Helge von Koch, shown in Figure 2. It starts as a straight line; in the first step of the iteration the line is divided into three segments and the middle segment is replaced by two segments, forming a sort of an open triangle. In the second step the procedure is repeated for every straight segment. The process continues in the third step and the iterations can, in theory, be continued to infinity. The result is an object that is neither a curve nor a surface but rather an infinite curve that fills the surface.

Let us now consider the same object from a different perspective. From a distance it looks like a line but when coming closer one sees more and more details. Thus, when measuring the total length of the Koch curve, the result depends on the length of the measuring rod. This leads towards a definition of the dimension, related to the number of self-similar objects that can be seen when dividing a larger object. In this case, by decreasing the radius to one third, the measurable length increases by a factor of four.

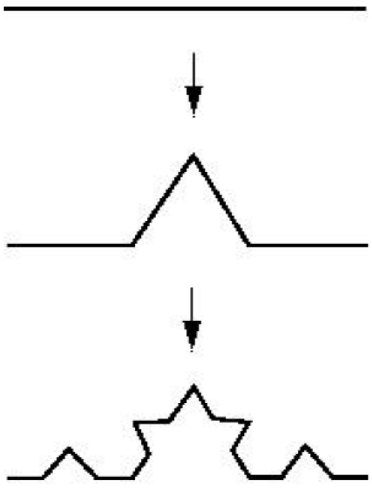


Fig 2 Three successive iterations of the Koch curve

The similarity dimension $\boldsymbol{D_f}$ is defined as:

$$D_f = \lim_{n \to \infty} \frac{\log\left(N(n)\right)}{\log\left(1/r\right)}$$

where ***N(n)*** is the number of self-similar objects seen in the ***n***-th iteration and ***r*** is the scaling factor.

In the case of the Koch curve, the dimension is thus $D_f = log(4)/log(3) = 1.2618$. By applying the same reasoning for a simple line, one obtains two objects when dividing in two (scaling factor 1/2), four in the next generation and so on leading to $D_f = 1$. For a square, repeatedly applying a scaling factor 1/2 (dividing each side in half) leads to 4 objects, then 16 and so on, thus the dimension is 2, as expected.

Fractals are thus a special case, their dimension taking usually fractional values and one can say that they are "something" between lines and surfaces, or between surfaces and volumes.

# 2. Structural changes in the brain

## 2.1 Evidence for morphometry changes in schizophrenia

The name schizophrenia was introduced in 1911 by the Swiss psychiatrist Eugen Bleuler; it comes from the Greek words “schizo” (split) and “phren” (mind) because of his observation that many patients seemed to oscillate between normal and abnormal states.

From a symptomatic point of view, schizophrenia could be described by loss of contact with reality and deterioration of thought and behaviour, including delusions and hallucinations as key symptoms. The onset is typically during late adolescence or early adulthood and the disorder usually lasts for the whole life. Taking into account the various forms of manifestation of schizophrenia, even if the disorder has been studied for more than a century, it is still an open question if the name schizophrenia covers one or several disorders.

Neuropathological studies have shown quantitative brain abnormalities such as low neuronal density, pyramidal cell disarray, altered neurotransmitter receptor and volume reduction in schizophrenia (Kasai et al, 2002). Schizophrenia patients also have markedly anatomical abnormalities with multiple absent, duplicated or mis-shaped gyri (Crow, 1997; Green, 1998; Leonard et al, 1999; Narr et al, 2001; Vogeley et al, 2000).

Among the results to be mentioned from other post-mortem studies are slightly increased neuronal density and reduced cortical thickness in prefrontal areas, increased cell packing of pyramidal and nonpyramidal neurons, reduced somal size of pyramidal neurons in cortical layer III and irregularities in the distribution of white matter cells. A possible interpretation could be that there is neuronal atrophy in the cortex of patients with schizophrenia rather than only neuronal loss (Pierri et al, 2001; Rajkowska et al, 1998;

Selemon et al, 1998). Besides their advantages, the post-mortem studies also have limitations, such as problems to correlate with functional data, difficulties in collecting detailed clinical information, and confounds of chronic illness and medication.

There is at least partly agreement that schizophrenia is a chronic brain disorder, since it affects function and structure, reflected by various changes in cortical and subcortical regions involved in cognitive, emotional, and motivational aspects of human behaviour (Kasai et al, 2002). However, there are also several methodological problems. Due to the complexity of the nervous system, it is difficult to find the appropriate means to characterize the differences between healthy and pathological subjects. A variety of techniques such as structural magnetic resonance imaging (sMRI), MR spectroscopy (MRS), and post-mortem studies are available but their results are not converging and are difficult to interpret or to generalize (Kasai et al, 2002). A common point seems however to be that sMRI, MRS, and post-mortem studies have suggested that schizophrenia is associated with morphological and histochemical abnormalities of the brain.

For a quantitative characterization, a first approach would be measures of brain volume that would be expected to show larger or smaller deviances in schizophrenia patients (DeLisi, 1999). Moreover, cerebral and third ventricle volumes, and markers of sulcal interruption or disturbed asymmetry in frontal, cingulate cortex and parietal association cortex have been analyzed. It should be noted, however, that particular attention has to be paid when conducting such measurements in order to avoid biased comparisons (Leonard et al, 1999).

In addition to recent demonstrations of functional impairments in schizophrenia, involving both behavioural (Elvevaag & Goldberg, 2000) and brain mapping techniques (Shergill et al, 2003), studies of brain morphology have consistently shown GM abnormalities in schizophrenia (DeLisi, 1999; Kubicki et al, 2002; Lawrie & Abukmeil, 1998; Puri et al, 2001; Sigmundsson et al, 2001; Sommer et al, 2001;Thompson et al, 2001;Wright et al, 1999; Wright et al, 2000) in individuals at high risk for developing schizophrenia (Job et al, 2005; Job et al, 2003) and in first-episode patients (Kasparek et al, 2006), that is not a side-effect of medication (Kim & Byun, 2003). Further evidence is given by the meta-analysis by Shapleske et al. (1999) and recent overviews by Shenton et al. (2001), Chitnis and Ellison-Wright (2003) and Niznikiewics et al. (2003).

Although different MRI techniques have been used, with different subgroups of patients, the majority of the studies have revealed substantial GM loss in the superior (STG) and middle (MTG) temporal gyri (including the hippocampus), middle frontal gyrus (MFG) as illustrated in Figure 3, and anterior cingulate (AC). Studies of cognitive impairment in

schizophrenia have implicated the same brain areas, e.g. the link of executive and attentional working memory to the prefrontal cortex (Weinberger, 2002); verbal memory to the hippocampus (Harrison, 1999; Lawrie & Abukmeil, 1998) and loss of initiative and apathy to the anterior cingulate cortex (Chitnis & Elison-Wright, 2003).

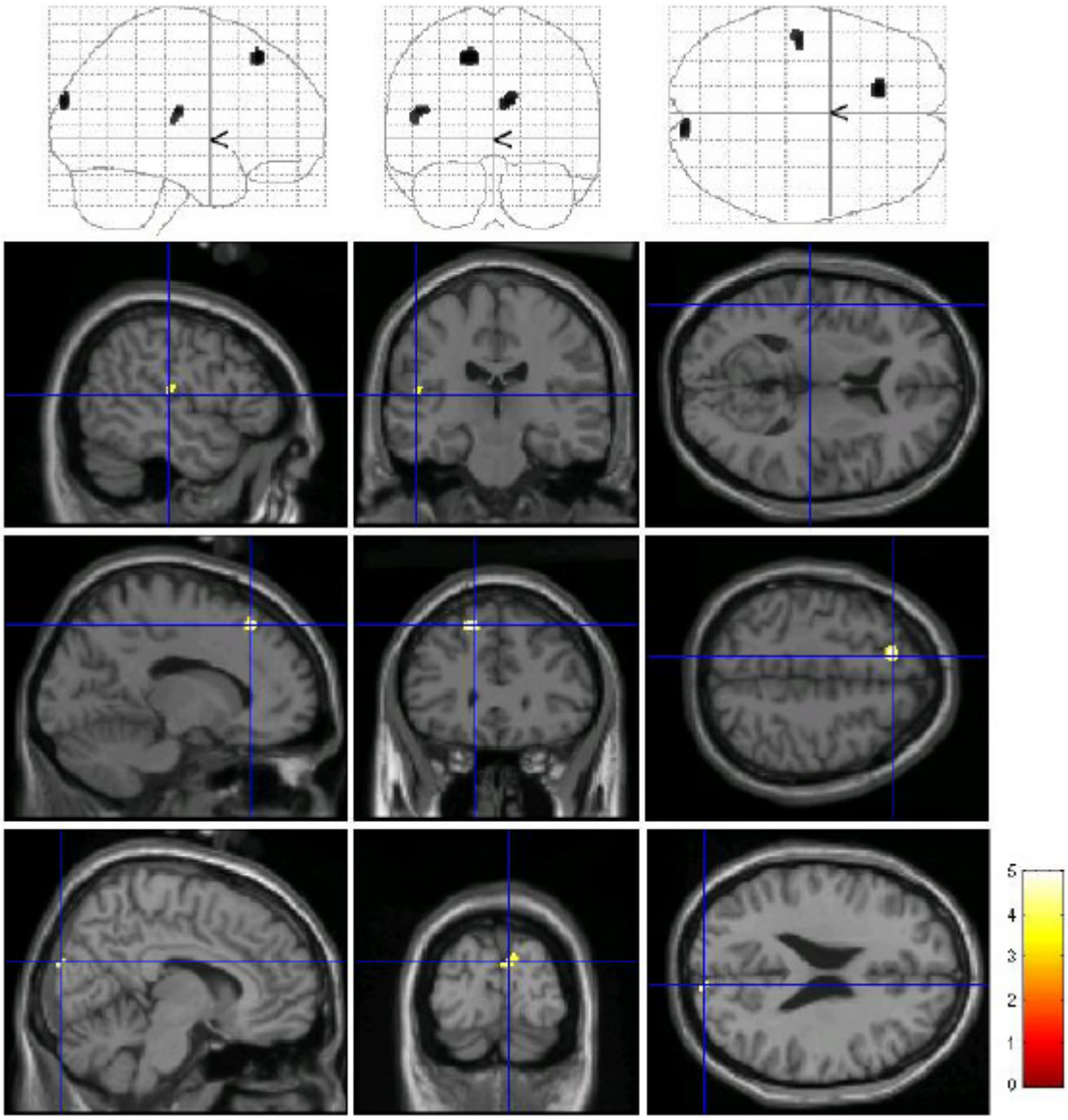



Fig. 3 Schematic representation of areas with significant reductions in GM in the schizophrenia patients compared with the healthy controls. The actual MR images are shown in the lower rows (sagittal, coronal, and axial views). Reproduced with permission from the Publisher (Neckelmann et al, 2006.)

MRI morphological studies provide a measure of voxel-based differences in GM volume or density, or of differences in cortical thickness, between patients with schizophrenia and healthy control subjects. There is however reason to believe that also other brain

morphological factors may be abnormal in schizophrenia, e.g. the gross cortical surface structure, or the architecture of the foldings of the cortical sheet.

## 2.2 Evidence for morphometry changes in dyslexia

The term dyslexia comes from two Greek words, “dys” meaning impaired and “lexis” meaning word. It was introduced in 1887 by the German ophthalmologist Rudolf Berlin, and refers to persons with language difficulties, particularly in reading which is not due to any factors such as visual impairment, reduced intelligence or improper education. Dyslexia has been named in different ways; for example Pringle Morgan in 1896 introduce the term of “Congenital Word Blindness”, while in 1925 the neuroradiologist Samuel Orton called the condition strephosymbolia, meaning “twisted signs” and referring to the difficulty encountered by affected persons to associate spoken words with their written form.

There are several theories attempting to explain dyslexia, reflecting its symptomatic complexity and the multitude of cognitive and reading processes involved. Among them the inaccurate encoding of phonological representations (Hulme & Snowling, 1992; Katz, 1986; Swan & Goswami, 1997) the difficulty in the perception of short or rapid varying sounds, the so-called auditory processing deficit (Tallal, 1980; Tallal et al, 1993) are perhaps the two most referred to models. Other authors propose that anomalies in the magnocellular cells affect other sensorial pathways, not only the visual, theory known as the magnocellular deficit (Stein, 2001) or the automaticity/cerebellar deficit (Nicolson et al, 2001) which states that a malfunctioning of the cerebellum impairs the motor control function necessary for speech or/and prevents the automatization of otherwise usual tasks such as reading. Still others have suggested anomalies in hemispheric asymmetry (Geschwind, 1984; Hugdahl et al, 1995).

Gross structural differences in the dyslexic brain have been known for some time. For example, in a series of benchmark studies on post-mortem tissue, Galaburda and colleagues (Galaburda, 1985; Galaburda & Aboitz, 1986; Galaburda & Kemper, 1979) revealed cortical structural irregularities in the brains of five adult individuals with dyslexia, caused by polymicrogyria, ectopias, and dysplasias. The post mortem studies have also revealed the existence of large number of small gyri and thinning of the corpus callosum of the same five boys and additional three females (Rosen et al, 1993). Obviously this approach has the disadvantage that it would require access to the brains of deceased patients, which would be difficult to correlate with e.g. behavioural and/or functional and structural imaging data.

The postmortem results have however been supported by MRI in vivo measurements in other individuals with dyslexia that have shown reductions in GM density and reduced hemispheric asymmetry, particularly in the auditory cortex and adjacent areas (Heiervang et al, 2000; Hynd & Semrud-Clikeman, 1989; Larsen et al, 1990; Leonard et al, 1993; Rosen et al, 1993), an example is given in the Figure 4. Other studies identified abnormalities also in other areas such as the inferior frontal gyrus (Eckert et al, 2003), inferior temporal gyrus (Silani et al, 2005), and cerebellum (Rae et al, 2002). Functional imaging in individuals at risk for developing dyslexia revealed different activation patterns in the left angular gyrus and inferior occipito-temporal regions compared to controls (Specht et al, 2008).

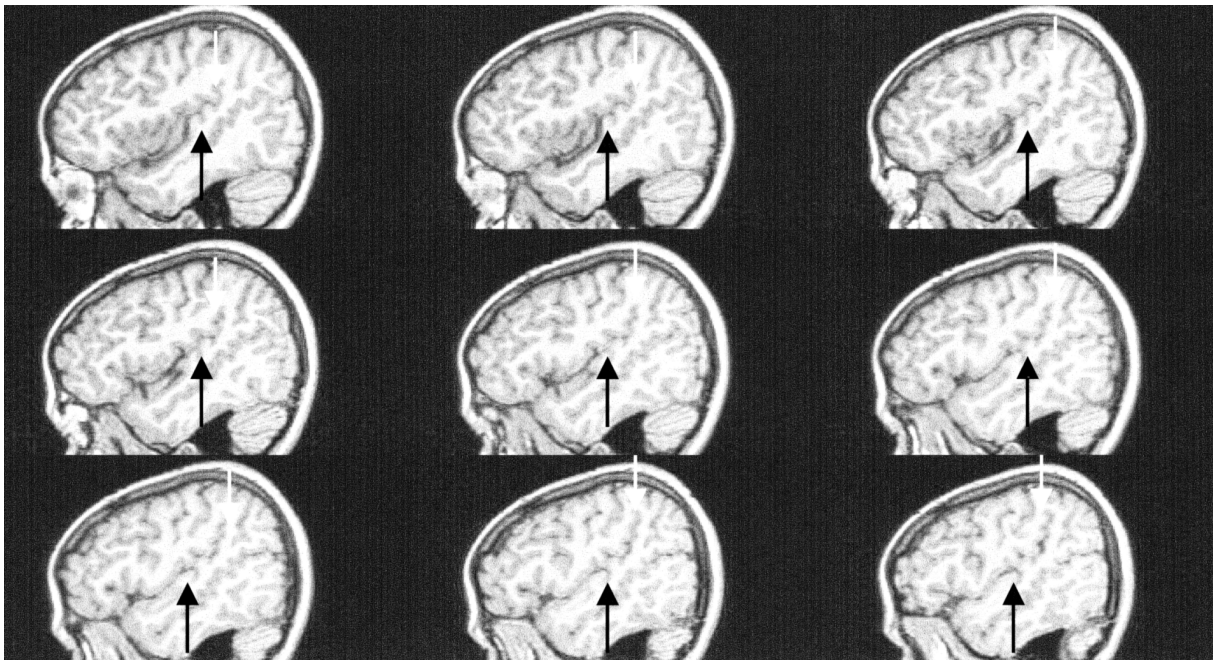


Fig. 4 Absence of the posterior ascending part of the Sylvian fissure. and duplication of Heschl's gyrus in a subject with dyslexia. The black arrow indicates the anterior border of PT and the white arrow indicates the posterior border of PT. Images are shown from medial (above left) to lateral (below right). Reproduced with permission from the Publisher (Heiervang et al, 2000).

From the multitude of results, it follows that more than one brain region is implicated in dyslexia (Leonard et al, 2006) and further brain functional studies are needed to get a more complete overview rather than continuing an endless effort trying to determine even more precise localizations (Eckert et al, 2003).

When considering the gender aspect, since there are about 4-5 times as many boys as girls with dyslexia (Badian, 1999; Heiervang et al, 2000), girls are underrepresented in most MRI studies. A sex difference in brain volume has however previously been reported (Eckert

et al, 2003). A recent study with a large sample (Siegel & Smythe, 2005) found however no significant differences between boys and girls in the incidence of reading difficulties. Similarly, Shaywitz et al. (1998) concluded that male vulnerability for dyslexia was a "myth", and that findings of more boys than girls among dyslexic individuals could be caused by increased incidence of attention and behaviour disorders in boys that would "disguise" as reading difficulties. On the other hand, Liederman et al. (2005) concluded that sex differences indeed do exist, after these authors had reviewing population-based studies that identified children with reading difficulty by objective, unbiased methods, including also studies that examined the gender ratio among affected relatives. Interestingly, there were still more boys than girls with reading difficulties when controlling for ascertainment biases. Differences between the boys and girls regarding incidence of reading difficulties and dyslexia is therefore still an open issue.

## 2.3 Developmental and gender-related morphometry changes

Human development is a complex process of growing to maturity and, closely coupled to this is gender differentiation with implications for brain development and behaviour.

The brain starts to develop in the 6th week of gestation. The neurons do not form in the cortex itself but in the ventricular zone where from they migrate along glial cells, a process that ends in the 24th week of gestation. A process of synapses formation occurs when each neuron extends its axon and dendrites followed by a selective elimination of synapses and neurons that have not been activated by being used. These processes continue during the life-span, even if not so prominently. There are, however, other processes that start to contribute to brain modification such as axon myelination and branching of dendrites. The rates of these changes vary from region to region and also with age, resulting in an intricate structure with complex dynamics (Bear et al, 2001; Marin-Padilla, 1999).

To add even more to the complexity, comparing the anatomical structures between males and females reveals both similarities and differences at all levels of analysis, from cellular to the whole brain architecture. One explanation might be the distribution of steroid receptors while another one is the level of certain neurotransmitters (Davis et al, 1996; Fernández-Guasti et al, 2000; Konradi et al, 1992; Wise, 2002; Wise et al, 2001). For example men have increased neuronal density in several cortical loci compared to women but have reduced density compared to women in the language regions, such as the planum temporale and Wernicke’s area (Jacobs et al, 1993; Rabinowicz et al, 1999; Rabinowicz et al, 2002). At

the macroscopic level, sex differences in GM, WM composition have been confirmed in several studies (Allen et al, 2003; Lenroot et al, 2007; Luders et al, 2006) and there is also decreased asymmetry in the female brain at the level of hemispheres and lobes.

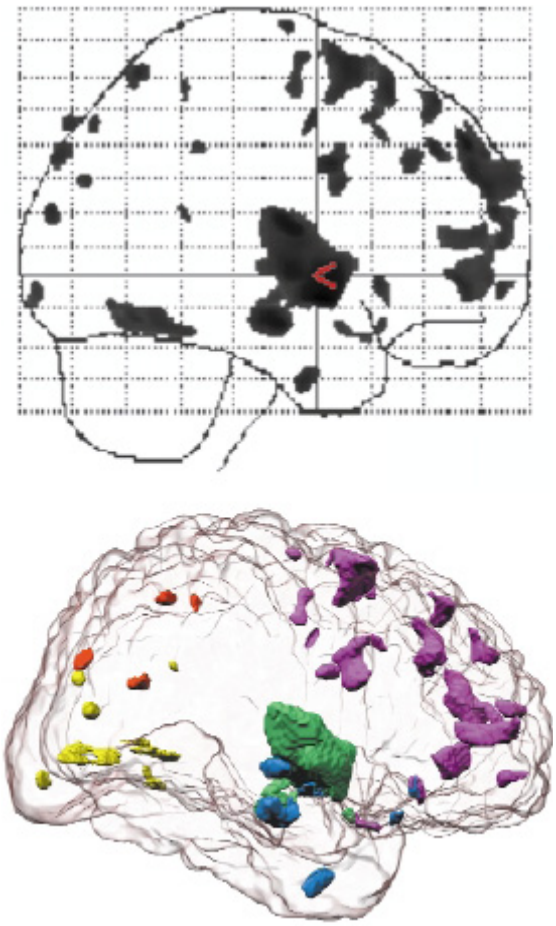


Fig. 5 Areas of significant changes in gray matter, images obtained for adolescents minus images obtained for adults. Clusters are color-coded according to lobe location. Reproduced with permission from the Publisher (Sowell et al, 1999)

The age interval between childhood and adulthood is an important transition for structural changes in GM and WM brain structure that would coincide with brain maturation (Sowell et al, 2007; Sowell et al, 2003; Sowell et al, 1999; Sowell et al, 1999; Sowell et al, 2001; Sowell et al, 2004; Thompson et al, 2005). For example Sowell and colleagues have found in a series of studies significant reduction of GM density from childhood to adolescence (Sowell et al, 1999) and from adolescence to young adulthood (Sowell et al, 1999) shown in Figure 5. On the other hand, from post-mortem studies it is known that cellular changes also occur during development that may underlie structural changes (volumetric or shape changes) that can be observed from MR images. It is known that axonal

myelination continues during childhood and adolescence together with regionally variable synaptic pruning. Interestingly, this age period is often overlooked in developmental studies of brain structure, although it constitutes a critical age period for general maturation and development, with cognitive, emotional and social implications. It is known for example that in children and adolescents the amount of GM in the frontal cortex is related to the cognitive ability (Sowell et al, 2004).

Analyzing brain structure in different stages of age development and in aging might provide a clue to the variation of cognitive performance seen throughout the human life span, not the least changes in cognitive performance seen in elderly individuals. Maturation and aging may be seen as two different processes which occur during the life-span, that are partly overlapping and without a clear demarcation between the two processes (Sowell et al, 2001; Thompson et al, 2005). During adolescence there is both increase of WM and decrease of GM in the frontal and parietal lobes. Increased density of GM in one lobe may be accompanied by a decrease in another lobe, even if the processes might be independent, for example the reduction of GM in the frontal lobe with increase in the temporal lobe (Giedd et al, 1999). This means that there could be regional specificity, as for example an overlapping of various effects in specific regions of the brain during the adolescence.

# 3. The structural complexity of the cortex

## 3.1 Previous research and motivation for the current thesis

### 3.1.1 Circumvolutions - the complex shape of the brain

The circumvolutions of the brain have been a source of both fascination and frustration for researchers. The problem is that the configuration and location of cortical sulci varies between individuals, and accurate and systematic comparisons are difficult to make (Van Essen & Drury, 1997). Even the mechanism behind the formation of circumvolutions is still not understood, with currently three different theories proposed, as reviewed by Rilling and Insel (1999). One possibility is that the folding is necessary to fit the growing cortical sheet into the limited space of the skull, another explanation can be the difference in growth rates between the inner and outer layers of the brain, while others have proposed the mechanical tension along axons as the cause for the cortical sulci and gyri.

Besides the complex geometry of the brain, there are also dynamic aspects to consider with structural changes occurring during the life span, or caused by lesions and/or diseases.

Although there are volumetric changes during development, it is the complexity of the structural architecture that makes the cortex so special, not only the amount of GM and WM. It is therefore reasonable to assume that such changes are best reflected in a shape analysis, or at least that by looking at the interaction of volumetric and shape changes that more can be learned about brain related development, aging and disease.

### 3.1.2 Previous research on brain structural complexity

While classical MRI morphological studies provide a measure of GM and WM volume or density, and of cortical thickness, they do not allow for a quantification of differences between groups and individuals in the cortical surface structure. The problem facing current brain in-vivo imaging techniques is that many organs in the human body, including the brain, have complex geometric structures, e.g. the folding pattern of the cortical sheet. Therefore, they cannot be completely characterized using only measures within classical Euclidean geometry (Mandelbrot, 1977). Such complex geometry can, however, be characterized by its shape properties at different scales, i.e. by fractal geometry. Fractal dimension (FD) provides a way of quantifying the shape complexity of objects into a single numerical value (Fernández & Jelinek, 2001; Mandelbrot, 1977; Russ, 1994).

Soon after the introduction of the notion of the fractal by Mandelbrot (1977), scientists started to apply this concept to many other fields of science, from mathematics to material science and, last but not least biology and medicine, notably the brain with is intricate degree of convolutedness. Thus, to quote the title of a paper by Kiselev et al. : ”Is the brain cortex a fractal?” (Kiselev et al, 2003), most researchers today seem to agree that the answer is "Yes".

There are several possible applications for fractal methods. For example, fractal dimensions could be estimated for the cortical structure of GM (outside border), inner border described by the interface with WM, skeleton of WM (Zhang et al, 2006) or on MR image slices (Free et al, 1996).

So far, the fractal complexity of the brain has been the topic of only a few studies that have been related to development during adulthood (Kiselev et al, 2003), sex differences (Luders et al, 2004) during childhood and adolescence (Blanton et al, 2001), and for the aging brain (Zhang et al, 2007; Zhang et al, 2006). Moreover, Im et al. (2006) found a relationship between the FD and intelligence and education. The FD can, thus, be a useful tool for the characterization of brain structural changes associated with different disorders and diseases and it has been studied in patients with epilepsy (Cook et al, 1995; Free et al, 1996),

obsessive-compulsive disorder (Ha et al, 2005), schizophrenia (Ha et al, 2005; Narr et al, 2004), William's syndrome (Thompson et al, 2005), multiple sclerosis (Esteban et al, 2007), post-stroke in relation to upper-extremity motor function (Zhang et al, 2008), and brain tumours (Uemura et al, 2000; Zook & Iftekharuddin, 2005).

## 3.2 Research questions

Post-mortem studies are difficult to conduct for many reasons as mentioned in the previous sections, thus, it would be advantageous to measure structural irregularities of brain architecture on in-vivo data, using magnetic resonance imaging (MRI). Volume measurements of the GM and WM are an obvious first choice but since sometimes the effects of abnormality and/or other changes are rather subtle, more refined methods such as the FD can provide additional information, particularly for measures of irregularities of the cortical folding.

By applying the fractal methods to schizophrenia, specific differences are expected. For example, it is known that schizophrenia is associated with changes in brain structure, as discussed in section 2.1. The very few previous studies of cortical surface irregularities in patients with schizophrenia have provided contradictory results. While Narr et al. (2004) found higher FD value in patients with schizophrenia compared to healthy controls, Ha et al. (2005) found lower FD value in schizophrenia patients. A possible explanation for this may be that Narr et al. (2004) compared first-episode schizophrenia patients with healthy controls, while Ha et al. compared schizophrenia patients with longer illness duration and they also contrasted the results with FD values obtained in obsessive-compulsive patients. It is therefore still an open question whether schizophrenia involves increased or decreased FD values, and thus increased or decreased irregularities of cortical surface geometry. The first study in the current thesis was therefore an attempt to bring new data to the issue on FD change in patients with schizophrenia by comparing adult patients with an age-matched healthy control group.

Changes in brain structure during the life-span are part of the normal process of development and aging are caused by the interaction of a multitude of factors, as reviewed in section 2.3. There have been studies on the complexity of the brain for different age intervals, but to our knowledge, no studies have focussed on shape complexity in the age interval between adolescence and early adulthood. Since it is known that cognitive performance improves and volumetric changes occur during this period of development, the question is therefore whether these changes are also reflected in alterations of shape complexity. Another

argument for studying this period is the fact that morphological changes are not only associated with age, they also vary according to gender and it would therefore be of interest to analyze such changes both in adolescence and in adulthood. As discussed above in section 2.3, maturation and ageing are two different things, although overlapping processes which occur during life, and it is not always easy to establish a clear border between them (Sowell et al, 2001; Thompson et al, 2005). Since there are known gender-related differences in brain structural development that may be due to hormones, such factors may underlie known gender differences in various disorders and impairments. Many child neuropsychological and psychiatric disorders affect boys more than girls, e.g. dyslexia, ADHD (Attention-Deficit Hyperactivity Disorders), SLI ( Specific Language Impairment), autism and others. A particularly interesting example is dyslexia, where it is known that there are more boys than girls being affected (Duffy & Geschwind, 1985; Heiervang et al, 2000). Since dyslexic individuals differ from age-controlled normal reading individuals in functional brain activation (Shaywitz & Shaywitz, 2005), it would be interesting to investigate if dyslexic boys and girls would differ in terms of both GM and WM volume as well as alterations of the FD value, and if this would affect one hemisphere more than the other (considering that reading and language is a typical left hemisphere functions).

Similarly, an additional question is how to differentiate between normal and abnormal structural changes. For example, how does age-related reduction in GM volume, that occur in normal development compare to similar processes during a disorder, such as schizophrenia? Do such changes manifest in a similar way with regard to shape structure, or are there different pathways and processes? Answers to such questions may thereby put forward the development of new and extended test batteries for a more differentiated diagnosis or even for screening.

# 4. Methods

## 4.1 Analysis of MR images

### 4.1.1 MRI data preprocessing

MRI data pre-processing was done using the software BrainVoyager (BV) QX 1.7.9 (Brain Innovation, Maastricht, the Netherlands). An overview over the processing steps is illustrated in Figure 6. Initially the T1-images were corrected for B1-inhomogeneities using a white matter (WM) pre-segmentation multiplicative method for better definition and

homogeneity of WM and GM. The brain images were then resampled to isotropic 1 $mm^3$ voxels, before being warped into the standardized coordinate system of Talairach and Tournoux (Talairach & Tournoux, 1988).

A second iso-voxel transformation (0.5 $mm^3$) was done in order to improve the accuracy of images using advanced segmentation tools in BVQX. In order to obtain only brain tissue images, the skull was stripped, cerebellum was removed and sub-cortical structures and ventricles were filled. Afterwards, manual corrections were performed in areas where automatic tissue labelling failed.

### 4.1.2 Segmentation and volume measurements

The MR images underwent several iterations of narrow sigma-filtering in order to enhance tissue contrast. Sigma filter is a Gaussian filter that operates within intensity value limits. Thereafter, the tissues were classified into WM, GM or CSF using region growing processes and information of continuity across tissue borders. The information content used in tissue classification ensured higher spatial resolution than voxel-resolution of the image (Fischl et al, 2002). Finally, the hemispheres were splited and all segments were visually inspected for quality of segmentation through superimposition onto the original T1-weighted image. The result was a discretized image with GM at one value and WM at another value.

By summing up the numbers of voxels for each type of tissue, it is also possible to get a separate volume measurement for GM and WM. In addition, the volume ratio of the GM and WM tissue was estimated.

## 4.2 Determination of the fractal dimension (FD)

In general, the estimation of the FD for a real, existing object by a direct application of the FD formulae is not always possible. Natural objects are not regular and they are self-similar only in a statistical sense. Therefore, various methods have been put forward for the determination of the FD, each having its advantages and disadvantages in terms of accuracy or required computation time. In this thesis, two different approaches were used, the box-counting and the Minkowski-Bouligand method. For both methods the segmented GM/WM boundary contour of the whole brain and each of the hemispheres served as input for the estimation of FD.

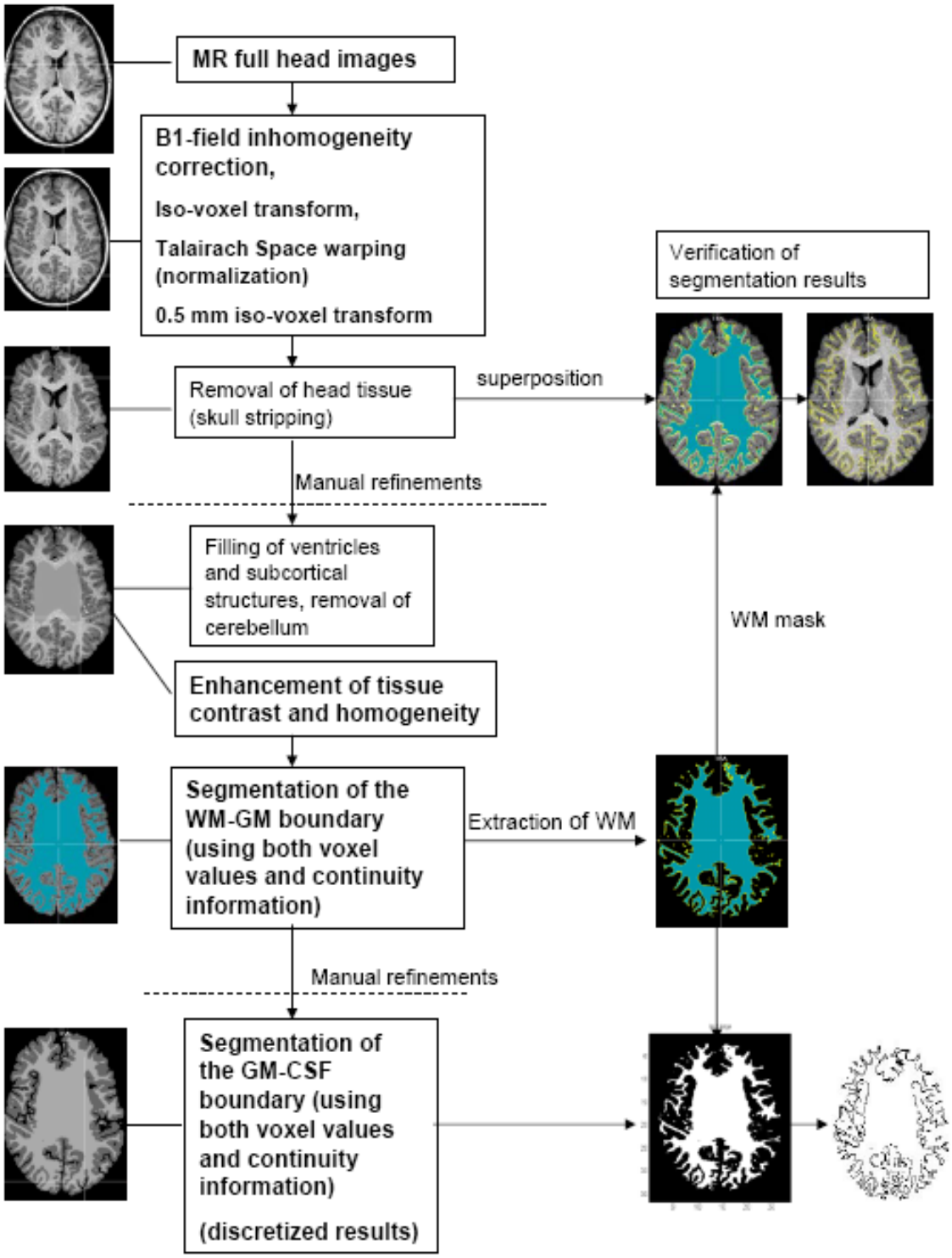



Fig. 6 Flowchart of preprocessing steps applied to the MR images

### 4.2.1 The box-counting method

The most widely used method for determining FD is the box-counting method in which the object to be analyzed is covered with 3D boxes, each of side length ***r***. For each cycle of the procedure, the linear size ***r*** of the boxes is increased. At each scale ***r***, the number of boxes ***N(r)*** that is necessary to cover the whole object structure is then assumed to vary according to $N(r) \sim (1/r)^D$, where ***D*** is the fractal dimension. For non-Euclidean objects, ***D*** is a non-integer number. In effect, the measurement at a given scale will ignore irregularities of the object at a smaller scale. This refers to the fine structure of the fractals; by decreasing the size of "the measuring stick" it is possible to see more details, thus the number of boxes varies in a different way than when dealing with a smooth or Euclidean object.

The process is exemplified in Figure 7a, where a middle transverse slice from one of the subjects participating in a study of this thesis is shown, covered with boxes of increasing size. To analyze the stack of contours representing the GM/WM boundary, the contour was traced with three-dimensional cubic boxes of side length ***r***. A box was counted as a "hit" if at least one voxel of the GM/WM boundary was located within the box. The lateral edges of the boxes were increased by one voxel per iteration, within the range ***r = 3-42*** voxels. The FD was estimated by plotting the logarithm of the number of box "hits", ***log N(r)*** against the logarithm of the box sizes, ***log r***. The absolute value of the slope of a linear regression line was then taken as the FD of the contour.

### 4.2.2 The Minkowski-Bouligand method

A complementary method is the Minkowski-Bouligand method, which uses a similar iterative concept as the box-counting method. Instead of using boxes, this approach uses spheres, which were placed around each voxel of the border resulting in a dilatation of the border, which becomes thicker in each iteration and, thereby, the details disappear after each step. In this case, the fractal dimension ***D*** of the border of the object is given by: $D = M - \log(V)/\log(r)$, where ***V*** is the volume covered by all spheres, ***r*** is the radius of the spheres and ***M*** denotes the dimension of the space in which the fractal is embedded (***M = 3*** in the present case, as the operation was performed on 3D volume data).

In practice, since the system of coordinates of the brain images is Cartesian, approximations of spheres are constructed around the border sites and stored as a mirror image, an additional 3D-array, resulting in an envelope whose volume was calculated. In this

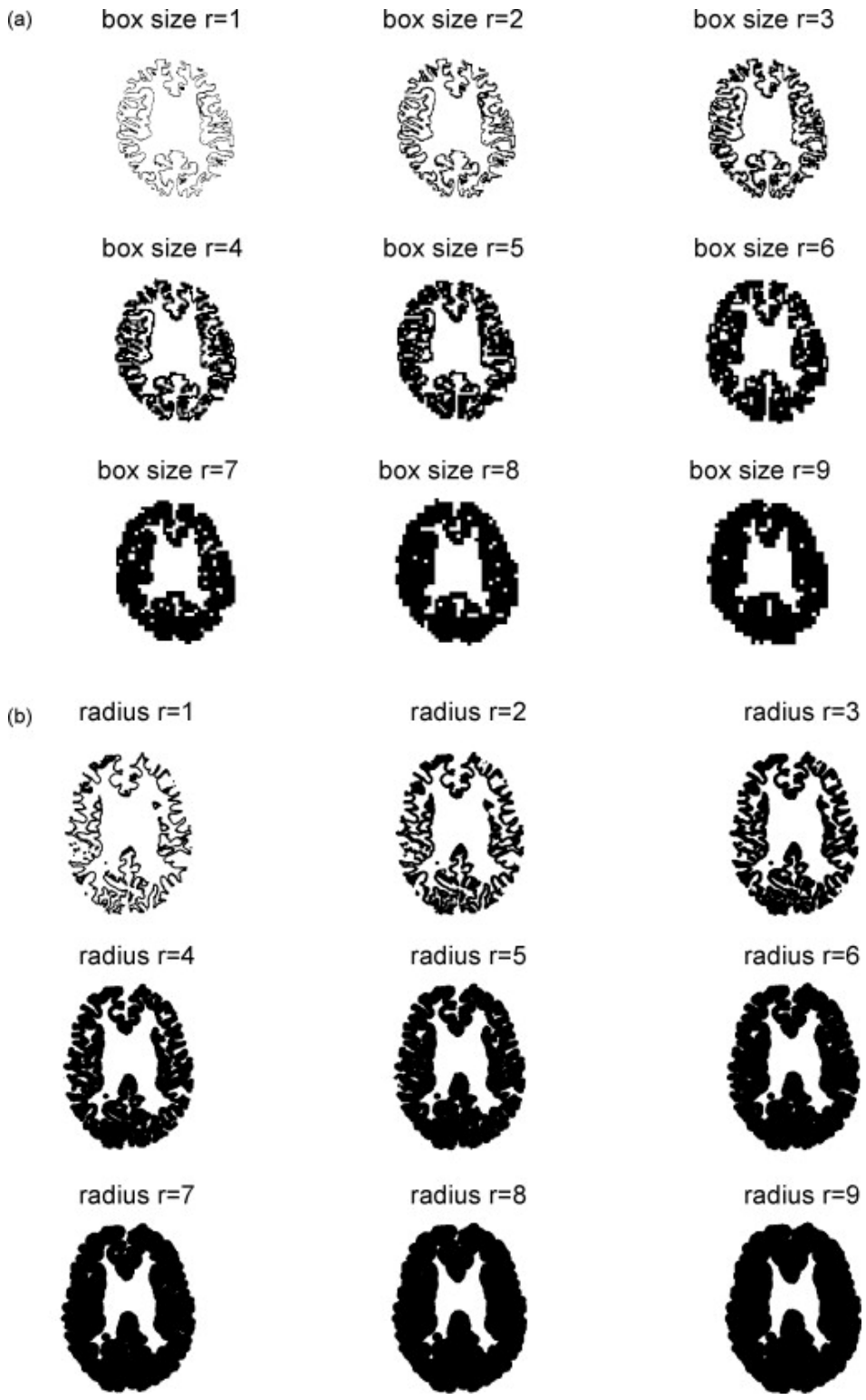



Fig. 7 (a) Illustration of the box-counting method. Successive images of the WM/GM boundary covered with boxes of increasing size. The middle transverse slice of the analyzed brain is extracted after the construction of the boxes on the three-dimensional border of the brain. (b) "Dilatation" of the border as described by the Minkowski–Bouligand method. Spheres of increasing size are constructed around the WM/GM boundary. The middle transverse slice is shown, as in (a).

new array the "spheres" were considered to be the points whose coordinates ***(i',j',k')*** fulfilled the condition $((i-i')^2 + (j-j')^2 + (k-k')^2)^{1/2} < r$, where ***(i,j,k)*** are the coordinates of the initial border point. Inside the spheres, all values of the array are set to 1. The resulting volume is determined by taking the total sum of the mirror image. The radius of the spheres is linearly increased by one voxel per iteration, within a range from $r = 4$ to $r = 20$ voxels. The FD was estimated by plotting the logarithm of the total volume of the spheres against the logarithm of their radius. As in the box-counting method, the slope of a linear regression determines the FD. In Figure 7b the result of this operation can be seen on the middle transverse slice. Notice that apparently the range of scales is different for the two methods, but the linear size of the boxes (***r***) in the box-counting method is equivalent to the diameter of the spheres (2***r***). This can be seen by comparing the figures 7a and 7b, that for different values of ***r*** in the two plots, the number of observable details is similar.

### 4.2.3 Validation of the FD methods

Prior to the analyses, both methods were validated by using digital phantoms with known fractal dimension. These digital phantoms were generated by in-house software, written in Matlab.

The first phantom represented a fractal volume (Fig. 8a) and only the box-counting method could be applied. The theoretical fractal dimension of the first phantom was $FD = \log(7)/\log(2) = 2.8074$ and the estimated fractal dimension was $FD = 2.8050$.

The second phantom was generated with a continuous fractal surface, thus closer to a brain surface (Fig. 8b). The theoretical fractal dimension of its border was $FD = \log(29)/\log(5) = 2.0922$. The estimated fractal dimension using box-counting (box range 1–40) was $FD = 2.0863$, and $FD = 2.1349$ using Minkowski–Bouligand (radius range 2–20).

Note that both phantoms had a regular structure while the brain has a more irregular surface. However, the results are close to the theoretical values, showing the reliability of the methods applied in the thesis.

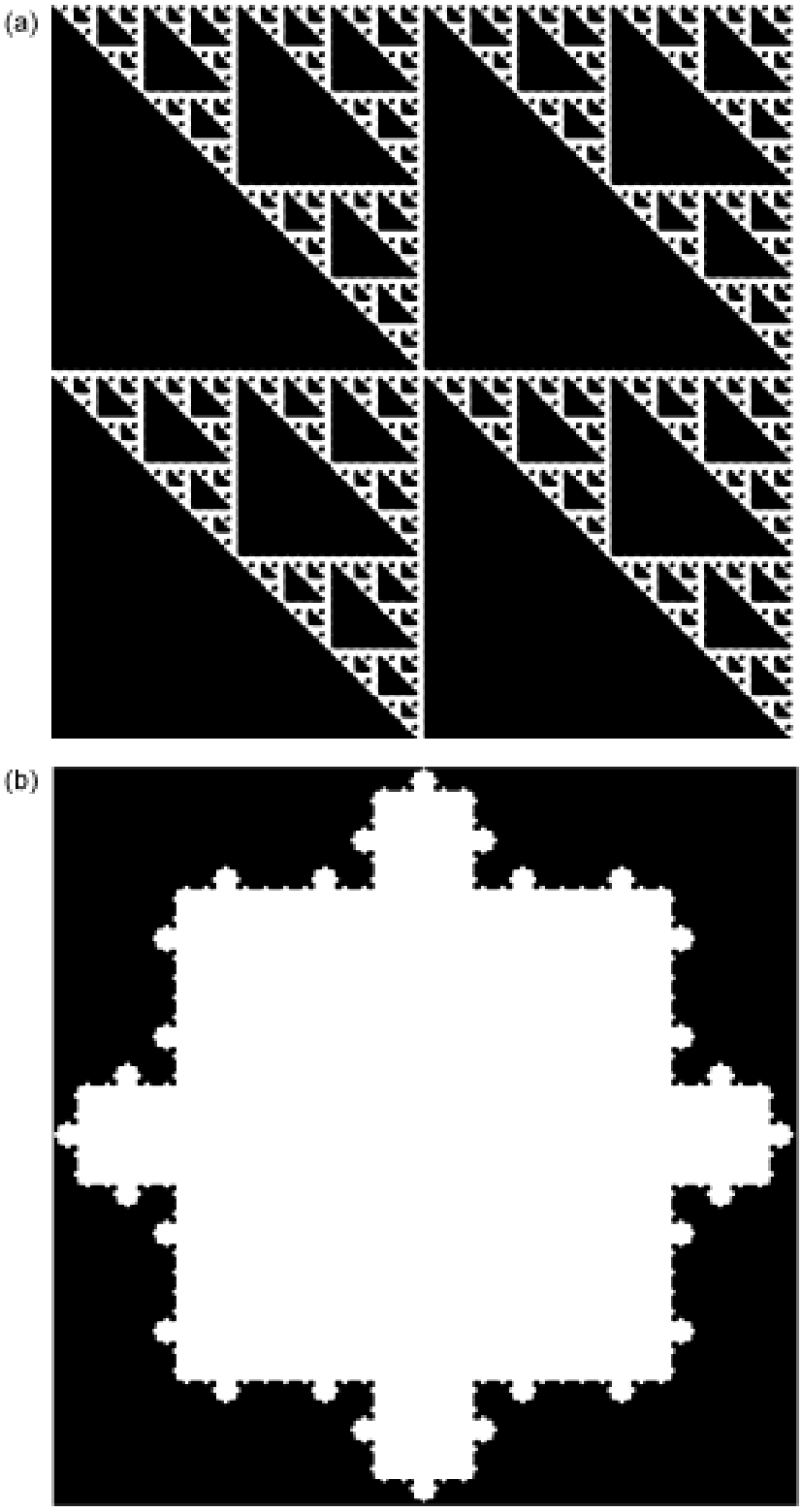



Fig. 8 Fractal phantoms used for the verification of our software (a) FD = log(7)/log(2) = 2.8074 and (b) FD = log(29)/log(5) = 2.0922.

# 5. Summary of the papers

## 5.1 Paper 1

The first study deals with two main aspects. First, it validated the developed methods for measuring the fractal dimension and, second, it applied the method for exploring abnormalities in the cortical folding in patients with schizophrenia compared to a healthy control group. In order to reveal structural anomalies not observed with traditional MRI morphometry methods, the FD was used. The estimation of FD provides a way of quantifying the shape complexity of objects into a single numerical value, which can be compared between groups of subjects.

After validating the method with digital phantoms, where the FD was known beforehand, the method was applied to the patient and control subject data. Thereby, the FD was calculated from MR images obtained from seven subjects with schizophrenia and six healthy control subjects. All subjects were scanned with a 3D FLASH pulse sequence on a 1.5T MR scanner (Siemens Vision). The DICOM images were first manually segmented into WM and GM sections using the BrainVoyager QX 1.7.9 software (Brain Innovation, Maastricht, the Netherlands). The pre-processed data then served as input for the calculation of the FD, which was computed with in-house software written in Matlab R2006a.

Both the box-counting and Minkowski–Boulingand methods revealed significant differences between the patient and healthy control groups. The estimation of FD was done for the whole brain (WB) volume as well as for the right hemisphere (RH) and left hemisphere (LH) separately. The results showed that patients with schizophrenia had significantly larger FD values than healthy control subjects for the WB volume and the RH, which indicates the existence of significant differences between the groups in architectural anomalies of the cortical foldings. The results are in agreement with other studies using MR morphometry methods as well as with the Narr et al. (2004) FD study showing that the right prefrontal cortex may be abnormal in patients with schizophrenia. This could be an underlying correlate of observed cognitive impairments and clinical symptoms.

## 5.2 Paper 2

In the second study, brain cortical irregularities in adolescent subjects with dyslexia were explored by combining GM and WM volume measurements, their ratio and the FD of the GM/WM border.

The data were collected from 13 dyslexic adolescent (8 boys and 5 girls) that were compared with 18 control subjects (8 boys and 10 girls). The pre-procesing of the data and the estimation of the FD followed the approach from the first paper, but only the box-counting method was applied. In short, MR images were first segmented, and the volume as well as the FD of the GM/WM border for the WB and for each hemisphere was calculated.

In addition to comparing dyslexia with control subjects, boys were compared with girls within each of the dyslexia and control group. The GM volume analysis showed that the control girls had significantly larger GM volume compared to the control boys, for the WB, while there was no significant sex-difference for the dyslexia group. The control girls also had increased GM volume in the RH compared to the dyslexia girls.

For the WM volume, significant differences were found for the WB, LH and RH measurements, with the dyslexia boys having increased WM volume compared to the dyslexia girls. No significant sex differences were found for the WM volume for the control group. There was however a tendency in the same direction as for the dyslexia group. In addition, significant group differences were found between the dyslexia and control girls, with reduced WM volume for all three measures for the dyslexia girls. No significant differences were found for the boys.

For the GM/WM ratio there were significant sex differences for all three measurements, for both groups. In addition, dyslexia girls showed significantly increased GM/WM ratio in the LH compared to the control girls.

The FD results showed a significant difference between the dyslexia and control girls for the LH measurement, with higher FD for the dyslexia girls.

The changes found in the measured volumes of both GM and WM reflected in the ratio of GM/WM and in the FD values, especially in the LH, suggest that brain structural abnormalities are associated with problems to learn to read. The brain morphometry changes were more marked for the dyslexia girls. From a developmental perspective there are two possible interpretations of the sex differences: 1) changes in brain morphometry should be more extensive in girls before they develop dyslexia, 2) girls show dyslexia symptoms later during development than boys, when the anatomical changes already have occurred. Thus, although dyslexia is less frequent in girls, the structural differences in the brain are more pronounced in their case, pointing to an increased vulnerability of the female brain to morphological changes associated with dyslexia.

## 5.3 Paper 3

The objective of the third study was to investigate age effects in brain structural development, focusing on adolescents and young adults. The volumes of GM, WM, the GM/WM ratio and the FD of gyri and sulci irregularities were calculated and used to assess sex-related differences between adolescents and adults.

MR images were used to acquire data on GM and WM volume as well as for the FD calculations. The study involved 18 adolescents (mean age 13.8 years) which were compared with 14 adults (mean age 23.7 years) for measures of WB volume and of each hemisphere separately.

The adolescent group had higher values for GM volume than the adult group, for all three measures (WB, RH and LH) and for both males and females, although more accentuated in the female case, and the girls had a significantly larger GM volume than the boys. There was an increase in WM volume in the adults compared with the adolescents, which was significant for the males, but not for the females.

When considering the GM/WM ratio, there was a significant difference between adults and adolescents, with the adults having a smaller ratio than the adolescents. The GM/WM ratio was also higher in the girls than in the boys. Thus, the GM/WM ratio can also be taken as a measure of developmental sex differences in the adolescent brain.

With regard to the FD measure a significant difference was found in the adolescent group, where the boys had a higher FD value than the girls.

The changes in brain structure were more pronounced in the RH, and in the females when comparing adolescents and adults. The results indicate a maturational effect with the RH leading the LH, and with young adolescent females showing GM and WM differentiation earlier than their male counterparts. Similar results were found for the FD, which indicates a sex difference also for brain shape complexity.

# 6. Discussion

## 6.1 General discussion

The novelty of these studies comes from the association between volumetric and structural complexity and irregularity measurements of the brain. Volumetric changes of two parameters, GM and WM respectively, which are intertwined to each other, are usually associated with changes of the shape of the brain, especially at the boundary between GM and WM. The questions are what would be the best way of describing those changes and what is the explanation for such changes. In this thesis, the focus lies on the changes during development, more precisely between adolescence and adulthood, as well as the changes associated with dyslexia and schizophrenia. The developmental aspect is further supplemented by including also sex differences.

Even though the fractal methods have been applied to previous studies on schizophrenia by other authors (e.g. Narr et al, 2004, Ha et al, 2005), the present thesis has contributed to sorting out some of the inconsistencies in previous findings. In addition, in the schizophrenia study, the focus was also achieving better FD reliability by using two different methods for calculations of cortical complexity. While the box-counting method had been used by other authors, the Minkowski-Bouligand method was applied for the first time in MR brain images. The results obtained with both methods were similar, underlining the robustness of the computations, and indirectly validating the FD measure for use in clinical populations. The fractal method was for the first time applied for exploring anatomical differences, associated with dyslexia and for studying the brain structural changes during the developments from adolescence to adulthood.

### 6.1.1 Whole brain and hemisphere regions

Morphometric changes in the brain can be manifest globally or can be localized to specific brain regions. In the case of developmental studies, it is reasonable to assume that the WB volume changes with age. A review of structural modifications occurring during the life span, including different methods ranging from post-mortem to in-vivo studies, is provided by Sowell et al. (2004). Gender-related differences, most likely due to exposure to gonadal hormones, are also spread in the WB (Goldstein et al, 2001; Neufang et al, 2008) and manifest from an early age in GM and WM, CSF, cortical thickness and convolution of the cortical surface (Luders et al, 2004; Luders et al, 2006). For example, it is known that girls are more

mature than boys of the same age, and it has been found that girls reach a fully developed brain about two years earlier than boys (Lenroot et al, 2007). However, the changes being present at the level of the WB do not imply that region-specific modifications do not occur, as e.g. in the two hemispheres, or in specific cortical lobes. The results presented in this thesis show that developmental changes in the GM and WM manifest at the level of hemispheres and that they are gender specific.

Another example of structural changes, which are present in the whole brain, is for individuals with dyslexia. It is well-known that several brain regions are implicated in dyslexia, as reviewed by Leonard et al. ( 2006). The post-mortem study of Galaburda et al. (1985) equally found anomalies such as increased incidence of polymicrogyria, molecular layer ectopias, and focal architectonic dysplasia distributed all over the brain (see also Galaburda & Kemper, 1979). It is therefore difficult, if not impossible, to pinpoint a single region of the brain whose malfunctioning would lead to dyslexia (Eckert et al, 2003; see also Hugdahl et al, 2003).

This does not preclude, however, that the functional implications of structural anomalies may be more serious in certain regions than in other regions. It is reasonable to consider left temporal lobe anomalies to have more serious functional consequences since the core deficits in dyslexia are related to problems with phonological decoding of single words and finding the phonological correspondence to a visual orthographic input (Stanovich, 1988; Vellutino et al, 2004). On the other hand, the complex relationship between brain structural and functional anomalies should not be underestimated by focusing only on a single brain region.

The dyslexia study in the present thesis showed that structural modifications in dyslexic individuals can already be detected at the level of the WB and the hemispheres. In addition, a comparison between the control and dyslexic group split for gender showed that although dyslexia is less frequent in girls, the structural differences in the brain were more pronounced in this sub-group, pointing to an increased vulnerability of the female brain to morphological changes associated with dyslexia. This finding is of particular interest since, due to the relative low frequency of dyslexia in girls compared to boys (Badian, 1999; Heiervang et al, 2000), they are underrepresented in most studies, see however (Eckert et al, 2003).

In case of schizophrenia, the observed morphometric changes were much more localized, as it is discussed above. It was found that patients with schizophrenia showed larger irregularities, although the effect was to a large extend driven by right hemisphere difference.

The results are confirmed by the study by Narr et al. (2004). The fact that the changes were more pronounced in the RH points to the importance of analyzing regions of interest, rather than the WB volume border. This may be especially important when comparing patients with schizophrenia and healthy controls, since it could be predicted that the patients may show regional abnormalities, related to e.g. negative or positive symptoms that would not show up in a whole brain volume analysis.

### 6.1.2 Grey matter and white matter volume

A greater amount of GM is generally associated with increased number of neurons but, rather counterintuitively, whether this means increased performance is still an open question. More neurons could on the one hand offer increased capacity for processing capacity, but on the other hand it might be the increased connectivity between them that leads to improved processing and performance.

Changes in GM volume are part of the normal development. There is an increase of GM volume that continues throughout childhood, with a peak in early or late adolescence and continuously decreasing afterwards, documented by previous studies (Giedd et al, 1999; Lenroot et al, 2007; Sowell et al, 1999; Sowell et al, 2004; Thompson et al, 2005). However, longitudinal studies show the heterochronous nature of brain development, in which the different lobes develop at different rates (Giedd et al, 1999; Sowell et al, 2005). Even if this happens at different time points during the development, the critical development is expected to take place during childhood or adolescence and most of the regions are supposed to have surpassed the main peak of development in adulthood.

For the age range considered in the third study, the adolescent group had higher values for GM volume than the adult group, for all three measures (WB, RH and LH) and for both sexes, although more accentuated in the female case. Summarizing several studies, based on a variety of techniques, such as post-mortem studies, electrophysiological, and positron-emission tomography (PET), Sowell et al. (1999) suggested that the neurophysiological mechanism behind this decrease in GM volume in adults is an increase in neuronal myelination and synaptic pruning, changes that predominate in the cortical neutrophil during childhood and adolescence, which also would play a role in the cognitive development (Sowell et al, 2004). A sex difference was observed in the adolescent group, where the girls had a significantly greater GM volume than the boys. This is in agreement with the results from a longitudinal study by Lenroot et al. (2007) that girls are more mature than boys of the

same age. In addition, a comparison between the control and dyslexic groups according to gender showed a significant difference for the girls in the RH. The control girls had a significantly larger GM volume than the dyslexia girls, which could lead to reduced brain asymmetry known to exist in dyslexia.

GM and WM changes can have different causes, for example a GM volume decrease, could be accompanied by an increase in WM volume in the adults compared with the adolescents, which was significant in males for WB volume but not observed to the same extent in females. These results are supported by other findings (Giedd et al, 1999; Schmithorst et al, 2008; Sowell et al, 2003; Sowell et al, 2004) and could be explained by myelination and axonal arborisation (Lenroot et al, 2007; Sowell et al, 2001).

Another significant difference in the control group was between males and females for the WB measurements, males having more WM than females (Allen et al, 2003). Gur et al. (1999) have suggested that the less WM and the higher relative GM composition of females' brain may compensate for smaller cranial volume, by devoting more of the available space to "computation" than to "information transfer".

The gender difference in the WM measurements were more marked in the study of the dyslexia group and the sex differences were present for all three measurements (WB, LH, RH) with the dyslexia girls also showing significantly reduced WM volume compared to control girls. The question that arises then is if in dyslexia axonal connections are also lost, at least for dyslexic girls, since they have already less WM than both control girls and dyslexia boys. This might indicate that these changes are perhaps more severe in their case, as discussed earlier.

Regarding the changes in WM in schizophrenia, there are studies that report a reduction (Breier et al, 1992), while others have reported a relative WM increase (Hazlett et al, 2008). One study which attempts to explain the formation of cortical convolutions through axonal tension suggests that changes in brain shape in developmental diseases, such as schizophrenia may result from changes in the connections (Hilgetag & Barbas, 2006), thus even if the WM volume could have different evolutions in schizophrenia, it seems to play an important role for brain shape.

### 6.1.3 Grey matter/white matter - volumetric ratio and border complexity

In view of the results obtained for the GM and WM separately, it might seem like a good idea to use measures that would take into account differences in both. Apart from the

GM/WM ratio, another option is the FD, which quantifies in more detail convolution of the GM/WM border. Volumetric changes are causing both changes in the GM/WM ratio and at the same time changes of the shape of the brain or tissue borders, thus, it could be expected to find a significant difference in the FD as well.

The GM/WM ratio in combination with the FD measure are robust measures for the characterization of development and gender related differences. For example, adults have a significantly smaller ratio than adolescents, which is expected since the GM is decreasing with age and the WM is increasing between adolescence and adulthood, more pronounced for males. The largest developmental differences were seen in the RH for the comparison between girls and women. Looking at the corresponding FD measurements, the adults seem to have a smaller FD values than the adolescents, even though the difference was not significant except for the RH when women are compared with girls. This is where also the largest difference for the GM/WM ratio appeared supporting the FD findings.

The sex differences were present in the adolescent group in all three measures for the WB, LH and RH, girls having a higher ratio than the boys. The same tendency was observable in the adult group, but the differences were not significant. For the WB as well as for the separate hemispheres, the GM/WM ratio was consistently higher in the girls than in the boys, which is in line with other studies (Allen et al, 2003; Goldstein et al, 2001; Gur et al, 1999). This is in accordance with the fact that boys had a higher FD than the girls.

It should be noted that the fractal complexity of the brain between adolescence and adulthood seems not to have been studied before, even though Sowell (1999) mentions that during the post-adolescence the density of GM is reduced in many regions of the brain, registering one of the biggest losses during the life span. There are, however, studies on other age intervals, such as between adults and elder people by Zhang (2006, 2007), where the FD was found to be decreased, or between the age 6 and 16 years by Blanton et al. (2001) where the FD was increased.

As mentioned earlier, the most prominent differences between adolescence and adulthood in ratio and FD were found in the RH in females. From a holistic perspective, the functions of the RH include simultaneously processing of multi-sensory input, visual and spatial skills and memory is stored for auditory, visual and spatial modalities. Thus a question arises, if the structural changes in the RH also have a functional counterpart.

The link between structure and function could be assessed in the dyslexia case but the chain of reasoning is rather inversed since the symptoms are known and we are looking for the structural differences.

The sex difference seen in the GM/WM ratio in controls was less pronounced in the dyslexia group. Looking at the comparison between the control subjects and dyslexia group, a significant difference in the GM/WM ratio was found, again for the dyslexic girls although only for the LH measurement. This effect was mainly caused by the fact that the LH demonstrated only significant differences for the WM, while the RH differed in both GM and WM which kept the ratio constant. In the LH also the FD was found to be significantly different between dyslexia and control girls.

The increased FD observed in patients with schizophrenia, for the WB and the RH, is most likely due to the loss of brain tissue, resulting in a shrinking of the surface with an increase in cortical microfoldings (as the volume is reduced). Another possible interpretation takes into account the origin of cortical convolutions, which might be the result of mechanical axonal tension (Hilgetag & Barbas, 2006). If it is accepted that schizophrenia is of a neurodevelopmental origin, the changes in connectivity will result in modifications of brain shape.

While the origin of the changes might be still unsolved, the results presented in the thesis are supported by the findings by Narr et al. (2004), who reported significant increases in cortical folding in the right superior frontal cortex in their male schizophrenic patients using FD and other morphometric measures; these results further suggest that male patients may be more vulnerable than female patients. The small sample size in the present study precluded however statistical assessment according to gender but the male patients had higher FD for all three measures.

### 6.1.4 Attempt at explanation

The reduction of GM between adolescence and adulthood most likely reflects myelination in peripheral regions of the cortex that may improve cognitive processing in adulthood. The findings from post mortem (Thompson et al, 1996) and in-vivo studies (Sowell et al, 2004) are supporting this hypothesis when focusing on regions of the frontal cortex. The findings from the developmental study, i.e. a significant reduction of GM, lead to the same interpretation, even though the reduction of GM was a global finding at the level of the WB. The frontal lobes being the largest in the brain, the developmental changes that occurred inside would lead to the same results for the WB. The frontal lobes are essential for many cognitive functions, which continue to develop between adolescence and young adulthood, such as response inhibition, emotional regulation, planning and organization

(Sowell et al, 1999). Beside myelination, the competitive elimination of neurons and dendritic and axonal arborization during development could contribute to the reduction of GM and increasing of WM. Significant remodelling of grey and white matter continues into the third decade of life, something that could not be fully appreciated until the MRI studies focused on them (Lenroot & Giedd, 2006).

There are studies which cover a broader age range, from late adolescence to old age, which describe a flattening and opening up of sulci with increasing age; in the meantime gyral crowns become narrower and sharper (Magnotta et al, 1999). Again, the question arises about the precise moment when development (e.g. pruning or activity-dependent changes) turns into a degenerative process. This is further complicated by the fact that in the human brain changes in gyral and sulcal shape occur during aging while the gyrification pattern seems conserved. Actually, the very origin of gyrification patterns is a question in itself.

Concluding, the neuronal pruning, the axonal and dendritic arborization and myelinization are also responsible for the reduction of the GM and the border between GM and WM becomes smoother in the adult case than in the adolescent one. A potential explanation is that the cranial box became bigger with aging.

Another aim of the thesis was to study dyslexic adolescents, where sex differences in the volumes of GM and WM were also present, with dyslexic girls being more affected than boys. From a developmental perspective there are two possible interpretations: first, the observed changes in brain morphometry are more extensive in girls before they develop dyslexia, or, second, girls show dyslexic symptoms later during development than boys, when the anatomical changes already have occurred. The GM/WM ratio and the FD confirmed once more that brain structural changes in dyslexic girls are more severe than in boys. Moreover, the stronger effects for the LH measures are supported by the findings of the post-mortem studies by Galaburda, see Galaburda and Aboitz (1986) for review. It may be of importance in this context that Humphreys et al. (1990) reported similar anomalies in post-mortem examination of three female dyslexic brains as found in male brains. These anomalies included increased incidence of brain warts, molecular layer ectopias, and focal architectonic dysplasia. Since brain warts and ectopias typically would affect microgyral regularities, the present findings of higher FD value in the dyslexic girls would be expected. Again, the overlap in the findings in the Humphreys et al. (1999) study and the present study may point to a more biologically founded reading disability in the girls. The argument is that dyslexic girls may have a biological vulnerability to a higher degree than dyslexic boys, and that the

additional measurements such as the GM/WM ratio or the FD may be a marker of such a vulnerability.

In the schizophrenia study, in-vivo neuroimaging studies corroborated with the results from post-mortem analyses provide evidence of structural irregularities; Vogeley et al. (2000; 2001) argue that the volumetric measurements only do not provide information about the mechanisms behind these changes. They assumed that a dys-connectivity syndrome in fronto-temporolimbic circuits may be one of the factors causing the structural brain abnormalities observed in schizophrenia, and our findings of increased gyrification complexity in the right hemisphere are in agreement with their hypothesis.

Among the mechanisms proposed for the abnormalities in gyrification (hypergyria) observed in schizophrenia are differences in growth "pressure" between cytoarchitectonic layers in the neocortex, differences in mechanical tension along axons, dendrites, or differences in glial processes connecting different brain regions (Hilgetag & Barbas, 2006) The patients with schizophrenia present abnormalities of gyrification and might be expected to have abnormalities of functional neural connectivity that could be demonstrated with fMRI.

## 6.2 Future research

Apart from the application of combined volumetric and FD measures on larger samples, there are numerous other perspectives, which can arise from the results of the present work.

Going beyond the hemispheres to the level of the lobes is one of them. In spite of the intrinsic limitations of the FD measure, discussed in the Methods section (chapter 4.2), which do not allow the application to arbitrarily small regions of interest, computing the fractal dimension of the lobes should be still feasible.

Another important way to follow is the application of the battery of measures developed in this thesis, fractal measures included, to the analysis of other diseases or impairments such as the Alzheimer's disease.

The relation between structure and function is an important aspect of brain research. Thus, studies on structural and functional parameters in the same sample of subjects are at the same time promising and challenging. Coupled with functional MRI studies of reduced neuronal activation in the same brain areas, a picture emerges that indicates anatomical correlates to neurocognitive impairment in schizophrenia.

When considering schizophrenia, in view of our first results, the analysis at various stages of the disease, for example first-episode schizophrenia, or maybe in the form of a longitudinal study, would allow a more precise description of the course of the illness. Clues could be found to the lasting question whether schizophrenia is indeed of neurodegenerative origin or not.

A longitudinal study would equally be of interest in the dyslexia case since it could help answering the question if the present sex differences should be interpreted as changes in brain morphometry being more extensive in girls before they develop dyslexia or if girls show dyslexic symptoms later during development than boys, when the anatomical changes already have occurred.

The use of multiple imaging methods for the characterization of the brain, including also measures of shape irregularity, like the FD in various studies such as on patients, children with dyslexia and during development seem to point to different mechanisms for the structural changes observed.

This is of particular importance, since of course, the ultimate goal in the development of fractal analysis methods, together with the classical voxel-based morphometry methods, would be to develop a screening method, sensitive enough for early diagnostic examinations of the impairments that affect the human brain, giving the possibility to prevent the clinical manifestation.

## 6.3 Conclusions

The main contribution of the present thesis to the field of neuroimaging is that it demonstrates the importance of shape characterization when analyzing the human brain. The fractal dimension, which allows the quantification of the shape irregularity and thus comparisons between subjects is useful not only as an independent method but it allows the extraction of more information even from a classical technique such as volume measurement and GM/WM ratio using for example Voxel Based Morphometry (VBM).

Special attention was given to the validation of the FD measure by use of phantoms as well as by the use of two different methods. The robustness of the method was further verified by comparing data from different scanners.

While the reduction of GM is usually considered to be accompanied by a corresponding increase of the FD (meaning a more irregular cortical structure), as in schizophrenia and dyslexia, in the developmental case the GM reduction was accompanied by

a decrease of FD. With the possibility of two different mechanisms for the GM reduction, a physiological mechanism resulting in a smoother surface and a pathological mechanism leading to increased irregularities, using multiple measures for the characterization of structural changes in the brain would be necessary.

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# Doctoral Theses at The Faculty of Psychology, University of Bergen

| | | |
|---|---|---|
| **1980** | Allen, H.M., Dr. philos. | Parent-offspring interactions in willow grouse (Lagopus L. Lagopus). |
| **1981** | Myhrer, T., Dr. philos. | Behavioral Studies after selective disruption of hippocampal inputs in albino rats. |
| **1982** | Svebak, S., Dr. philos. | The significance of motivation for task-induced tonic physiological changes. |
| **1983** | Myhre, G., Dr. philos. | The Biopsychology of behavior in captive Willow ptarmigan. |
| | Eide, R., Dr. philos. | PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway. |
| | Værnes, R.J., Dr. philos. | Neuropsychological effects of diving. |
| **1984** | Kolstad, A., Dr. philos. | Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge. |
| | Løberg, T., Dr. philos. | Neuropsychological assessment in alcohol dependence. |
| **1985** | Hellesnes, T., Dr. philos. | Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring. |
| | Håland, W., Dr. philos. | Psykoterapi: relasjon, utviklingsprosess og effekt. |
| **1986** | Hagtvet, K.A., Dr. philos. | The construct of test anxiety: Conceptual and methodological issues. |
| | Jellestad, F.K., Dr. philos. | Effects of neuron specific amygdala lesions on fear-motivated behavior in rats. |
| **1987** | Aarø, L.E., Dr. philos. | Health behaviour and sosioeconomic Status. A survey among the adult population in Norway. |
| | Underlid, K., Dr. philos. | Arbeidsløyse i psykososialt perspektiv. |
| | Laberg, J.C., Dr. philos. | Expectancy and classical conditioning in alcoholics' craving. |
| | Vollmer, F.C., Dr. philos. | Essays on explanation in psychology. |
| | Ellertsen, B., Dr. philos. | Migraine and tension headache: Psychophysiology, personality and therapy. |
| **1988** | Kaufmann, A., Dr. philos. | Antisosial atferd hos ungdom. En studie av psykologiske determinanter. |

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| | Mykletun, R.J., Dr. philos. | Teacher stress: personality, work-load and health. |
| | Havik, O.E., Dr. philos. | After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness. |
| **1989** | Bråten, S., Dr. philos. | Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier. |
| | Wold, B., Dr. psychol. | Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents. |
| **1990** | Flaten, M.A., Dr. psychol. | The role of habituation and learning in reflex modification. |
| **1991** | Alsaker, F.D., Dr. philos. | Global negative self-evaluations in early adolescence. |
| | Kraft, P., Dr. philos. | AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour. |
| | Endresen, I.M., Dr. philos. | Psychoimmuniological stress markers in working life. |
| | Faleide, A.O., Dr. philos. | Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems. |
| **1992** | Dalen, K., Dr. philos. | Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach. |
| | Bø, I.B., Dr. philos. | Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk. |
| | Nivison, M.E., Dr. philos. | The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors. |
| | Torgersen, A.M., Dr. philos. | Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence. |
| **1993** | Larsen, S., Dr. philos. | Cultural background and problem drinking. |
| | Nordhus, I.H., Dr. philos. | Family caregiving. A community psychological study with special emphasis on clinical interventions. |
| | Thuen, F., Dr. psychol. | Accident-related behaviour among children and young adolescents: Prediction and prevention. |
| | Solheim, R., Dr. philos. | Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk. |
| | Johnsen, B.H., Dr. psychol. | Brain assymetry and facial emotional expressions: Conditioning experiments. |
| **1994** | Tønnessen, F.E., Dr. philos. | The etiology of Dyslexia. |
| | Kvale, G., Dr. psychol. | Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy. |
| | Asbjørnsen, A.E., Dr. psychol. | Structural and dynamic factors in dichotic listening: An interactional model. |

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| | Bru, E., Dr. philos. | The role of psychological factors in neck, shoulder and low back pain among female hospitale staff. |
| | Braathen, E.T., Dr. psychol. | Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG. |
| | Johannessen, B.F., Dr. philos. | Det flytende kjønnet. Om lederskap, politikk og identitet. |
| **1995** | Sam, D.L., Dr. psychol. | Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation. |
| | Bjaalid, I.-K., Dr. philos | Component processes in word recognition. |
| | Martinsen, Ø., Dr. philos. | Cognitive style and insight. |
| | Nordby, H., Dr. philos. | Processing of auditory deviant events: Mismatch negativity of event-related brain potentials. |
| | Raaheim, A., Dr. philos. | Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications. |
| | Seltzer, W.J., Dr.philos. | Studies of Psychocultural Approach to Families in Therapy. |
| | Brun, W., Dr.philos. | Subjective conceptions of uncertainty and risk. |
| | Aas, H.N., Dr. psychol. | Alcohol expectancies and socialization: Adolescents learning to drink. |
| | Bjørkly, S., Dr. psychol. | Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients |
| **1996** | Anderssen, N., Dr. psychol. | Physical activity of young people in a health perspective: Stability, change and social influences. |
| | Sandal, Gro Mjeldheim, Dr. psychol. | Coping in extreme environments: The role of personality. |
| | Strumse, Einar, Dr. philos. | The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway. |
| | Hestad, Knut, Dr. philos. | Neuropsychological deficits in HIV-1 infection. |
| | Lugoe, L.Wycliffe, Dr. philos. | Prediction of Tanzanian students' HIV risk and preventive behaviours |
| | Sandvik, B. Gunnhild, Dr. philos. | Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning |
| | Lie, Gro Therese, Dr. psychol. | The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania |
| | Øygard, Lisbet, Dr. philos. | Health behaviors among young adults. A psychological and sociological approach |
| | Stormark, Kjell Morten, Dr. psychol. | Emotional modulation of selective attention: Experimental and clinical evidence. |
| | Einarsen, Ståle, Dr. psychol. | Bullying and harassment at work: epidemiological and psychosocial aspects. |

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| **1997** | Knivsberg, Ann-Mari, Dr. philos. | Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation. |
| | Eide, Arne H., Dr. philos. | Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students. |
| | Sørensen, Marit, Dr. philos. | The psychology of initiating and maintaining exercise and diet behaviour. |
| | Skjæveland, Oddvar, Dr. psychol. | Relationships between spatial-physical neighborhood attributes and social relations among neighbors. |
| | Zewdie, Teka, Dr. philos. | Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs. |
| | Wilhelmsen, Britt Unni, Dr. philos. | Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents. |
| | Manger, Terje, Dr. philos. | Gender differences in mathematical achievement among Norwegian elementary school students. |
| **1998** | | |
| V | Lindstrøm, Torill Christine, Dr. philos. | «Good Grief»: Adapting to Bereavement. |
| | Skogstad, Anders, Dr. philos. | Effects of leadership behaviour on job satisfaction, health and efficiency. |
| | Haldorsen, Ellen M. Håland, Dr. psychol. | Return to work in low back pain patients. |
| | Besemer, Susan P., Dr. philos. | Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products. |
| H | Winje, Dagfinn, Dr. psychol. | Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988. |
| | Vosburg, Suzanne K., Dr. philos. | The effects of mood on creative problem solving. |
| | Eriksen, Hege R., Dr. philos. | Stress and coping: Does it really matter for subjective health complaints? |
| | Jakobsen, Reidar, Dr. psychol. | Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene. |
| **1999** | | |
| V | Mikkelsen, Aslaug, Dr. philos. | Effects of learning opportunities and learning climate on occupational health. |
| | Samdal, Oddrun, Dr. philos. | The school environment as a risk or resource for students' health-related behaviours and subjective well-being. |
| | Friestad, Christine, Dr. philos. | Social psychological approaches to smoking. |
| | Ekeland, Tor-Johan, Dr. philos. | Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar. |

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| H | Saban, Sara, Dr. psychol. | Brain Asymmetry and Attention: Classical Conditioning Experiments. |
| | Carlsten, Carl Thomas, Dr. philos. | God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing. |
| | Dundas, Ingrid, Dr. psychol. | Functional and dysfunctional closeness. Family interaction and children's adjustment. |
| | Engen, Liv, Dr. philos. | Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling. |
| **2000** | | |
| V | Hovland, Ole Johan, Dr. philos. | Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon. |
| | Lillejord, Sølvi, Dr. philos. | Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver. |
| | Sandell, Ove, Dr. philos. | Den varme kunnskapen. |
| | Oftedal, Marit Petersen, Dr. philos. | Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte. |
| H | Sandbak, Tone, Dr. psychol. | Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology |
| | Eid, Jarle, Dr. psychol. | Early predictors of PTSD symptom reporting;<br>The significance of contextual and individual factors. |
| **2001** | | |
| V | Skinstad, Anne Helene, Dr. philos. | Substance dependence and borderline personality disorders. |
| | Binder, Per-Einar, Dr. psychol. | Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori. |
| | Roald, Ingvild K., Dr. philos. | Building of concepts. A study of Physics concepts of Norwegian deaf students. |
| H | Fekadu, Zelalem W., Dr. philos. | Pridicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context. |
| | Melesse, Fantu, Dr. philos. | The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study. |
| | Råheim, Målfrid, Dr. philos. | Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter. |
| | Engelsen, Birthe Kari, Dr. psychol. | Measurement of the eating problem construct. |
| | Lau, Bjørn, Dr. philos. | Weight and eating concerns in adolescence. |
| **2002** | | |
| V | Ihlebæk, Camilla, Dr. philos. | Epidemiological studies of subjective health complaints. |

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| | Rosén, Gunnar O. R., Dr. philos. | The phantom limb experience. Models for understanding and treatment of pain with hypnosis. |
| | Høines, Marit Johnsen, Dr. philos. | Fleksible språkrom. Matematikklæring som tekstutvikling. |
| | Anthun, Roald Andor, Dr. philos. | School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential |
| | Pallesen, Ståle, Dr. psychol. | Insomnia in the elderly. Epidemiology, psychological characteristics and treatment. |
| | Midthassel, Unni Vere, Dr. philos. | Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools |
| | Kallestad, Jan Helge, Dr. philos. | Teachers, schools and implementation of the Olweus Bullying Prevention Program. |
| H | Ofte, Sonja Helgesen, Dr. psychol. | Right-left discrimination in adults and children. |
| | Netland, Marit, Dr. psychol. | Exposure to political violence. The need to estimate our estimations. |
| | Diseth, Åge, Dr. psychol. | Approaches to learning: Validity and prediction of academic performance. |
| | Bjuland, Raymond, Dr. philos. | Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach. |
| **2003** | | |
| V | Arefjord, Kjersti, Dr. psychol. | After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients. |
| | Ingjaldsson, Jón Þorvaldur, Dr. psychol. | Unconscious Processes and Vagal Activity in Alcohol Dependency. |
| | Holden, Børge, Dr. philos. | Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling. |
| | Holsen, Ingrid, Dr. philos. | Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship. |
| | Hammar, Åsa Karin, Dr. psychol. | Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis. |
| | Sprugevica, Ieva, Dr. philos. | The impact of enabling skills on early reading acquisition. |
| | Gabrielsen, Egil, Dr. philos. | LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole. |
| H | Hansen, Anita Lill, Dr. psychol. | The influence of heart rate variability in the regulation of attentional and memory processes. |
| | Dyregrov, Kari, Dr. philos. | The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help. |

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| **2004** | | |
| V | Torsheim, Torbjørn, Dr. psychol. | Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives. |
| | Haugland, Bente Storm Mowatt Dr. psychol. | Parental alcohol abuse. Family functioning and child adjustment. |
| | Milde, Anne Marita, Dr. psychol. | Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis. |
| | Stornes, Tor, Dr. philos. | Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence. |
| | Mæhle, Magne, Dr. philos. | Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children. |
| | Kobbeltvedt, Therese, Dr. psychol. | Risk and feelings: A field approach. |
| **2004** **H** | Thomsen, Tormod, Dr. psychol. | Localization of attention in the brain. |
| | Løberg, Else-Marie, Dr. psychol. | Functional laterality and attention modulation in schizophrenia: Effects of clinical variables. |
| | Kyrkjebø, Jane Mikkelsen, Dr. philos. | Learning to improve: Integrating continuous quality improvement learning into nursing education. |
| | Laumann, Karin, Dr. psychol. | Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices. |
| | Holgersen, Helge, PhD | Mellom oss - Essay i relasjonell psykoanalyse. |
| **2005** | | |
| V | Hetland, Hilde, Dr. psychol. | Leading to the extraordinary? Antecedents and outcomes of transformational leadership. |
| | Iversen, Anette Christine, Dr. philos. | Social differences in health behaviour: the motivational role of perceived control and coping. |
| **2005** **H** | Mathisen, Gro Ellen, PhD | Climates for creativity and innovation: Definitions, measurement, predictors and consequences. |
| | Sævi, Tone, Dr. philos. | Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter. |
| | Wiium, Nora, PhD | Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour. |
| | Kanagaratnam, Pushpa, PhD | Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence. |
| | Larsen, Torill M. B. , PhD | Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools. |

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| | Bancila, Delia, PhD | Psychosocial stress and distress among Romanian adolescents and adults. |
| **2006** | | |
| V | Hillestad, Torgeir Martin, Dr. philos. | Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling. |
| | Nordanger, Dag Øystein, Dr. psychol. | Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia. |
| | Rimol, Lars Morten, PhD | Behavioral and fMRI studies of auditory laterality and speech sound processing. |
| | Krumsvik, Rune Johan, Dr. philos. | ICT in the school. ICT-initiated school development in lower secondary school. |
| | Norman, Elisabeth, Dr. psychol. | Gut feelings and unconscious thought:<br>An exploration of fringe consiousness in implicit cognition. |
| | Israel, K Pravin, Dr. psychol. | Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting. |
| | Glasø, Lars, PhD | Affects and emotional regulation in leader-subordinate relationships. |
| | Knutsen, Ketil, Dr. philos. | HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt. |
| | Matthiesen, Stig Berge, PhD | Bullying at work. Antecedents and outcomes. |
| **2006** | | |
| **H** | Gramstad, Arne, PhD | Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy. |
| | Bendixen, Mons, PhD | Antisocial behaviour in early adolescence: Methodological and substantive issues. |
| | Mrumbi, Khalifa Maulid, PhD | Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses. |
| | Hetland, Jørn, Dr. psychol. | The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors |
| | Kakoko, Deodatus Conatus Vitalis, PhD | Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects |
| | Mykletun, Arnstein, Dr. psychol. | Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study |
| | Sivertsen, Børge, PhD | Insomnia in older adults. Consequences, assessment and treatment. |
| **2007** | | |
| V | Singhammer, John, Dr. philos. | Social conditions from before birth to early adulthood – the influence on health and health behaviour |

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| | Janvin, Carmen Ani Cristea, PhD | Cognitive impairment in patients with Parkinson's disease:<br>profiles and implications for prognosis |
| | Braarud, Hanne Cecilie, Dr.psychol. | Infant regulation of distress: A longitudinal study of transactions between mothers and infants |
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