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Chapter 1

Structure-Function Relationships in Human Cognition: A Highly Selective Review of Relationships Between Individual Differences in Brain Structure, Electrophysiology and Cognitive Performance

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Abstract

During the last few years, methodological and analytical developments have greatly increased the utility of structural brain imaging in cognitive neuroscience. Automated and semi-automated approaches to structural magnetic resonance imaging (sMRI) analysis enable investigators to measure the volume and thickness of brain structures with a very high resolution with much less manual intervention than a few years back. The development in techniques to acquire and analyze diffusion tensor imaging (DTI) data has been even more dramatic. DTI gives information about the microstructure of the brain's white matter. This is a measure of brain structure relevant to understanding connections between various parts of the brain, and how distributed brain activity is related to complex cognitive processes. Still, the relationship between these measures of brain structure and indexes of brain activity and cognitive function is not well understood. The aim of the present article is to give a general overview of how individual variation in brain structure – sMRI, DTI, and to some extent, lesion data, is related to brain activity as measured by electrophysiological event-related potentials – ERP, and cognitive function. The field is broad, and a full review of relevant research can unfortunately not be presented within the present paper, which is highly selective. Focus is on individual differences in healthy people, as well as aging and Alzheimer dementia. It can be concluded that structural and functional measures of brain characteristics give important information on the biological basis of normal cognitive age changes,

pathological changes, and learning. However, it is premature to assume that structure-function relationships can be interpreted in the same manner in development and aging, and in health and disease. Structure-function relationships are often of a complex nature, and this complexity must be investigated.

Introduction

Recent technical progress in the methods used to measure and visualize brain structure in vivo has increased the potential usefulness of structural brain imaging. Structural brain imaging can be used to test anatomical differences between patients and controls, to follow disease progress over time, and to map the development and aging of the brain (Fischl et al., 2002; Thompson et al., 2007; Walhovd et al., 2005). One principal reason for the interest in using structural brain imaging is that it is reasonable to believe that variations and changes in brain structure have implications for cognitive abilities. Thus, insight in the relationship between cognitive function and structural brain anatomy is important to understand various neurological and neuropsychiatric diseases, as well as the processes of development and aging. In addition, the brain structure - function relationship is interesting also from a theoretical point of view.

The aim of the present article is to present some of the background for structural brain imaging, with a focus on brain morphometry and diffusion tensor imaging (DTI). Further, examples of structure – function relationships will be given and discussed. We will start with presenting examples of an approach to morphometric analysis and an approach to DTI analyses. Further, we will present some background for, examples of, and applications of a method for measuring brain activity – electrophysiological event-related potentials (ERP). In part four, we will discuss the basis for structure-function relationships in normal cognition, and in part five, we will present examples from normal aging, Alzheimer dementia, and plasticity as a result of intensive training.

2. How to Measure Brain Structure? Automated Techniques

We will shortly review two methods that are used for measuring structural properties of the brain: morphometry and diffusion tensor imaging (DTI) analysis. The technical advancements in these methods have been large over the last few years, so they will be briefly covered for the interested reader. First, we will give an example of an analysis strategy for morphometric data. Here, we will focus on the freely available software package Freesurfer (see below) developed by Dale, Fischl and colleagues (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl et al., 2004). Next, we will give a short overview of the principles behind DTI, and present some information about how DTI data can be analysed and used in cognitive studies. Here, we will use Tract Based Spatial Statistics (TBSS) (Smith et al., 2006; Smith et al., 2004) as the example (see below).

2.1. Morphometry: Measuring the Structure of the Brain

Morphometric studies of the human brain can potentially provide detailed quantitative information about the shape, size, volume and thickness of cortical and subcortical structures *in vivo*. As will be detailed below, this information can together with information about cognitive function, disease state, other neurobiological measures (e.g. CSF measures) be very useful for understanding the characteristics of the brain and their significance. Current morphometric studies of the human brain usually involve magnetic resonance imaging (MRI). Utilizing the different cerebral tissues' magnetic properties, MRI techniques yield high resolution mappings of the living human brain. Quantitative morphometric data can indirectly provide information about the neurobiological building blocks of the brain, and allow for comparisons of participants or groups of participants. The recent advances in analytical tools have allowed researchers to obtain specific measures of cerebral morphometry from MRI volumes.

Analysis of volumetric data can be performed with different program packages, many of which the developers have generously made freely available to the scientific community. A main difference in analysis of such data is whether manual drawing of the structures of interests are involved, or whether structures are defined in an automated or semi-automated way. We will present a rough overview of one such program for automated/ semi-automated structural analyses. Freesurfer is a toolkit developed by researchers at Harvard Medical School ((Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 2002; Fischl et al., 1999; Fischl et al., 2004). This program can be used for measuring thickness of the cerebral cortex at each point on the brain surface as well as volumetric measurements of a number of subcortical structures. In the following, some information about the main strategy used within the Freesurfer package is presented.

For estimation of cortical thickness, models of the boundary between white matter and cortical gray matter, in addition to the pial surface, are constructed. Given representations of these surfaces, different anatomical measures are made available. Cortical thickness is represented as the distance between the white matter and the cortical surface at every point along the surfaces (Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 1999). This surface based approach also allows for estimates of surface area and curvature. The surfaces can be inflated, facilitating visualization of cortical regions usually hidden due to the cortical curvature pattern. Aligning subjects' surfaces to a spherical surface-based cortical atlas, mapping each vertex to the same vertex in every subject yields corresponding mapping of each point over subjects or groups of subjects. This makes inferences about regional specific effects across groups possible.

The final subcortical segmentation is generated using both subject-independent probabilistic atlases and subject-specific measures (Fischl et al., 2002; Fischl et al., 2004). The labeling of each voxel is partly dependent upon the pre-probability of each voxel belonging to a certain structure, given the probability atlas, but also the probability given the neighboring voxel. This permits a high degree of continuity across the segmented volume. The probabilistic labeling of each voxel is done a number of times, using both voxel and neighboring voxel probability information, reducing the level of error and allowing the atlas to be customized and fitted for each data set. This method has been shown to be of comparable accuracy to manually labeling (Fischl et al., 2002).

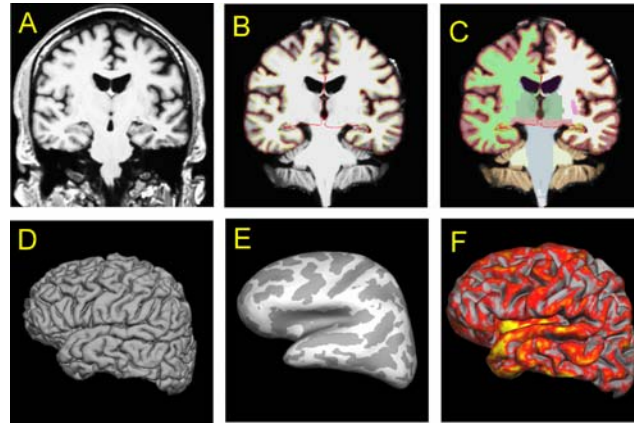


Figure 1. Surface and volume segmentation in Freesurfer. Sample figures from different steps in the Freesurfer segmentation process of a T1-weighted MP-RAGE volume from a middle aged healthy male enrolled in one of our studies. (A) Two MP-RAGE volumes averaged, intensity normalized and corrected for motion artifacts. (B) A skulled stripped and surface segmented version of the same volume. The red line represents the brain surface, and the yellow line the border between grey and white matter. The distance between these lines represents the cortical thickness at every point in the cortical mantle. (C) Automatic subcortical segmentation. The colors depict different structures. (D) A lateral view of the digital reconstruction of the surface of the left hemisphere. (E) An inflated representation of the same hemisphere. The dark grey areas represents sulci. (F) A thickness map overlaid a semi inflated representation the same hemisphere. Grey: 0-2 mm, red: 2-3,5 mm, yellow: 3,5-4,5 mm thickness of the cortical surface.

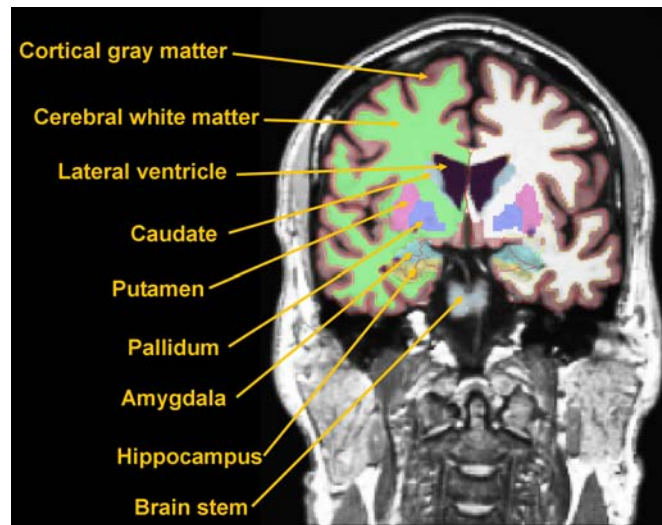


Figure 2. Subcortical segmentation and labeling in Freesurfer. The figure shows a sample of the automatically segmented structures from a T1 weighted volume from a middle aged healthy participant in one of our studies. The arrows show structures in the right hemisphere only.

The resulting volume and surface based segmented brain volumes can be used for a broad specter of statistical testing and analysis. Freesurfer incorporates the general linear model

(GLM), allowing for statistical fitting of each vertex at the cortical mantle to a linear model of the effect of covariates like age, gender, and group membership, or behavioral measurements like cognitive variables. The statistical results can then be visualized and color coded on an average surface, and subjected to different kinds of testing for multiple comparisons, including false discovery rate, permutation testing (Golland & Fischl, 2003), and Monte Carlo simulations. Morphometric and volumetric studies have led to interesting hypotheses concerning the nature of the structure/function relationships, which we will come back to below.

In addition to volumetric data, measures of the fiber connections of the brain have gained a lot of recent interest in neuroscientific research. Complex cognitive functions are supported by distributed networks of cortical and subcortical structures. Thus, optimal cognitive functions are dependent upon efficient and integrated connections between the different brain structures. DTI, yielding information about white matter connectivity and integrity, is a potentially very interesting method to study neuronal fiber connectivity and its relation to cognitive functions. Because broad application of the method is relatively modern, and the tools to quantify and analyse specific regional tracts have just recently become publicly available, the published literature focusing on DTI-measures and cognition in healthy samples is still limited. We will in the next section present a promising tool to analyse DTI-derived measures of fiber connectivity.

2.2. Diffusion Tensor Imaging: Measuring Connections in the Brain

Diffusion is random movement of water molecules in accordance with physical laws described by among others Einstein and Brown (Le Bihan, 2003; Mori, 2007). In MRI, movement results in signal loss in the obtained MR volume, usually disturbing or biasing the interpretations of the volumes. Diffusion tensor imaging utilises the random movement of water molecules from one time point to another. By applying two successive gradients separated by an interval (*b* value), the signal loss between the two gradients is a marker of movement of water molecules. Since the physical laws describing this random motion are known, these algorithms can be used to explicate the relative direction and strength of this movement in each voxel in the MR volume (Alexander, Lee, Lazar, & Field, 2007; Catani, 2006; Mori, 2007; Sullivan & Pfefferbaum, 2006; Wozniak & Lim, 2006).

The diffusion properties and distribution of non-constrained water molecules are randomly defined. The probability of movement in one direction is equal to the probability of movement in any direction in space. This is often referred to as isotropic diffusion, and the random distribution of one water molecule from *t*₁ to *t*₂ can be visualised as a sphere (Alexander et al., 2007). In biological tissues, the diffusion of water molecules is usually relatively restricted in one compared to other directions. In brain tissue, the diffusion is restricted among other things due to myelinated axon walls. The random movement of water molecules in restricted environments is best visualised as an ellipse, with the greatest radius in the ellipse representing the principal diffusion direction. In brain tissue, the principal direction will usually equal the direction of the fibre pathway, and the shortest radius will be perpendicular to this pathway (Mori, 2007).

The relative strength and direction of diffusion in a three dimensional space can be expressed by eigenvectors ($\epsilon_1, \epsilon_2, \epsilon_3$) and eigenvalues ($\lambda_1, \lambda_2, \lambda_3$). Each eigenvector denotes

the direction in the principle, secondary and tertiary direction. The eigenvalues assigns the strength of diffusion of each vector. Collectively, these values can be used to describe the diffusion properties in a three dimensional space in every voxel in a diffusion weighted MRI volume. By the means of diffusion tensor imaging, the relative strength and direction can be used to infer the direction and integrity of the white matter fibre in each voxel. By fitting the eigenvectors and λ -values to a tensor model in each voxel, the relative direction and strength can be indexed within the framework of fractional anisotropy (FA). FA indexes the relative strength of the principal diffusion direction compared to the radial diffusion directions, and is a number between zero and one (Basser & Pierpaoli, 1996, 1998). Completely non-restricted random diffusion yields $FA = 0$, and completely restricted diffusion gives $FA = 1$. In biological tissues, as in cerebral white matter, large FA means more restricted and smaller FA means less restricted diffusion of water molecules. High FA is often understood as a marker of high integrity of white matter, due to highly myelinated axon walls restricting water movement along the perpendicular directions. This is supported by the relatively high FA in large white matter fiber pathways, such as corpus callosum, compared to the relatively lower FA in grey matter and smaller pathways closer to the cortical surface.

Indexing the relative strength of diffusion in the principal compared to the radial directions, FA is thought to be sensitive to both axonal degeneration and degree of axonal myelinisation. This is probably just partially true. FA is only sensitive to the relative difference between the principal and radial directions. This means that at least two factors can contribute to a reduction in FA: (1) a reduction of the principal eigenvalues or (2) an increase in the radial eigenvalues. Being a valid estimate of the relative difference between the strength of the different diffusion directions, though, FA is probably not sensitive to differentiated biological processes affecting white matter connectivity. It has been shown that estimates of radial diffusion ($(\lambda_2 + \lambda_3)/2$) is more sensitive to demyelination than estimates of the principal diffusion (λ_1) (Song et al., 2003; Song et al., 2002; Song et al., 2005). On the other hand, principal diffusion may be more sensitive to axonal degeneration. The combination of FA with the direction-specific parameters may provide a fruitful approach to the study of integrity of white matter fibre pathways. This is supported by a developmental study by Giorgio et al. (in press), reporting increased age related FA in a group of children/adolescents. Closer investigations of the directional substance of this increase suggested that it was driven by reduced radial but not increased principal diffusivity, indicating myelinisation without changes in axon integrity. In a similar manner, Anjari et al. (2007) analyzed FA in a group of preterm compared to term born babies, and found several areas with decreased FA in the pre term group. Closer examination of λ_1 , λ_2 and λ_3 revealed that the decrease in FA were due to increased radial diffusivity (λ_2 or λ_3), and not decreased principal diffusivity (λ_1).

Thus, combining these measures allows for more finely tuned hypothesis testing regarding the exact nature of the change in fractional anisotropy. As such, this could be a promising way to study the precise biological underpinnings leading to reduced or increased FA in various conditions.

Due to the complexity and the inter-subject variability of the three dimensional properties of fibre pathways in the brain, comparing regional connectivity parameters across subjects and groups of subjects is a challenge. This is partially solved by implementing regions of interest (ROI) based analysis. Manually defining fibre pathways of interest increases the likelihood that the same underlying white matter structure in each subject is included in the

analysis. The hypothesis-driven nature of this strategy is also by many characterized as an advantage of this method. It also restricts the number of comparisons made in the analysis, reducing the challenges of statistical correction procedures for multiple comparisons. A clear drawback of the ROI-based method is that it is highly time consuming, it is operator dependent and it restricts the potential for exploratory analysis of the entire brain.

Various attempts to facilitate whole brain voxel based GLM analyses of diffusion weighted data have been made. One of the greatest challenges has been to generate algorithms for nonlinear registration and aligning of different volumes to a standard or common space allowing for direct comparison of the same underlying white matter structure across subjects. Due to the highly complex three dimensional properties of fibre pathways, typical linear registrations into the same space, is probably not efficient in order to make voxel based inferences and comparisons across subjects.

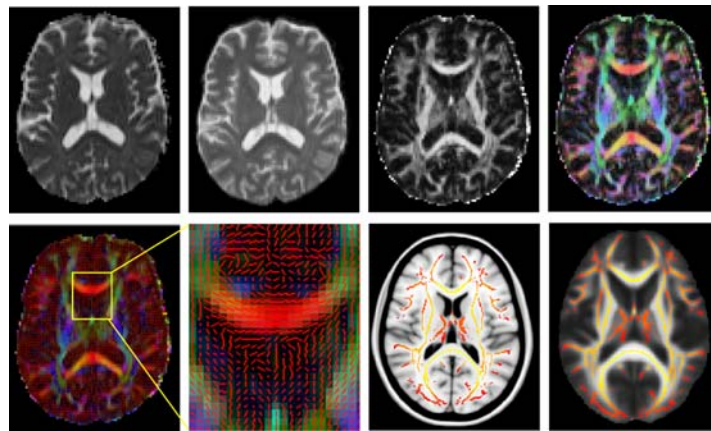


Figure 3. Processing of diffusion weighted images in FSL. Sample figures from different steps in the processing steps of diffusion weighted images in FSL. Top row, left: non diffusion weighted volume (b0), mean diffusivity (MD), eddy and motion corrected FA-volume (light colors = high FA), color coded FA-volume (red: commissures, green: longitudinal/association fibres, blue: corticospinal/pyramidal fibres). Bottom row: A line coded vector map overlaid a color coded FA-volume, the lines clearly follow the commissural fibres in the genu of corpus callosum, the tract invariant skeleton generated by TBSS overlaid on a standard MNI template (REF?), the same skeleton overlaid on a mean FA volume of 88 middle aged healthy participants from one of our current studies.

A promising attempt to deal with these issues is given by tract based spatial statistics (TBSS) (Smith et al., 2006), a part of the analyses software FSL (Smith et al., 2004, <http://www.fmrib.ox.ac.uk/fsl>) developed and maintained by researchers at fMRIB, Oxford University. By the means of finely tuned nonlinear registration procedures followed by projection of DTI-parameters onto an alignment-invariant tract representation (“skeleton”), TBSS provides a possible solution to the challenges of voxel based statistics on three dimensional tract specific MRI data. The cross-subject mean FA volume is used to generate a tract “skeleton”. This is done by thinning the white matter tracts in the mean FA volume, thresholded at a certain FA-value. The skeleton consists of one voxel thick contiguous tracts over the entire volume, and as such, representing the mean centre of each tract. Then the individual subject’s FA values are warped onto this skeleton map. TBSS searches for the maximum FA value perpendicular to the skeleton in each subject in order to restrict analysis

to the centres of the tract, and thus minimizing partial voluming effects of voxels in the area close to tissue borders. The voxel based analysis is then carried out on voxels included in the skeleton only, and as such maximizing the probability of comparing the same underlying fibre structure across subjects.

It is not known whether this method is optimal in the study of individual differences in healthy cognition. The skeleton based analysis allows only for the centre voxels to be compared across subjects. It is an empirical question whether these voxels is sensitive for normal variation in cognitive skills, or whether this variation should be attributed to fibre pathways not included in the skeleton, e.g. smaller pathways closer to the cortical surface. Thinly myelinated associative pathways has been reported to be more susceptible to reductions due to normal aging compared to thickly myelinated pathways (Bartzokis, 2004; Kochunov et al., 2007; Sullivan & Pfefferbaum, 2006), and might therefore also be more sensitive to age related reductions in cognitive function. If this is true, TBSS might not include all pathways believed to play an important role in subtle individual or age related changes in cognitive functioning. Any diffusion weighted volume can be fed into the TBSS pipeline, and the same analyses can be carried out on FA, principal eigenvalues and radial diffusion properties respectively. This makes further interpretations of the biological underpinnings of the FA changes possible, and could lead to interesting hypotheses regarding specific white matter connectivity variables and cognition.

3. Event-Related Potentials: Measuring Electrophysiological Responses of the Brain

There are several classes of techniques for measuring brain activity that are used in studies of cognitive processes. This article will focus on electroencephalography, or more specifically, on event-related potentials. Electroencephalography is the recording of electrical activity of the brain. The signals represent a summation of post-synaptic potentials mainly from large groups of pyramidal neurons in the cerebral cortex. In cognitive studies, event-related potentials (ERP) are often used. ERPs reflect the electrophysiological activity time-locked to an event, that is, a stimulus or a response. The two main scientific advantages of the technique are that actual neural activity is measured (not e.g. a vascular response as in fMRI), and that the temporal resolution is excellent (in terms of milliseconds). The two main limitations are that the spatial resolution is inferior to e.g. fMRI, and that a lot of the neural activity in the brain will have little influence on the scalp recorded signal. EEG/ ERP is mainly sensitive to post-synaptic activity from brain areas where the dendrites are organized in parallel and open layers, which fortunately is true for most of the cortex. Further, EEG/ ERP are mainly sensitive to activity generated in superficial layers in the cerebral cortex, i.e. the upper parts of the gyri, and perpendicular to the skull. Dendrites deeper in the cortex, i.e. in the sulci, or in deep structures, e.g. hippocampus, or dendrites that produce signals that are tangential to the skull, will contribute relatively less to the scalp recorded EEG/ ERP signal. Adding to these problems, conductivity properties of the CSF/skull/scalp will affect the scalp recorded potentials and reduce the spatial accuracy. Some of these shortcomings can partly be dealt with. The localization of EEG/ ERP sources can be improved by using structural MR scans to quantify the CSF/skull/scalp for each person. This information may be used to

improve the localization (Dale et al., 2000; Dale, 1993; Liu, Dale, & Belliveau, 2002), which makes it possible to estimate cortical neural sources with an error of about 2 cm with high density recordings (e.g. 128 electrodes). Further, MEG is sensitive to activity tangential instead of perpendicular to the skull, and so MEG and ERP are complementary methods. MEG is insensitive to the conductivity profile of the head tissue, which may contribute to higher spatial accuracy than EEG (Huang et al., 2007), getting down to about 3 mm in studies using realistic phantoms (Hansen, Ko, Fisher, & Litt, 1988; Leahy, Mosher, Spencer, Huang, & Lewine, 1998), while EEG localization accuracy is about 10 mm with use of such phantoms (Leahy et al., 1998) and about 10-20 mm with implanted electrodes in presurgical epilepsy patients (Krings et al., 1999). With accurate models of the conductivity profile of the head, EEG/ ERP localization error is not very different from that of MEG (Liu et al., 2002). It is now possible to do simultaneous recordings of ERP and MEG, which have been shown to be beneficial for both methods in terms of the amount and accuracy of information obtained (Huang et al., 2007).

Thus, even though event-related potentials have some shortcomings, the strengths of the method have made it a valuable tool in research on brain-cognition relationships, and, to a lesser degree, brain structure – function relationships. During years of research, several ERP components have been discovered. Two ERP components which have received much attention is the P300 components (P3a/ P3b) and the error-related negativity (ERN). We will briefly discuss these two components, and try to show their relationship to measures of brain structure. This review is as mentioned highly selective, and no attempt is made to cover all the relevant research done on these ERP-components.

3.1. P300 (P3a/ P3b)

The P300 consists of two subcomponents. Slightly different tasks are usually used to elicit the two components. Both are regarded as rather modality-independent, however, and can be elicited to various types of stimuli, even though visual and auditory are almost exclusively used. The classical P300, the so-called P3b, is elicited to infrequent targets in an oddball-task. This is a positive-going potential with parietal maximum amplitude, and a peak latency of about 300– 600 ms in young adults, or somewhat earlier if auditory, rather than visual stimuli are used. P3b latency is often regarded as a measure of the relative timing of the stimulus evaluation process (Rugg, 1995), and P3b amplitude is held to index resource allocation (Polich, 1996). An example of the P3b-eliciting target in a 2-stimulus task can be a large circle occurring 20% of the times, and the standard can be a smaller circle occurring 80% of the times (Comerchero & Polich, 1998). In addition to the P3b, a P3a can be recorded to deviant non-target stimuli (a distractor). In the novelty-paradigm, the distractors are different novel patterns that are not repeated (Courchesne, Hillyard, & Galambos, 1975), while in the 3-stimulus paradigm, a third, infrequent type of highly deviant stimulus is inserted into the sequence of target and standard stimuli (Squires, Squires, & Hillyard, 1975). Agreement has not been reached on the exact nature of the neurocognitive processes underlying the component, but it can be argued that P3a reflects involuntary, transient allocation of attention to salient stimuli changes and novel stimuli (Courchesne et al., 1975). An example of a 3-stimulus oddball paradigm, and the corresponding ERP curves, is given in figure 4.

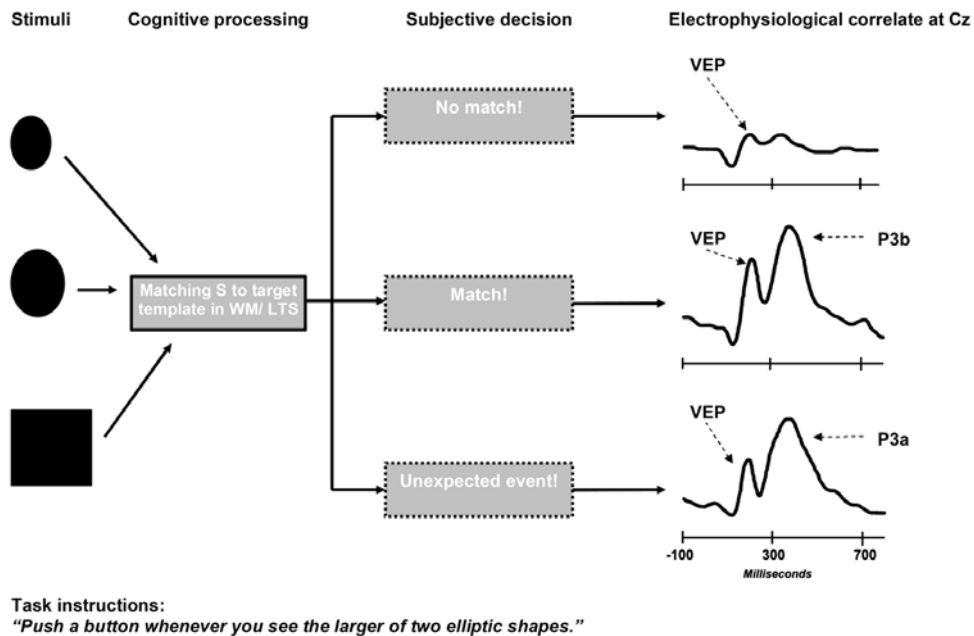


Figure 4. P300 visual oddball task. This is an example of a P300 visual oddball task, yielding a P3a to the distractor and a P3b to the target. Different versions of this task is used in a number of studies using P300 as an index of neurocognitive processing (Comerchero & Polich, 1999; Fjell et al., 2007; Fjell & Walhovd, 2005; Fjell et al., 2005).

The P3a and the P3b differs in terms of latency (P3a is usually earlier), amplitude (P3a is usually larger), and scalp topography (P3a typically has a more fronto-central scalp distribution, while P3b has a more parietal scalp distribution). In addition, P3a and P3b have at least partly different neural generators. Depth electrode studies, lesion studies, and source localization studies in combination with functional imaging techniques, have established that P3a and P3b are supported by widely distributed neural networks (Jeon & Polich, 2003; Linden, 2005; Polich & Comerchero, 2003; Reese & Polich, 2003). (Linden, 2005) argued that strong evidence exists for lateral prefrontal cortex, inferior parietal lobe/ temporoparietal junction, and medial temporal lobe involvement in P3a generation. Somewhat weaker evidence exists for involvement of inferior frontal gyrus/ insula and anterior cingulate cortex. For P3b, the posterior cingulate cortex/ superior parietal lobe, inferior parietal lobe/ temporoparietal junction, inferior frontal gyrus/ insula, and anterior cingulate cortex seem to be involved, while there is more limited evidence for medial temporal lobe generators for P3b. This means that there are similarities between localization of P3a and P3b generators, but also generators that are not common, indicating that the two components although similar, are supported by partly distinct neuroanatomical areas. This is supported by lesion studies. Reduced amplitudes to P3a, but not to P3b, have been observed in patients with unilateral damage to the posterior hippocampus (Knight, 1996). In other studies prefrontal lesions have been found to have large impact on P3a, but not to affect P3b (Daffner et al., 2003; Knight, 1984). Lesions in the temporoparietal junction seem to affect the P3a across modalities (Knight & Scabini, 1998), while for P3b, this effect is larger for auditory than visual stimuli (Verleger, Heide, Butt, & Kompf, 1994).

fMRI studies have yielded supplementary information about the generators of P3a/ P3b. These studies indicate that even though P3b often is spared in patients with frontal lesions, frontal areas are often activated in target detection tasks, e.g. anterior cingulate gyrus (Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Kiehl & Liddle, 2001), insular cortex (Linden et al., 1999), middle frontal gyrus (Clark, Fannon, Lai, Benson, & Bauer, 2000; Kiehl et al., 2001; Kiehl & Liddle, 2001), and inferior frontal gyrus (Kiehl et al., 2001; Kiehl & Liddle, 2001). For instance, Bledowski et al (Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004; Bledowski et al., 2004) found that distractor stimuli increased the activity in large parietal areas in both hemispheres, i.e. postcentral gyrus and superior parietal gyrus, and especially in left lateral prefrontal areas (the middle frontal gyrus). Insular, temporoparietal, and parietal activations were observed for target stimuli.

Very few studies have looked at the relationship between P300 and neuroanatomical variation in healthy individuals. It is possible that a larger regional number of neurons or synaptic connections in brains with greater regional volumes (Pakkenberg & Gundersen, 1997), may cause a positive relationship between cortical thickness and P300 amplitude, and a negative relationship with P300 latency, which may benefit cognitive processing. A thicker cortex may be able to process information in a faster and more efficient way due to a larger number of neurons and possibly synaptic connections, generating large and fast scalp-recorded potentials. This general view is further supported by moderate correlations between P300 and cognitive functions (Walhovd et al., 2005), even though some discrepant results have been reported (Houlihan & Campbell, 1998). P300 is largely generated in the cerebral cortex, and may therefore potentially be sensitive to subtle changes in regional cortical thickness. Thus, it is important to establish whether ERPs may be more sensitive to thickness differences than behavioral cognitive or psychometric tests.

A few studies have correlated volumetric brain measures with ERPs. Correlations between auditory P3a and P3b and cortical volume in an age-heterogeneous (21-60yrs) male sample have been reported (Ford et al., 1994). The regional correlations (frontal, parietal, temporal lobes) showed that frontal lobe gray matter was significantly related to P3a amplitude, while parietal lobe volume was significantly related to P3b amplitude. These relationships were, however, attenuated when age was included in the regressions. In another study, a total gray matter volume estimate was used in a sample of young, but no significant correlations between gray or white matter volume and the amplitude of the auditory P300 was found (Egan, 1994). The discrepancies between these studies may be explained by a larger age-range in the latter. Three studies with overlapping samples have found relationships between P300 and brain morphometry. In one study, P3a latency was related to total cortical volume and fluid intelligence (Walhovd et al., 2005). In a later publication, it was demonstrated that both P3a and P3b topographical shifts with high age were related to the thickness of specific areas of the cerebral cortex (Fjell, Walhovd, & Reinvang, 2005). In a third report, it was found that P3a and P3b correlated with regional cortical thickness in elderly participants, but not in young (Fjell, Walhovd, Fischl, & Reinvang, 2007). Further, P3a amplitude was more strongly related to cortical thickness than P3a latency, while the opposite pattern was true for P3b. Path modeling of the results showed that cortical thickness in the temporoparietal cortex predicted P3a amplitude which predicted executive function, and that thickness in orbitofrontal cortex predicted P3b latency which predicted fluid function. When age was included in the model, the relationship between P3 and cognitive

function vanished, while the relationship between regional cortical thickness and P3 remained.

So far, most efforts have focused on localizing P300 generators. However, in a recent study, it was found that white matter (WM) volume was more related to the scalp-recorded ERPs, especially P3b latency, than the grey matter volumes (Cardenas et al., 2005). It was concluded that the connections between the P3 generators seemed to matter more for the scalp-recorded potentials than the size of the generators themselves. This result warrants a closer look also at WM effects on ERPs, for instance by use of DTI.

As can be seen from the review above, only a few studies have investigated the relationship between P300 and brain structure in healthy participants. The results are not entirely consistent, but there seems to be a moderate relationship between the thickness of the cerebral cortex and the amplitude, latency, and topography of this ERP component. More studies are needed, however, integrating both measures of cortical volume/ thickness, as well as measures of cognitive function, and white matter characteristics. As far as we know, no studies have reported correlations between for instance FA and ERP components.

In addition to P300-studies of healthy populations, P300 is used in studies of normal aging and in studies of clinical groups. It has been shown that for both P3a and P3b, latency is prolonged and amplitude is reduced with increasing age (Fjell & Walhovd, 2004; Polich, 1996; Walhovd & Fjell, 2001). The latency increase may be interpreted as reduced speed of processing with higher age, and the amplitude reduction as a sign of less available processing resources for the given task. Also, increasing age is characterized by relatively more frontal relative to parietal activation (Fabiani, Friedman, & Cheng, 1998). This is a robust phenomenon which is observed in most studies, for both visual and auditory tasks. It has been reported that individual differences in frontal activation is related to lower executive function (Fabiani et al., 1998), but discrepant findings exist (Fabiani et al., 1998). This may be related to the diversity of cognitive functions involved in executive tests, so that quite different functions are often measured across studies. In one study it was shown, however, that elderly participants with a frontocentral maximum amplitude had thicker cortex in specific areas than participants with parietal maxima (Fjell et al., 2005), both for P3a and P3b. The only exception was that participants with a parietal P3b maximum had thicker cortex in parts of the anterior cingulate. However, the cognitive significance of these findings is not clear, so more knowledge is needed on how age-related changes in scalp potentials are related to cognitive function.

In addition to being sensitive to normal aging, P300 has been used in studies of probable Alzheimers disease (AD). An overview in a review paper showed that 17 studies have reported latency differences in P300 between Alzheimer patients and healthy controls, while six failed to find this difference. For amplitude, twelve studies found differences, while nine did not. Thus, it seems that latency prolongation of P300 is a more sensitive marker of the neurocognitive deficits involved in Alzheimer than amplitude reductions.

P300 has been used in several other clinical groups than AD, but it is outside the scope of the present highly selective review to present these studies here. We will only mention that P300 has also been used as a biomarker in neuropsychiatric research (Jeon & Polich, 2003). In a large meta-analysis, it was found that P300 amplitude was reduced and P300 latency increased in non-psychotic relatives to schizophrenic patients, and it was suggested that P300 amplitude and especially P300 latency may be endophenotypes for schizophrenia (Bramon et al., 2005).

3.2. Error Related Negativity

The error-related negativity (ERN) is a negative electrophysiological potential observed after commission of a behavioural error in speeded response tasks, lasting for about 100 ms (Taylor, Stern, & Gehring, 2007). It has a fronto-medial maximum, and is thought to reflect anterior cingulate (ACC) activity in response to commission errors (Elton, Spaan, & Ridderinkhof, 2004; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Holroyd & Coles, 2002; van Veen & Carter, 2006) or behavioural conflict (Gehring & Fencsik, 2001; Stahl & Gibbons, 2007; van Veen, Holroyd, Cohen, Stenger, & Carter, 2004). Several studies have confirmed ACC involvement in error processing. Using source localization, Herrmann et al. (2004) located the source of the ERN to ACC. In an fMRI study of subjects performing a go/no-go task, Mathalon et al (2003) located the error related BOLD response to dorsal and caudal parts of ACC. Debener et al. (2005) reported converging evidence of ACC involvement in error processing from concurrent fMRI and ERP in subjects performing a version of Eriksen's Flanker Task (Eriksen & Eriksen, 1974). See also figure 5.

An example of the error related negativity recorded in our own lab is given in figure 6, showing activity locked to correct and erroneous responses, respectively. The recording was done while the subject was performing the Flanker Task (figure 5). To control for possible electrophysiological conflict related effects, we selectively report recordings from incongruent trials. The topographic distribution of the ERN is given in figure 7. The figures clearly demonstrate that the ERN is a temporally and topographically well defined component behaviourally specific to errors.

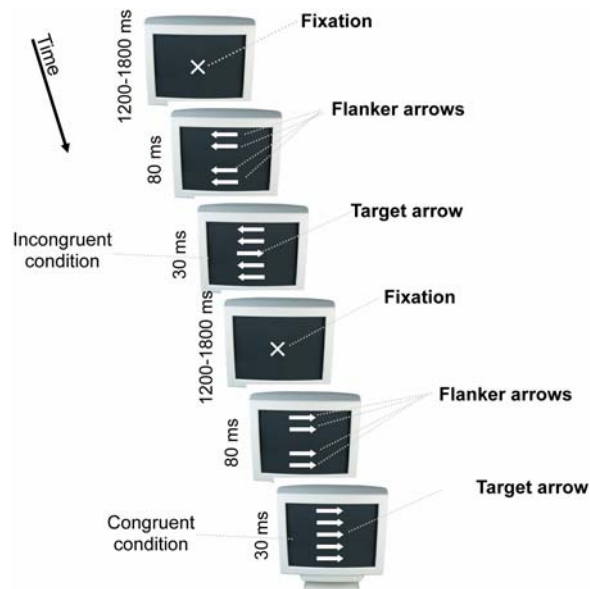


Figure 5. The Flanker task. A schematic representation of the version of Eriksen Flanker Task used in our lab to measure the error related negativity. The subjects are instructed to indicate as quick and accurate as possible via a response box if the target arrow points to the left or to the right. In the incongruent condition, the flanker arrows point to the opposite direction as the target arrow.

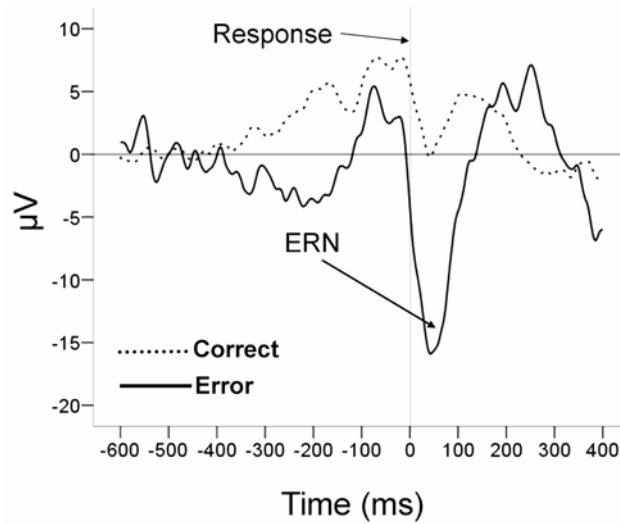


Figure 6. The Error Related Negativity. The graph depicts the mean response locked electrophysiological activity measured at the frontomedial electrode FCz in a healthy middle aged woman after correct (dashed line) and incorrect (solid line) responses in the Flanker task. To avoid stimulus conflict induced negativity, only incongruent trials are included. The activity is measured relative to a 100 ms baseline from -600 ms before response onset.

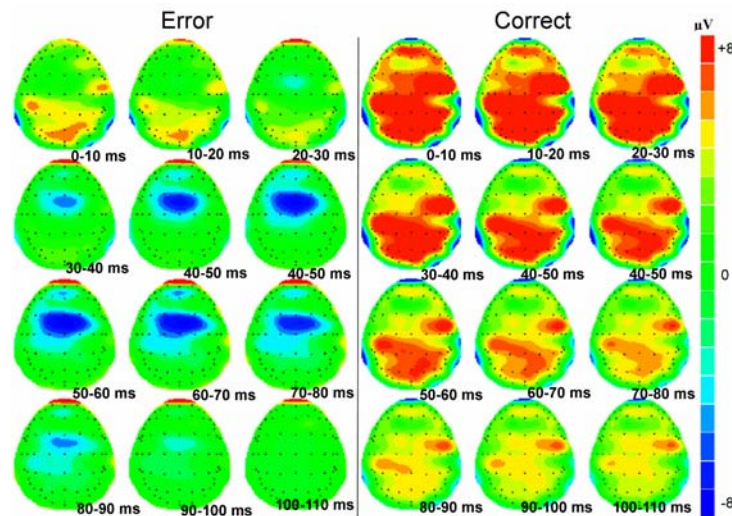


Figure 7. Topographic distribution of the Error Related Negativity. The topographic distribution of the electrophysiological potential measured after erroneous (left) and correct (right) responses in the incongruent condition from the Flanker Task. The distribution is estimated from 128 electrodes (black dots). 0 ms = response. The left figure clearly shows the frontomedial distribution negativity peaking approx 60 ms after erroneous responses. This error related negativity probably reflects anterior cingulate activity.

There is converging evidence suggesting ACC involvement in the generation of ERN, but some studies also suggest distributed cerebral involvement. It has been argued that ERN reflects processing initially executed in striatal areas in response to processing of

reinforcements (Holroyd & Coles, 2002; Holroyd, Hajcak, & Larsen, 2006; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003; Nieuwenhuis, Holroyd, Mol, & Coles, 2004). This theory postulates a frontostriatal reinforcement sensitive neuronal circuit, responsible for detection and processing of negative and positive reinforcements. This is in accordance with neurophysiologic evidence from animal research suggesting highly integrated frontostriatal circuits involved in reinforcement learning (Matsumoto, Matsumoto, Abe, & Tanaka, 2007; Schultz, 2002, 2007; Schultz, Dayan, & Montague, 1997). Schultz has in several papers established evidence for altered phasic dopamine firing pattern in response to reinforcements in ventral tegmental areas including the nucleus accumbens. In a single cell recording study, Matsumoto et al (2007) reported reinforcement sensitive neuronal activity in response to positive and negative reinforcements in medial frontal areas in macaque monkeys. Some groups of cells were sensitive to positive reinforcements, while other cells were sensitive to negative reinforcements. These cells were found in the medial frontal cortex, with no evidence for reinforcement sensitive cells in more lateral areas. Together with Holroyd & Coles (Holroyd & Coles, 2002), these studies suggest that the ERN is an electrophysiological fingerprint of basal frontostriatal reinforcement processing. This is supported by studies reporting evidence for a feedback related negativity in response to negative feedback (Cohen & Ranganath, 2007; Gehring & Willoughby, 2002; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Nieuwenhuis et al., 2004; Ruchow, Grothe, Spitzer, & Kiefer, 2002).

Are individual variations in brain structure related to ERN in healthy participants? As far as we know, no studies have reported any relationship between MRI-derived structural indices and ERN in healthy participants. Beste et al (in press) reported a positive correlation between ERN and gray matter volume in the right medial frontal gyrus (BA 9) in a group of patients diagnosed with Huntington's disease. They found no correlation between neither white nor gray matter volume in a group of presymptomatic subjects, however.

Several lesion studies of ERN exist, establishing a link between this component and gross changes in brain structure. Gehring & Knight (Gehring & Knight, 2000) reported reduced ERN in patients with lateral prefrontal cortex lesions, suggesting distributed frontal involvement in error processing and ERN. Stemmer et al (2004) found evidence for dissociated involvement of the ACC in error processing and generation of ERN. Patients with ACC lesions exhibited reduced ERN, supporting ACC involvement in this component. However, they did not necessarily show reduced error awareness or reduced error correction. That is, ERN may follow error awareness and correction, but is perhaps not necessary for the detection and correction of errors. This hypothesis is supported by evidence suggesting distributed cortical and subcortical involvement in error detection and correction (Hester, Fassbender, & Garavan, 2004; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006; Ullsperger & von Cramon, 2006). In line with the notion of distributed involvement in error processing and ERN, Hogan et al (2006) reported reduced cognitive control functions as well as decreased ERN amplitude in a patient group exhibiting frontal white matter lesions. As none of these patients had lesions in the cerebral gray matter, the decreased ERN amplitude was probably due to white matter damage alone. These findings suggest that DTI measures of white matter connectivity may be of great interest in the study of electrophysiological measures and cognition in general, and especially the ERN and error processing. This is also in accordance with Ullsperger & von Cramon (2006), reporting reduced ERN in a group of nine patients with basal ganglia lesions and seven patients with lateral prefrontal lesions. Even though they found no evidence for

reduced error processing in the same patients, a third patient group exhibited both reduced ERN and decreased error processing. These patients had lesions in frontal lateral regions, as well as the underlying white matter. These findings also underline the importance of white matter connectivity to ERN and error processing.

No studies have yet been reported on the relationship between electrophysiological measures and white matter connectivity in healthy subjects. As ERN is thought to directly reflect synchronous neuronal activity in ACC and neighbouring areas, and also might be sensitive to variability in cognitive control functions, at least in patient groups, further studies on the relationship between MRI-derived structural indices and ERN are warranted.

4. Structural Correlates of Normal Cognition

High resolution MRI measures of the brain enable tracking of subtle changes in brain structure accompanying changes in cognitive function due to e.g. aging, neurodegenerative conditions, neuropathological or psychiatric illnesses. As argued by Van Petten (2004), the relationship between structure and function is often expected to be pretty robust in studies focusing on patient groups. That is, a “brain deficit” is accompanied by “deficient cognitive processing”. Investigating the same relationships in healthy participants, though, might not yield the same relations. It is not given that normal variability in structural indices, for instance regional cortical thickness or white matter connectivity, is a good predictor of cognitive variability (Van Petten, 2004). Later in this article, examples of relationships between changes in brain structure, brain function, and cognitive performance in normal aging and Alzheimer dementia are given.

The relationship between volumetric measures and cognitive functions is less clear in healthy participants than in different patient groups and groups with wide age ranges.

A considerable number of studies have addressed the question of structure-cognition relationships directly by assessing a wide array of cognitive functions in healthy participants, and correlated the results with volumetric measures. Walhovd et al. (2004) investigated long term memory functions in a healthy sample in age ranging from 20-88 years. They found no age-independent relation between memory after standard neuropsychological retention intervals (5/30 min) and hippocampal volume, in accordance with Van Petten (2004). However, extending the retention interval to 11 weeks yielded positive correlations between hippocampal volume and verbal memory. That is, hippocampal volume was predictive of individual differences in verbal long term memory, but only after a long time interval.

In a study from the same group, Walhovd et al. (2005) reported a positive correlation between performance IQ and cortical volume, and a negative correlation between P3a latency (as a measure of speed-of-processing) and cortical volume. Larger cortical volume predicted higher performance IQ and faster speed-of-processing. Path analyses showed that volumetric and latency measures had complementary roles in prediction of performance IQ. In a recent study, Narr et al. (2007) reported regional positive correlations between cortical thickness and an estimate of full scale IQ in a group of healthy participants. Significant correlations were found bilaterally in the prefrontal and posterior temporal cortices. These results are in accordance with a meta-analysis reviewing the relationship between brain volume and intelligence (McDaniel, 2005), finding clear evidence for positive correlations. The neurobiological foundation for this correlation pattern is not evident, though. Larger brains

may facilitate optimal cognitive abilities due to an extended number of neurons (Pakkenberg & Gundersen, 1997) and more synapses (Wickett, Vernon, & Lee, 2000), and thus allowing more differentiated and specialized afferent processing. Larger volume may also be accompanied with a higher neuronal complexity, an extended number of dendritic spines and more densely myelinated axonal walls (Deary & Caryl, 1997), which could allow for more complex, faster and more synchronous neuronal firing patterns. However, the relationship between brain volumetry and cognitive function is complex, and more research is needed to understand the mechanisms behind the observed relationships. Further, it is reasonable to expect that correlations between brain morphometry and cognitive function do have different causes in different types of samples. For instance, thinning of the cerebral cortex will probably have different causes and different cognitive consequences in development versus aging.

A few studies have related ERP to morphometry. Studies of P300 and morphometry were reviewed above. Other ERP components than the P300 have also been used, however. Walhovd et al. (2006) tested the relationship between an ERP component called the parietal old/new effect, related to memory processing, brain morphometry, and memory performance. It was observed that elderly participants tended to have relatively more frontal old/new activity than younger. Within the group of elderly participants, the frontal shift was not related to cortical or hippocampal volume. Further, the strength of the old/new-effect correlated with the volume of the cerebral cortex, but not the volume of the hippocampus. Finally, the participants with the most anterior distribution of activity showed the poorest recognition memory performance.

In this study, the correlation between the old/new effect and cortical volume was dependent on the common influence of age. The age influence is a common factor often accounting for much of the variance reported in both cerebral morphometry and cognitive function studies. There are several possible reasons for this age influence. One is that life span samples including old participants often contain more variance, both in morphometric and functional measures. This makes statistical inferences easier. Homogenous samples may not exhibit enough variation to obtain statistical significance. A second possibility is that some old participants may be in the beginning of an age related, and perhaps disease-related structural and cognitive decline. That is, significant relationships between structural indices and electrophysiological or cognitive variables may be a result of below-normal functioning, even though the decline at study time does not fit with any diagnostic criteria. Yet another hypothesis may be that relationships between cognitive function and MRI-derived structural measures are strengthened by change in structure and function. Development or change in structural indices of brain health may tell us more about cognitive function than an absolute measure. This may be true for both patient groups and healthy subjects, and probably in all parts of the life span. Throughout life, changes in brain structure and cognitive function will inevitably happen, and this may create or strengthen a relationship between brain structure and cognitive function that was not present or weak in young persons. Consequently, this suggests that structural indices will be more predictive of cognitive function in age spans where structural variance and change is more pronounced, for instance in early development or late in life.

This prediction was partly tested in a longitudinal study with elderly participants by Kramer et al. (2007). They found that a longitudinal decrease in hippocampal volume was associated with a decline in memory functioning while a decline in cortical gray matter was

associated with a decline in executive functioning. These volumetric results support the change hypothesis, but more studies are needed, also in younger cohorts. The change hypothesis is not exclusively applicable to volumetric and thickness studies. The same arguments could be made regarding white matter connectivity. We will in the next section discuss some applications of DTI in the study of normal cognition.

4.1. White Matter Connectivity as an Index of Brain Health and Function

As a parameter of white matter connectivity and integrity, DTI is potentially a highly interesting structural measure indexing one parameter of the biological basis of neuronal communication in distributed networks. As is well documented, the neurochemical communication between neurons is facilitated by sheaths of myelin covering the axon walls. Facilitating speeded signal transmission along the axon walls, myelin allows immediate and synchronous communication between highly specialized and integrated neuronal networks (Bartzokis, 2004). As argued, complex cognitive processing is probably subserved by widely distributed cortical and subcortical networks. Any parameter estimating the potential for speeded neuronal communication between these regions must be regarded as highly interesting in the study the cerebral and biological underpinnings of cognitive processing.

White matter integrity as indexed by FA has been reported to decline as a function of normal aging (Charlton et al., 2006; Kochunov et al., 2007; Moseley, 2002; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Pfefferbaum & Sullivan, 2003; Salat et al., 2005; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Sullivan & Pfefferbaum, 2006; Wozniak & Lim, 2006), supporting the disconnection hypothesis of normal aging and accompanied cognitive decline (Bartzokis, 2004; Charlton et al., 2006; Charlton et al., in press; Grieve, Williams, Paul, Clark, & Gordon, 2007; Moseley, Bammer, & Illes, 2002; O'Sullivan, Barrick, Morris, Clark, & Markus, 2005; O'Sullivan et al., 2004). Reduced FA compared to normal controls has been reported in groups of patients with schizophrenia (Cheung et al., 2007), multiple sclerosis (Ge, Law, & Grossman, 2005) and Alzheimer's disease (Huang & Auchs, 2007). As broad application of DTI is relatively recent, only a few studies have addressed questions regarding healthy cognitive functioning in relation to DTI parameters. Increased DTI measures have been associated with better reading abilities in children (Deutsch et al., 2005). Madden et al. (2004) reported negative correlations between FA in the internal capsule and RT in a speeded response task, while Tuch et al (2005) found the opposite pattern. The finding that higher FA predicted higher RT was surprising.

Tuch et al. (2005) argues that FA is not solely an index of degree of myelination and white matter connectivity, but is, as mentioned earlier, also influenced by factors like axon diameter and crossing fibres. Larger axon diameter could increase the radial diffusivity, and thus decrease FA. In regions with crossing fibres, the FA is highly influenced by the number and direction of these fibre tracts, complicating the biological interpretations of FA. Even though some methods to estimate and differentiate several fibres in each voxel have been developed

(Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Tuch, 2004; Tuch, Reese, Wiegell, & Wedeen, 2003), the challenge of crossing fibre tracts in DTI studies has not been resolved. Despite these methodological challenges, DTI is considered an interesting tool to estimate white matter connectivity in vivo, and DTI studies have successfully pinpointed

biological variability underlying normal variation in higher order cognitive function in healthy adults.

Charlton et al (in press) studied the relationship between age-related variance in executive function and DTI variables in a sample of middle aged and old participants. Testing their data against existing theoretical and empirical path models, they found evidence for a direct association between white matter connectivity in a predefined ROI covering a major part of the brain's white matter and working memory functions. This implies that DTI variables might be a valid marker of brain structure supporting higher order cognitive processes, also in healthy samples. Since the analyses were restricted to voxels included in the ROI, this study is not informative of regional contribution to cognitive variability. Grieve et al (2007), using a ROI-based approach, reported an age-related decline in FA of 3 % per decade in frontal areas. Using a relatively unrestricted voxel based approach, they detected two bilateral frontal areas showing the most profound age related reduction in FA. Further, this decrease significantly contributed to an age-related decrease in executive functions in their healthy adult sample. Thus, this study localized bilateral frontal white matter regions both sensitive to aging and variability in cognitive measures of executive function.

Though the application of DTI in the study of cognition in healthy samples is intuitively attractive, further studies are clearly needed. It is also of great interest to combine different structural imaging techniques in order to shed light on the dynamics of the contribution of structural brain characteristics to cognition. For instance, it is not known how regional white matter volume, which has been found predictive of cognitive function, (Raz & Rodrigue, 2006) is related to diffusion properties in the same region. Further, it is not known how variability in regional cortical thickness is related to structural properties of the underlying white matter. As reviewed, studies of healthy children, adolescents and adults suggest highly complex and dynamic interactions between these structural measures and cognitive variability, in a developmental perspective, and also as longitudinal predictors of intersubject variability.

4.2. Variability as an Index of Brain Function

It is possible that structural brain variables may be more sensitive to behavioural and electrophysiological variability than standard neuropsychological composite scores or ERPs, which typically treat inter subject variability as noise or measurement errors. Intrasubject variability has been linked to brain structure and CNS function (MacDonald, Nyberg, & Backman, 2006). Walhovd & Fjell (2007) found a negative correlation between white matter volume and a measure of intrasubject variability in RT (standard deviation, sdRT) in a speeded response task. Interestingly, white matter volume was also found to predict performance intelligence through the influence on sdRT. In a similar study, Fjell & Walhovd (2007) reported positive correlations between age and trial-to-trial variation in attention related electrophysiological potentials (P3a/P3b), and a negative correlation between intelligence and variability. ERP variability also correlated negatively with cortical thickness in the temporoparietal junction (TPJ) and frontal regions. Thus, variability may be a valid measure of brain function. The biological underpinnings of behavioral and electrophysiological variability are not well enough known, but a link to white matter and myelin function is appealing. DTI studies may be able to explore these associations further.

4. Themes in Studying Structure-Function Relationships

Below, three example themes within which changes in brain structure and changes in cognitive function can be studied are presented. First, the relationship between structural cerebral changes with healthy aging and changes in cognitive function are discussed. Second, a rough overview over pathological age-changes in brain and cognition in Alzheimer Disease (AD) is given, and contrasted to normal aging. Finally, structural plasticity and the potential to induce changes in brain structure detectable by MRI are discussed.

4.1. Healthy Aging: Changes in Brain Structure and Cognitive Functions with Normal Aging

Most people experience a reduction in mental capacities with increasing age. For instance, processing speed, memory function, executive function, and visual reasoning, change with age. This does not need to be related to disease processes, but occurs also as a result of normal aging. Other functions, especially related to verbal knowledge, are easier to maintain on a high level also with advancing age. Still, the cognitive reductions most will experience with age are almost certainly partly caused by structural changes in the brain. MRI studies have shown that the volume of the brain is reduced with age (Allen, Bruss, Brown, & Damasio, 2005; Blatter et al., 1995; Courchesne et al., 2000; Fotenos, Snyder, Girton, Morris, & Buckner, 2005; Good et al., 2001; Jernigan et al., 1991; Jernigan et al., 2001; Murphy et al., 1996; Pfefferbaum et al., 1994; Raz et al., 1997; Resnick et al., 2000; Salat et al., 2004; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004; Taki et al., 2004; Walhovd et al., 2005). The decrease in brain volume is caused by reductions in the volume of the cerebral cortex, white matter, and several subcortical structures. In one study looking at 16 different brain structures, it was found that age correlated significant with 14, with only two structures being marginally significant (Walhovd et al., 2005). The highest age correlation was observed for the volume of the cerebral cortex ($r = -.78$), while also white matter volume ($r = -.51$) and the volume of the lateral ventricles ($r = .70$) showed high correlations. Similar results are found in dozens of studies. Even though most studies are cross-sectional, volume reductions are replicated in longitudinal studies also (Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Raz, Rodrigue, & Haacke, 2007). Examples of age effects from one such study can be found in Figure 8.

All higher cognitive functions are supported by the cerebral cortex. According to the principle of modular organization of functional neuroanatomy, specific cortical areas will support specific cognitive processes. Thus, it is reasonable to expect that since different cognitive abilities change with age at different rates, age effects on the cerebral cortex will also vary. To a certain extent, we would expect that the cognitive functions that are reduced most with age are supported by areas in the cerebral cortex which are especially vulnerable to the effect of aging. Studies looking at different structures in the cerebral cortex have revealed that there is substantial variation in the effects of age. Practically all studies find thinning or volume reductions in frontal or prefrontal areas (Abe et al., 2006; Brickman, Habeck, Zarahn, Flynn, & Stern, 2007; Good et al., 2001; Kalpouzos et al., 2007; Raz et al., 2007; Salat et al.,

2004; Sato, Taki, Fukuda, & Kawashima, 2003; Taki et al., 2004). This fits well with the so-called “last in, first out” hypothesis. According to this view, the parts of the brain that develop last, will be the first to undergo changes. The hypothesis is applied both to ontogenetic and phylogenetic development. A very nice feature of this model, is that it incorporates development and aging within the same frame work. Thus, development and aging are seen as connected processes, and it will be beneficial for the understanding of age-changes to also understand neurocognitive development. Based on the “last in, first out” hypothesis, it is natural to expect that frontal or prefrontal areas of the brain will be vulnerable to age-changes, since these cortical areas are maturing late in development (Gogtay et al., 2004). This also fits well with the finding that executive functions are vulnerable to normal age-changes (Head, Snyder, Girton, Morris, & Buckner, 2005)

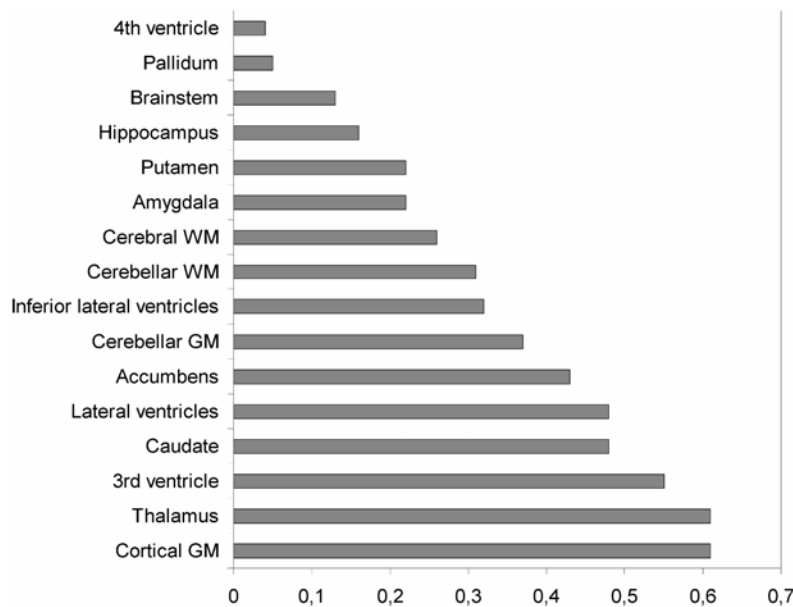


Figure 8. Age effects on neuroanatomical volumes. The bars show the estimated effects of age on neuroanatomical volume. The numbers on the x-axis are proportions (equal to R^2). Data are taken from (Walhovd et al., 2005). GM: Gray matter; WM: White matter.

Even though age effects may be marked in frontal regions, these are by no means the sole areas to undergo volumetric age reductions. The occipital lobes is often found to be reduced in volume or thickness (Abe et al., 2006; Kalpouzos et al., 2007; Salat et al., 2004; Taki et al., 2004), but the cognitive or functional significance of these changes is less clear. Age effects in the parietal cortex are also common (Abe et al., 2006; Brickman et al., 2007; Good et al., 2001; Salat et al., 2004), although the exact localization of the effects may vary somewhat between studies. Often, effects around the central sulcus are found (Good et al., 2001; Salat et al., 2004). It is possible to speculate that these effects may contribute to the sensory and motor changes observed in normal aging, but we are aware of no studies that have tested this explicitly.

As an example of another parietal effect, was the finding by Salat et al. (2004) that an area dorsal in the left parietal cortex was thinner in elderly. This area overlapped to some

degree with the precuneus, which is known to be involved in episodic memory retrieval (Buckner, 2004; Cavanna & Trimble, 2006). Episodic memory is one of the mental abilities that is reduced with increasing age (Lezak, 1995), so this also suggests a possible structure-function correlate in aging. Precuneus also projects to medial parietal cortex areas, i.e. posterior cingulate cortex and retrosplenial cortex, which also constitute a part of a cortical memory network (Buckner, 2004). Walhovd, Fjell, Dale et al. (2006) have shown that cortical thickness in this area is related to verbal episodic memory over long time intervals, independently of hippocampal influence. Thus, volumetric changes in such parietal areas may contribute to changes in memory performance. Fjell et al. (2006) found that cognitively high-functioning elderly had thicker cortex in the posterior cingulate. However, there are still controversies about whether structural changes in the part of the cortical-subcortical episodic memory network comprising medial temporal and parietal areas are the prime cause of decrements in memory function in normal aging. The episodic memory network also involves frontal areas, and for instance Buckner (2004) argues that the relatively mild memory problems often seen in normal, non-pathological aging is caused by gray matter atrophy and also white matter changes in fronto-striatal systems, in addition to changes in corresponding neurotransmitter systems. As argued, frontal areas undergo significant structural changes with age. Walhovd, Fjell, Reinvang, Lundervold et al., (2005) found that the same was true for striatum also. Thus, this view also fits well with the observed volumetric changes in the brain in normal aging. Further, Buckner (2004) argues that degeneration of especially MTL areas of the abovementioned memory network is a trait associated with very early Alzheimer's disease (AD), and that pathological changes in these areas may be manifested before clinical symptoms can be found. Thus, according to Buckner (2004), memory decline in normal aging and in Alzheimer disease is caused by separate processes: Atrophy and structural changes in the frontostriatal network is the primary cause of memory problems in normal aging, while AD preferentially affects memory-related neural circuits including the medial temporal lobe (MTL, e.g. hippocampus) and as a consequence, also areas with dense MTL connections, including medial parietal areas (e.g. retrosplenial cortex and posterior cingulate). Support for this view is given by Head et al. (2005). This short discussion shows that studies of brain structure can inform us on the causes and cognitive effects of normal and pathological aging, and that more research is needed to better understand the relationship between structural and cognitive changes in aging.

Studies of cortical thickness or volume tend to find that these are mainly linearly related to age from early adulthood (Fotenos et al., 2005), i.e. the reductions are of the same amount throughout most of the adult life-span. However, this pattern is not characteristic of all brain structures. For instance, hippocampal volume has been found to be non-linearly related to age (Walhovd et al., 2005). Also, white matter volume has been found to be related to age in a quadratic fashion (Allen et al., 2005; Walhovd et al., 2005), where volume increase is found until middle age, followed by later decline. This may indicate that myelination of nerve fibers is a slow process, and that the ability of different brain areas to communicate with each other is developing during a large part of the adult life-span. It is also possible to speculate that there is a relationship between white matter growth and cortical thinning, and that these processes in combination can explain more of the cognitive changes that happen during this time. Age-related changes in the white matter of the brain are assumed important for age-related changes in cognition. As argued above, complex cognition involves the interplay between a large number of cortical areas, and this requires the connections between the

different brain areas to be efficient to allow fast signal transference between distant brain areas. Thus, if the brain's nerve fibers are affected by normal age processes, this will likely exert an effect on cognition. George Bartzokis argues that neural circuits involved in motor activity start to undergo demyelination already from the fourth decade of life, which may contribute to explain the age-related reductions in speed of processing and reaction time that occur about the same time. However, Bartzokis further argues that myelination continues in brain areas involved in higher reasoning in middle-aged, and that this makes our judgment better in late than early adulthood: "*Fifty is when we're fully myelinated and our intellectual powers soars*" (Interview in Discover, Spring 2007, p. 14).

In addition to volumetric studies of white matter, DTI-studies of age-related changes in the FA index tend to find rather large decreases in FA with increasing age (Charlton et al., 2006; Salat et al., 2005; Salat et al., 2005). As discussed earlier, whether this primarily is caused by demyelination or axonal degeneration is not known. In a review paper, it is argued that both changes in axons, myelin loss, and increase in extracellular space contribute to the reductions in FA seen in normal aging (Moseley, 2002). Anyway, the changes in FA show substantial overlap with the morphometric cortical effects. Salat, Tuch, Hevelone et al. (2005) found that FA decreases were especially pronounced in prefrontal regions, which corresponds well both to the known cortical volumetric reductions in the prefrontal cortex, and to the reduced executive capabilities seen in elderly. In a recent study, it was found that reductions in white matter integrity with age, as measured by FA, directly affected working memory performance (Charlton et al., in press). The authors suggested that white matter integrity may be especially important for cognitive processes that involve large neural networks, as is the case with working memory (D'Esposito, 2007). A correlation between working memory and DTI parameters were also found in a previous study (Charlton et al., 2006). Another recent study also demonstrated a relationship between FA in frontal brain areas and executive functions (Grieve et al., 2007), and it was concluded that FA may provide an early means for the detection of age-related cognitive change.

The relationship between white matter integrity and white matter volume is not much studied (Wozniak & Lim, 2006), and probably not straight-forward. Salat, Tuch, Hevelone et al. (2005) found that even though white matter volume is increasing until middle age, FA was significantly reduced in mid-life. It is an important task for future research to uncover the relationship between DTI measures and white matter volumetry. As suggested earlier, one way of doing that is to compare changes in principal as compared to radial diffusion, to better characterize the diffusion as related to axonal degeneration or demyelination.

As shown above, the brain undergoes large changes in structure and volume throughout the adult life-span. These changes are accompanied by changes in cognitive abilities, and there is substantial overlap between age-changes in structure and age-changes in the cognitive functions that depend on the various brain structures. However, in addition to the normal changes in structure and function, pathological aging, e.g. AD, is characterized by accelerations in brain aging and in cognitive reductions. We now turn to AD, and will give a short overview of some of the neurobiological processes that accompanies this progressive disease, how these differ from normal aging, and the cognitive deficits that follow.

4.2. Pathological Age-Changes: Alzheimer Disease (AD)

Alzheimer's disease (AD) is a progressive disorder that ultimately leads to deterioration of major parts of the brain and large cognitive deficits. A related condition is mild cognitive impairment (MCI), which greatly increases the likelihood of developing AD. For patients with MCI, there is an annual conversion rate from to AD of 6-25% (Petersen et al., 2001). A cardinal trait of MCI is episodic memory deficit, while other cognitive functions often are relatively spared. Thus, it may be tricky to differentiate early stages of MCI from normal aging based on neuropsychological tests alone, since also normal aging is accompanied by at least some reductions in episodic memory abilities.

To be able to better diagnose and begin proper treatment of patients as early as possible, it is of vital importance to be able to identify early brain changes in MCI. Thus, we need to get an understanding of the pathophysiology of AD. Measures of brain metabolism provided by Positron Emission Tomography (PET) have also proved to be of value in detecting AD-related changes (e.g. Mosconi et al., 2007), but PET scanning is so far not widely available. Structural MRI and CSF biomarkers are available methods in most modern hospitals, and are of special importance in addition to neuropsychological tests. It is consistently found that MCI and AD are characterized by volumetric changes detectable by MRI. In AD compared to controls, hippocampal reductions are found (de Leon, George, Stylopoulos, Smith, & Miller, 1989; Fischl et al., 2002), in addition to bilateral thinning of most parts of the cerebral cortex, with especially large effects in parietal and temporal areas (Du et al., 2007). Consistent differences in brain morphometry are also found when MCI patients are compared to healthy controls, especially in the hippocampus and the surrounding temporal cortical areas (Bell-McGinty et al., 2005; Du et al., 2001; Karas et al., 2004; Singh et al., 2006). However, recent results also indicate differences in frontal and parietal cortical areas (Singh et al., 2006). These effects correspond rather well to the already described cerebral networks involved in episodic memory, i.e. temporal (hippocampus, parahippocampal and entorhinal cortex) and parietal (precuneus, posterior cingulate, retrosplenial cortex) areas (Buckner, 2004).

In addition to the morphometric effects, AD is further characterized by amyloid beta ($A\beta_{42}$) deposits (possibly due to increased plaque sequestration) and neurofibrillary tangles composed of the microtubule-associated protein tau. Especially hippocampal and surrounding areas are hit by tau-related pathology early in the disease (Guillozet, Weintraub, Mash, & Mesulam, 2003). Thus, the brain areas that are affected most by tau pathology in early stages are areas that are very important for normal memory function. It is likely that the tau pathology contributes to the observed memory problems (de Leon et al., 2006). Further, it has been suggested (de Leon et al., 2006) that the morphometric hippocampal damage is secondary to the pathological depositions of intracellular neurofibrillary tangles (Price & Morris, 1999) and extracellular amyloid (Arriagada, Marzloff, & Hyman, 1992; Thal, Rub, Orantes, & Braak, 2002). de Leon et al. (2006) suggested that while CSF levels of $A\beta_{42}$ and T-tau (a marker of neuronal damage) are not specific to AD, P-tau (hyperphosphorylated tau) is uniquely elevated in AD, and that elevations found in MCI are useful in predicting the conversion to AD. Also, de Leon (2006) argued that elevations of the P-tau level are highly correlated with reductions in the MRI hippocampal volume, and that by using CSF and MRI measures together one improves the separation of controls and MCI. This is supported by Bouwman et al. (2007), who found that patients with an abnormal CSF profile ($A\beta_{42}$ and tau)

and medial temporal atrophy had a fourfold likelihood of progressing from MCI to AD over 19 months.

The levels of CSF biomarkers A β 42 and T-tau are highly correlated with age, as is the reduction of brain volume in specific areas. Thus, these biomarkers do not constitute unambiguous signs of MCI or AD, but do also reflect normal age changes. The prevailing view is that the symptoms seen in MCI/ AD is more than just acceleration of normal age processes, but constitute a unique specter of symptoms with distinct pathological causes. As mentioned, Buckner (2004) argues that memory deficits in AD is characterized by atrophy of the MTL memory system, that normal aging is characterized by atrophy in the frontal-striatal system, and that the mild memory problems seen in normal aging may be secondary to executive deficits caused by disruptions in the network specifically supporting these functions (Head et al., 2005). Still, as argued above, there is also considerable overlap between normal age changes in brain and cognition, and the changes that come with early stages of the development of MCI. For instance, most morphometry studies find that normal aging affects both MTL structures (e.g. hippocampus), and frontal and striatal structures. The pattern of different symptoms, however, seems to distinguish MCI/ AD from normal aging. In a paper that probably will be influential in the years to come, Dubois et al. (2007) suggest new criteria for AD. They argue that the often used criteria of the DSM-IV-TR system are falling behind the scientific knowledge. They suggest that in addition to early and significant episodic memory impairment, there must be at least one abnormal biomarker among structural neuroimaging with MRI, molecular neuroimaging with PET, and CSF analysis of A β 42 or tau proteins, to make the AD diagnosis in research.

The advancement in DTI methodology during the past years has lead to large interest in mapping white matter changes in MCI/AD, and to study how the microstructure of white matter in AD differs from normal aging. In a recent study, FA differences between AD patients and controls were found in the left temporal area and the left hippocampal region, but MCI patients and normal controls did not differ in terms of FA (Fellgiebel et al., 2004). Another study, however, demonstrated that both MCI and AD patients had reductions in regional FA in multiple posterior white matter regions (Medina et al., 2006). A great overlap between effects in AD and MCI was seen, which indicates that changes in the microstructure of the white matter occur prior to the development of AD. This conclusion fits with the results of another study where reduced FA in the limbic parahippocampal subgyral white matter, right thalamus, and left posterior cingulate was found in MCI patients compared to normal controls (Rose et al., 2006). These effects overlap with a neural network for episodic memory. Regional measures of FA were found to correlate with neuropsychological functioning. Similar findings have also been made by Naggara et al. (2006), who found that FA was decreased bilaterally in the WM of the temporal lobe, the frontal lobe, and the splenium of the corpus callosum in AD patients compared to controls. The authors interpret their findings to be in accordance with disruptions of temporal-to-frontal connections. Duan et al. (2006) also found reduced FA in the splenium of the corpus callosum, as well as in frontal, temporal, and parietal white matter. In addition, FA was strongly positively correlated with cognitive functioning (MMSE scores). Longitudinal data have further suggested that hippocampal mean diffusivity is a better predictor of conversion from MCI to dementia than hippocampal volume (Fellgiebel et al., 2006). Thus, several studies now provide coherent results that (1) FA is reduced in MCI/ AD patients, (2) These reductions are often found in areas relevant for episodic memory, and (3) FA in these patient groups seems to correlate with cognitive

function. In addition, some authors, e.g. (Choi, Lim, Monteiro, & Reisberg, 2005; Wozniak & Lim, 2006), have argued that the often-found decreases in white matter integrity in frontal areas is consistent with the “last in, first out” theory or the theory of “retrogenese”, according to which pathological processes in AD proceed in an opposite manner to normal developmental patterns.

In addition to studies using the FA metric, attempts to disentangle the FA effects in AD-pathology into measures of axial and radial diffusivity have been made. Recently, it has been found that compared to normal controls, AD patients have decreased FA and increased radial diffusivity in frontal, temporal, parietal, and occipital lobes, in addition to reduced axial diffusion in temporal areas (Huang, Friedland, & Auchus, 2007). Further, MCI patients had lower FA and decreased axial diffusivity in temporal white matter, in addition to decreased FA and higher radial diffusivity in parietal areas. These effects had cognitive correlates, in that temporal FA correlated with episodic memory, frontal FA correlated with executive function, and parietal FA correlated with visuospatial abilities. Thus, evidence for functionally relevant microstructural changes in white matter was demonstrated in patients with MCI and AD. The authors interpreted their findings to be preliminary evidence for axonal degeneration in the temporal lobe. Looking at the results, we see that a mixture of axonal degeneration and demyelination seem to accompany MCI and AD.

Even though a considerable number of studies relating MCI/ AD to DTI measures are published the last couple of years, much more research is needed to understand the cognitive correlates and neurobiological significance of this measure. More longitudinal studies are needed, as well as more studies combining DTI measures with CSF biomarkers, PET data, and volumetric data of both white matter and cortical gray matter.

4.3. Training/Plasticity

Cerebral macro- and microstructure have obvious implications for how the brain mediates and control behaviour and cognition. Still, the impact of behavioural and cognitive training on change in structural integrity has not been extensively studied. It is well documented that memory is supported and accompanied by relatively lasting changes in synaptic functioning through the means of long term potentiation (LTP) (Cooke & Bliss, 2006). Cognitive rehabilitation studies in patients with traumatic brain injury (TBI) or suffering from various neuropathologic or vascular diseases like stroke have shown that cognitive improvement does take place (Ryan & Warden, 2003), even in rather severe cases (Zhu, Poon, Chan, & Chan, 2007). Cognitive rehabilitation has also been found to be accompanied with functional reorganization as measured with neuroimaging techniques (Jones et al., 2006; Matthews, Johansen-Berg, & Reddy, 2004; Rossini, Calautti, Pauri, & Baron, 2003). However, the potential for experience and training related structural change and reorganization in healthy subjects have been less studied (Nyberg et al., 2003). Draganski et al (2004) obtained structural MRI scans prior to and after extensive juggling practice. They reported transient structural changes induced by training in mid-temporal areas bilaterally and in the left posterior intraparietal sulcus. These changes were reduced when the practice sessions ceased. This study clearly shows the brain’s ability to temporarily alter its structural properties in response to intense motor learning. In another study, Draganski et al (2006) found a significant increase in posterior and lateral parietal cortex gray matter bilaterally in

students preparing for a hard exam. These were still present three months after the exam, suggesting lasting abstract learning induced structural changes. They also reported a similar long lasting learning induced increase in hippocampal volume. These two longitudinal studies, along with a number of cross-sectional data showing experience-correlated structural brain differences (e.g. Maguire et al., 2000) support the notion of the brain as a plastic biological structure. However, the exact neurobiological processes responsible for these observed structural changes are not known. Potential mediators include learning induced synaptic growth which is thought to represent and support relatively stable cellular changes maintaining long-term cognitive changes (Bailey, Kandel, & Si, 2004). In support of this synaptic plasticity, Trachtenberg et al., (2002) reported a relatively high degree of experience related dendritic spine plasticity in adult mice. This was suggested to reflect sensory experience driven formation and elimination of synapses underlying learning induced remodelling of neural circuits. Whether these structural changes appear in adult humans or not, and whether the change dynamics are equivalent to those observed in mice, is not known. Independently of possible biological causes, learning induced brain structural changes have been observed. It is of great interest, both theoretically and clinically, to study these changes in detail. Implementation of DTI analyses could provide an interesting window into the potential for white matter plasticity, and the combination of different neuroimaging methods, including regional cortical thickness, electrophysiology and DTI, might collectively represent an excellent window into the dynamics of brain plasticity.

Conclusion and Further Research

Structural and functional measures of brain characteristics give important information on the biological basis of normal cognitive age changes, pathological changes, and learning. In our opinion, one of the great challenges, as well as foundations of further research, is to accept that structure-function relationships are, more often than not, of a complex nature, and this complexity must be investigated. It is premature to assume that structure-function relationships can be interpreted in the same manner in development and aging, and in health and disease. Instead of arguing about whether bigger is better, or more brain activity is good or bad, one might ask “When is bigger better, and when is bigger poorer?” and “When is bigger activation better, when is it signifying compensatory processes, when does this yield successful cognition, and when not?” Only then can the regularities be found and mapped. Measures of microstructural characteristics, derived by DTI, are among the new promising methods that can be applied in the study of cognition. In conclusion, multimodal investigation of the biological potential for structural and cognitive change is among the most interesting and promising current neuroscientific research topics.

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