Brain characteristics of memory decline and stability in aging

Contributions from longitudinal observations

Sara Pudas
To my grandmother, Viola
Abstract

Aging is typically associated with declining mental abilities, most prominent for some forms of memory. There are, however, large inter-individual differences within the older population. Some people experience rapid decline whereas others seem almost spared from any adverse effects of aging. This thesis examined the neural underpinnings of such individual differences by using longitudinal observations of episodic memory change across 15-20 years, combined with structural and functional magnetic resonance imaging of the brain. Study I found significant correlations between volume and activity of the hippocampus (HC), and memory change over a 6-year period. That is, individuals with decline in HC function also had declining memory. In contrast, Study II showed that successfully aged individuals, who maintained high memory scores over 15-20 years, had preserved HC function compared to age-matched elderly with average memory change. The successful agers had HC activity levels comparable to those of young individuals, as well as higher frontal activity. Study III revealed that individual differences in memory ability and brain activity of elderly reflect both differential age-related changes, and individual differences in memory ability that are present already in midlife, when age effects are minimal. Specifically, memory scores obtained 15-20 years earlier reliably predicted brain activity in memory-relevant regions such as the frontal cortex and HC. This observation challenges results from previous cross-sectional aging studies that did not consider individual differences in cognitive ability from youth. Collectively the three studies implicate HC and frontal cortex function behind heterogeneity in cognitive aging, both substantiating and qualifying previous results from cross-sectional studies. More generally, the findings highlight the importance of longitudinal estimates of cognitive change for fully understanding the mechanisms of neurocognitive aging.

Keywords: aging, episodic memory, individual differences, longitudinal assessment, magnetic resonance imaging, hippocampus, frontal cortex
List of studies

This doctoral thesis is based on the following studies:


Contents

Introduction .................................................................................................................. 13

The study of human memory ....................................................................................... 15
  Overview of memory systems ................................................................................. 15
  Magnetic resonance-based neuroimaging .............................................................. 17
  Episodic memory in the brain .................................................................................. 19
    Medial temporal lobe contributions to memory .................................................... 20
    Frontal cortex contributions to episodic memory ................................................. 21
    Frontal – medial temporal interactions in memory processing ......................... 24
  Other memory-relevant brain regions ..................................................................... 25

Aging and memory ..................................................................................................... 26
  Individual differences and their determinants ....................................................... 29

Brain aging ................................................................................................................. 33
  Structural brain changes in aging .......................................................................... 33
    Structure-cognition relations ................................................................................ 35
  Functional brain changes in aging .......................................................................... 37
    Frontal cortex ........................................................................................................ 38
    Medial temporal lobe ............................................................................................. 41
    Synthesis and summary of MTL and PFC function in aging ............................ 43

Aims of the thesis ....................................................................................................... 45

Methods ...................................................................................................................... 46
  The Betula study ....................................................................................................... 46
  Study samples and selection procedures ............................................................... 47
    The ImAGen cohort ................................................................................................. 47
    Study I participants ................................................................................................ 48
    Study II participants .............................................................................................. 49
    Study III participants ............................................................................................ 51
  Assessing selection effects ..................................................................................... 51
  Longitudinal memory measure ............................................................................... 53
  Statistical classification for Study II ....................................................................... 55
  Scanner tasks ............................................................................................................ 56
    Study I: Incidental encoding of words .................................................................. 56
    Study II and Study III: Face-name paired associates ......................................... 56
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain imaging</td>
<td>57</td>
</tr>
<tr>
<td>Preprocessing and analysis of imaging data</td>
<td>58</td>
</tr>
<tr>
<td>Functional data</td>
<td>58</td>
</tr>
<tr>
<td>Structural data</td>
<td>60</td>
</tr>
<tr>
<td>Diffusion Tensor Imaging</td>
<td>61</td>
</tr>
<tr>
<td>Overview of empirical studies</td>
<td>63</td>
</tr>
<tr>
<td>Study I</td>
<td>63</td>
</tr>
<tr>
<td>Study II</td>
<td>65</td>
</tr>
<tr>
<td>Study III</td>
<td>67</td>
</tr>
<tr>
<td>Discussion</td>
<td>70</td>
</tr>
<tr>
<td>The hippocampus and the medial temporal lobe</td>
<td>70</td>
</tr>
<tr>
<td>Structural findings</td>
<td>73</td>
</tr>
<tr>
<td>Incidental findings</td>
<td>74</td>
</tr>
<tr>
<td>Frontal cortex contributions to memory in aging</td>
<td>76</td>
</tr>
<tr>
<td>Left inferior frontal cortex</td>
<td>77</td>
</tr>
<tr>
<td>Right inferior frontal cortex</td>
<td>80</td>
</tr>
<tr>
<td>Left superior frontal cortex</td>
<td>82</td>
</tr>
<tr>
<td>Synthesis and summary of frontal cortex findings</td>
<td>82</td>
</tr>
<tr>
<td>Contributions of longitudinal data</td>
<td>84</td>
</tr>
<tr>
<td>Limitations and future directions</td>
<td>85</td>
</tr>
<tr>
<td>Concluding remarks</td>
<td>87</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>89</td>
</tr>
<tr>
<td>References</td>
<td>90</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>APOE</td>
<td>apolipoprotein E</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood-oxygen-level-dependent</td>
</tr>
<tr>
<td>BPM</td>
<td>biological parametric mapping</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>HC</td>
<td>hippocampus</td>
</tr>
<tr>
<td>LIFC</td>
<td>left inferior frontal cortex</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTL</td>
<td>medial temporal lobe</td>
</tr>
<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
</tr>
<tr>
<td>PHG</td>
<td>parahippocampal gyrus</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SPM</td>
<td>statistical parametric mapping</td>
</tr>
</tbody>
</table>
Introduction

Aging will affect us all. The common notion is that it entails a decline in both physical and mental abilities. However, this does not need to be the case. The degree of decline varies substantially in the older population, and some individuals seem to be almost spared from any negative effects of aging. This thesis will deal with the neural underpinnings of these large individual differences in mental abilities in aging. The specific focus will be on our memory ability, since memory failure is one of the most common complaints in the older population, and its effects on daily activities of elderly individuals can be substantial.

Today there is already a wealth of knowledge of how memory functions change in aging, and also about the neural underpinnings of such changes. However, as will be become clear in the following sections of this thesis, controversies still persist. What is the reason for this? One reason could be that most of what is known about the effects of aging on cognition and the brain is derived from studying age-differences between young and elderly individuals, neglecting the variability within the older population. More recently this variability has become acknowledged and studied, but most investigations have still only studied individuals at one point in time, with so-called cross-sectional designs. These designs only provide a snapshot of the age-related processes affecting individuals, and are at risks of confusing variability in memory ability from youth with age-related changes. That is, one can fail to detect age-related memory decline in an initially high-performing individual who still performs above average in older years. Or mistakenly infer memory decline in an elderly individual who has had a low memory ability from youth. Therefore, in this thesis, I have used longitudinal data on memory performance change measured in the same group of individuals during 15-20 years. This approach offers improved sensitivity and specificity when addressing the neural underpinnings of age effects on memory ability.

Throughout the empirical studies in this thesis I have used magnetic resonance imaging (MRI) to study the brain characteristics of elderly individuals. To the larger part I have focused on functional MRI (fMRI) to study age-related changes in brain function, while the research participants are performing memory tasks. fMRI assesses brain function by measuring changes
in blood flow in response to task requirements. I have also looked at age-related change in brain structure, for instance shrinkage of brain structures that are relevant for memory. MRI as a brain imaging method has several advantages. MRI scanners are commonly available at most large hospitals, and do not expose research participants to radiation, hence making them suitable in longitudinal studies of brain function.

The scope of this thesis is restricted to age-related changes within the normal range. That is, aging in the absence of pathological conditions, such as Alzheimer’s disease, that compromise memory and other mental abilities. Getting a better understanding of the processes that dictate normal aging will make it easier to differentiate and diagnose pathological conditions early in their progression. Also, by better understanding normal aging processes one can devise interventions to attempt to mitigate their negative effects on memory function in elderly individuals. On the other hand, learning what characterizes the brains of those who are successfully aged could guide the search for ways to preserve such brain structures and functions in a larger proportion of the aging population. Ultimately, I hope that the work presented in this thesis will take us one step (no matter how small) towards alleviating the societal burden of an aging population, and increasing the quality of life for older individuals.
The study of human memory

It is generally agreed that human memory is not a unitary concept, but comprises several interrelated subsystems or functions. This thesis will deal with age-related decline and stability of a specific subsystem referred to as episodic memory. Episodic memory is a consciously accessible long-term memory system that involves personally experienced events, tied to a specific place and time (Tulving, 1972). Although the definition might seem cumbersome at first glance, episodic memory encompasses much of what we think of as everyday memories. This can include things like the name of your first grade teacher, the birthday presents you received for your last birthday, and items from a word list you were given as a part of a psychology experiment 10 minutes ago. In the following sections I will first provide an overview of the memory systems humans are thought to possess, in order to illustrate what distinguishes episodic memory from the other types of memory. Then, a brief overview of neuroimaging methods will be provided, before turning to the subject of how episodic memory is represented in the brain and affected by aging.

Overview of memory systems

Memory can be defined in many different ways. A straightforward definition is that it involves the retention of information that is no longer available to the senses. More poetically, some forms of memory have also been referred to as “mental time travel” (Tulving, 2002). A long line of memory research has shown that human memory is not a unitary concept (Gazzaniga, Ivry, & Mangun, 2009; Squire, 2004). Distinctions can be made on several grounds. First, and perhaps most fundamentally, there is usually a distinction based on the temporal interval at which information is retained. Short-term memory is usually thought to last over seconds or minutes, unless conscious effort is made to rehearse the retained information. This type of memory has been shown to be distinct from long-term memory since some patients with brain injuries seem to have selective deficits in short term retention (Warrington & Shallice, 1969). Nowadays the concept of short-term memory has been extended, and is usually referred to as working memory (Baddeley & Hitch, 1974). This is to allow for the fact that information held in short-term memory can also be manipulated, or “worked” on.
Long-term memory is thought to operate on the time span of days to years, and decades, although tasks employed in memory research can have a much shorter time scale than that. Long-term memory is considered to be distinct from short-term memory, but there is also interaction between these two memory systems. For instance, one can intentionally rehearse information in working memory to attempt to encode it into long-term memory. Commonly, long-term memory is subdivided based on different types of knowledge that can be stored. Firstly, there is usually a separation between explicit and implicit long-term memories, also referred to as declarative and non-declarative (Squire, 1992a). This distinction is based on whether one has conscious access to, and can account for, the stored knowledge. Implicit memory covers a wide variety of memory abilities that include, for instance, procedural memory and priming. The former involves various types of skill learning, such as learning to ride a bike. Priming is a type of implicit memory, which is observed when a response to a stimulus is facilitated by prior experience, even in the absence of conscious recollection of that experience. Various types of implicit memories can be intact in otherwise amnestic patients (for reviews, see Squire, 1992, 2004).

Explicit long-term memory is conventionally thought to comprise two different types of knowledge, episodic and semantic (Tulving, 1972). Semantic memory refers to decontextualized general world knowledge and facts, for instance the meanings of words, the capital of France, or what a fork is used for. Episodic memory on the other hand, involves personally experienced events that can be tied to a spatial and temporal context. Episodic and semantic memory can be viewed as parallel and partially overlapping information processing systems (Tulving, 1972). These two types of memory have been distinguished from each other based on reports of brain injured patients with episodic, but not semantic memory deficits (Rosenbaum et al., 2005; Vargha-Khadem et al., 1997), although the reverse pattern has not been clearly established. Also, neuroimaging studies have shown partially different brain regions engaged when participants are performing episodic and semantic memory tasks (Cabeza & Nyberg, 2000). And, importantly for this thesis, these two memory systems also display different trajectories of age-related changes (e.g., Rönnlund, Nyberg, Bäckman, & Nilsson, 2005), with episodic memory being more sensitive to the effects of age. Since episodic memory impairment is also one of the earliest signs of Alzheimer’s disease (Bäckman, Small, & Fratiglioni, 2001) it is highly relevant to study in relation to aging.

In research on declarative long-term memory there is typically a distinction between three different stages of memory processing (Gazzaniga et al., 2009). Memory formation begins with encoding, during which information
is acquired and consolidated into brain networks, in which it is stored. Finally, the last stage is retrieval, when the stored information is accessed and used. In practice there is most likely interaction and partial overlap between these phases (Fletcher & Henson, 2001). For instance, encoding of new information is likely to involve reactivation of previous knowledge related to the information to be encoded. Also, retrieval of previously acquired information may act as a form of recoding of the stored memory trace, strengthening, weakening, or otherwise changing it. And, in principle, memory failure in aging and other situations could result from disturbance of any of these phases or processes.

Although the characterization of different memory systems presented here is commonly used, it should be viewed as a simplification since our understanding of the organization of human memory is still evolving. Some object to the notion of there being neatly separable memory “systems” (see e.g., Roediger, Buckner, & McDermott, 1999), and it is commonly acknowledged that the boundaries between the different types of memory are vague. Most researchers would however agree that memory is not a unitary concept. The categorization given above does capture some broad distinctions in the data and is a useful way to frame discussions about human memory function. Although I refer to different memory systems in this thesis, the interpretation of system should not be taken too literally. I could equally well refer to different memory functions, processes or mechanisms, which are accomplished in the brain by partially overlapping and interacting neural mechanisms.

Magnetic resonance-based neuroimaging

Before turning to the topic of how memory is implemented in brain, I will review the basics of structural and functional MRI. Although a large share of the knowledge on the neural bases of memory derives from lesion and animal studies, functional neuroimaging techniques have provided a unique opportunity to study memory processes in the healthy human brain. But in a strict sense MRI, like other neuroimaging methods, only allows observations of neural events that co-occur, or accompany, for instance, changes in memory ability. One can not necessarily conclude that the observed neural events cause changes in memory. Luckily, there is often converging evidence from lesion, pharmacological, and other types of studies to support conclusions from neuroimaging.

The principle behind structural MRI is to utilize magnetic properties of hydrogen atoms in organic tissue to create images. For a detailed description of MRI principles, see Huettel, Song, and McCarthy (2009). In brief, the constant motion of protons in atomic nuclei (spinning around their principal
axis), generates small magnetic fields. An MRI scanner has a large magnet that generates a static magnetic field, which orients the protons in organic tissue so that their principle axis is parallel to that magnetic field. Thereafter, radio frequency (RF) pulses are passed through the tissue, which causes the protons to absorb energy and thereby change the direction of their orientation in a predictable manner. When the RF pulse is turned off, the protons return to the orientation determined by the external magnetic field of the scanner, at the same time emitting the energy absorbed from the RF pulse. This energy is picked up by detectors in the head coil of the scanner. The information from the scanner is then sent to a computer, where complex algorithms construct an image out of it. The fact that different classes of brain tissue, such as gray and white matter, have different density of protons makes the contrast between them appear on structural MR images.

Functional MRI operates on similar principles as structural MRI. But instead of contrasting between tissue classes, it distinguishes between oxygenated and deoxygenated blood, due to their different magnetic properties. When neural tissue becomes active, blood flow is increased to that brain area in order to accommodate metabolic demands. This results in an increase in oxygenated blood, which exceeds the amount of oxygen that is consumed by the active neural tissue. This excess forms the basis for the blood-oxygen-level-dependent (BOLD) signal (Ogawa, Lee, Kay, & Tank, 1990). Although the BOLD signal does not measure neural activity directly, it is generally considered to be a reasonable proxy (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Mukamel et al., 2005), shown to reflect predominantly the input to and intracortical processing of a given brain area (Logothetis et al., 2001). Therefore, throughout this thesis, the BOLD signal will be considered equivalent to neural activation.

By contrasting BOLD-images of the brain while the participant is performing a cognitive task, with images acquired during some (typically) low-level control condition, one can identify brain areas that are more engaged by the task. During an fMRI experiment there are typically repeated acquisitions of task and control conditions in an alternating manner. Experiments are commonly set up in either blocked or event-related designs, the former assessing neural activation during extended blocks of time, while the latter measures activation in response to short events, such as a single item in a memory experiment. Event-related designs allow for more analytical flexibility, for instance, sorting items of a memory experiment based on whether they were subsequently remembered or forgotten (e.g., Wagner et al., 1998).

MRI can also be used to study the microstructural properties of white matter in the brain. The integrity of white matter can be compromised by disease and aging, which has consequences for memory and other cognitive func-
tions (Gunning-Dixon & Raz, 2000). Investigation of white matter integrity can be performed by quantifying the diffusion of water molecules by application of controlled magnetic gradients in the RF pulse sequence, a technique known as diffusion tensor imaging (DTI). This technique takes advantage of the fact that thermal energy causes water molecules to move randomly (i.e., diffuse) at all temperatures above absolute zero. In brain white matter this movement is constrained by white matter fibers so that diffusion is anisotropic, that is, not equal in all directions. Since diffusion attenuates the MR-signal, the magnitude and preferred direction of diffusion can be quantified for each voxel (i.e., three-dimensional image element) in the brain. For each scan, however, only diffusion in the direction of the specific magnetic gradient can be detected. Therefore, repeated scans with systematically applied gradients in different directions are required to collect as many directions of diffusion as possible (usually at least six). More anisotropic diffusion at a given location in the brain generally reflects more intact white matter at that location. There are, however, acknowledged problems with some of the most common DTI-derived measures of anisotropy. Specifically, they can produce unreliable results in brain regions with crossing white matter fibers, which are commonly occurring across the brain (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2012). In such cases, increased anisotropy can result from age- or illness-related degeneration of crossing fibers (Douaud et al., 2011). Hence, caution is needed when interpreting anisotropy measures.

Episodic memory in the brain

The focus of this section will be on how our episodic memory ability is thought to be implemented in the brain. Although a lot is known about the cellular and molecular bases of memory, this overview will be held on the more macroscopic level, covering phenomena that can be observed with functional neuroimaging techniques such as fMRI.

Memory encoding, storage and retrieval have been shown to engage large-scale brain networks (Cabeza & Nyberg, 2000; Nyberg et al., 2000), but there are also some key regions in these networks that have been shown to be specifically important for declarative memory processes. As will be described, these include the hippocampus (HC) and the surrounding medial temporal lobe (MTL), including the entorhinal, perirhinal and parahippocampal cortices; as well as the frontal cortex. Importantly, these structures have also consistently been shown to be among the ones that are the most sensitive to the effects of age (e.g., Grady, 2008; Raz et al., 2005). Therefore the MTL and the frontal cortex were chosen to be the main focus of this
thesis, and the discussion in the remaining sections will be restricted to these brain regions.

Medial temporal lobe contributions to memory

The importance of the MTL for declarative memories has been acknowledged for a long time. The first convincing demonstrations came from brain-injured patients who had lost portions of the medial temporal lobe, perhaps most famously, the case of patient H.M. (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). These patients generally lose their ability to form new declarative long-term memories, while most aspects of short-term memory and skill learning are usually spared. Some sparing of an ability to form new semantic-like memories has been reported (Rosenbaum et al., 2005), but this could reflect a perceptual type of learning occurring directly in the neocortex (Squire, Stark, & Clark, 2004). These MTL patients usually also display a retrograde amnesia extending backwards months or years prior to the injury, with newer memories being more vulnerable than older ones. These observations, as well as a vast literature on animal and functional neuroimaging studies, suggest that the MTL structures are crucial for initial encoding, as well as consolidation of new declarative memories (e.g., Squire, 1992b). The consolidation aspect is supported by the retrograde amnesia in these patients, which is thought to result from a consolidation failure. The fact that older memories are not as affected by MTL lesions reflects, according to the same reasoning, that they have been successfully consolidated into neocortical networks that are independent of the MTL for their reactivation. The long-term storage of declarative memories is thus believed to be in the neocortex, within the modality-specific areas responsible for processing the information when it first enters the brain (Wheeler, Petersen, & Buckner, 2000).

There is also an alternative account, that states that some aspects of episodic, but not semantic, memory continues to be dependent on the MTL even years and decades after the memories were first acquired (reviewed by Winocur & Moscovitch, 2011). According to this account some episodic memories are transformed over time, so that they lose their contextual details and become represented in an abstract, gist-like form, i.e., as semantic-like memories, independent of the MTL. Other episodic memories retain their rich, contextual details, and are dependent on the MTL for their retrieval no matter how old they are (Rekkas & Constable, 2005).

The MTL thus seems crucial for the acquisition of new episodic memories, as well as for retrieval of recently, and perhaps also remotely acquired episodic memories. In contrast, the MTL does not appear to be crucial for retrieval of semantic memories. This view was formed predominantly on the
basis of evidence from lesion and animal studies, but functional neuroimaging studies have brought converging evidence, showing MTL activation during episodic memory encoding and retrieval tasks (Squire et al., 1992; Stern et al., 1996). Neuroimaging studies also provide unique opportunities for studying aspects of episodic memory in healthy humans. As previously mentioned, event-related designs make it possible to separate items during a memory encoding task into those that were subsequently remembered, and those that were later forgotten. These type of studies have confirmed the importance of the MTL by showing more activation in the HC (Fernández et al., 1998) and parahippocampal gyrus (Wagner et al., 1998) during encoding of subsequently remembered compared to forgotten words.

There are indications that the different structures in the MTL are responsible for somewhat different types of processing (Eichenbaum, 2004), although they all contribute in some way to declarative memory (Squire et al., 2004). The HC proper is for instance hypothesized to act by linking together information stored in different locations of the brain (Eichenbaum, 2004). Regarding the function of the extrahippocampal structures, neuroimaging studies have helped to clarify the distinction between two different processes postulated to underlie recognition memory; familiarity and recollection (Yonelinas, 2002). The former is thought to occur when one encounters a previously seen stimulus, and it is recognized as familiar, but no contextual details about its encounter can be retrieved. Recollection on the other hand involves the full episodic memory traces, including where and when the stimulus was previously seen. The general pattern seems to be that extrahippocampal structures in the MTL, specifically the perirhinal cortex, supports familiarity-based processing, while the hippocampus proper supports recollection-based experiences (Eichenbaum, Yonelinas, & Ranganath, 2007), although contradicting evidence has also been found (e.g., see summary by Squire et al., 2004). In animal studies it is difficult to separate these processes, and lesion studies on humans often include damage to more than one MTL region. Therefore neuroimaging evidence has been valuable, making it possible to dissociate aspects of familiarity and recollection. For instance, a study by Ranganath et al. (2004) showed that encoding-related brain activity in the rhinal cortex predicted familiarity-based recognition, while activity in the HC proper and parahippocampal cortex contributed selectively to recollection.

Frontal cortex contributions to episodic memory

While restricted frontal lesions do not produce as severe amnesia as MTL lesions, frontal lobe patients can display significant impairment on declarative memory tasks (Wheeler, Stuss, & Tulving, 1995). Frontal lobe patients have been described as having particular problems with aspects of memory
that pertain to, for instance, contextual information and temporal order (Buckner & Wheeler, 2001; Dickerson & Eichenbaum, 2010), and their deficits are often worse when assessed with tests requiring free recall than tests based on recognition (M. A. Wheeler et al., 1995). This latter finding is thought to reflect the differential processing demands of the two types of tasks, with recognition tests being relatively easier since they entail representation of the previously encoded items during testing. A different line of evidence for frontal cortex involvement in episodic memory comes from functional neuroimaging studies, that consistently show frontal activity both during episodic memory encoding and retrieval (Cabeza & Nyberg, 2000). The exact role played by the frontal cortex in episodic memory processing is still unclear, but it is commonly believed that it involves high-level cognitive control processes that support and optimize encoding and retrieval in concert with the structures in the MTL (Fletcher & Henson, 2001), as well as the execution of more consciously driven memory strategies. It is important to keep in mind that the frontal cortex is strongly implicated in a number of cognitive control, attentional, and working memory functions (Cabeza & Nyberg, 2000; Corbetta & Shulman, 2002; Duncan & Owen, 2000; Fletcher & Henson, 2001), even in the absence of explicit long-term memory demands or task instructions. It is often suggested that the same frontally-mediated cognitive processes that are engaged in, for example, working memory tasks are recruited during long-term memory processing as well (Fletcher & Henson, 2001). For instance, during episodic encoding, information likely needs to be maintained and perhaps also rehearsed in working memory.

In addition to the functions discussed in the previous paragraph, many other, more memory-specific functions have been ascribed to PFC activation during episodic memory tasks. For instance, during encoding it has been suggested to represent generation, maintenance, or selection of semantic associations to support encoding (Fletcher & Henson, 2001), which is commonly hypothesized to occur in the left ventrolateral PFC. PFC involvement during encoding could also be related to attentional processing, such as selecting which features to attend to and which to ignore in the to-be-remembered material (Blumenfeld & Ranganath, 2007). For instance, the right lateral PFC is thought to be particularly important for inhibitory functions across different cognitive tasks (Aron, Robbins, & Poldrack, 2004). Another suggestion is that organization and manipulation of the information to be remembered is a crucial aspect of the frontal involvement during memory encoding, which is thought to be handled by the dorsolateral regions of the PFC (Blumenfeld & Ranganath, 2007). During episodic retrieval, similar frontal cognitive control processes are thought to be responsible for search, verification and monitoring of stored representations in memory (Fletcher & Henson, 2001). In these processes, the ventrolateral PFC regions are be-
lieved to be more involved in search and temporary maintenance of retrieved information, while dorsolateral regions are thought to perform verification and monitoring.

Functional neuroimaging studies have suggested that frontal engagement during episodic memory tasks is lateralized to some extent, so that encoding tends to involve more left- than right-sided PFC activation, while retrieval taxes the right PFC more than the left. This pattern of results has been referred to as the hemispheric encoding-retrieval asymmetry (HERA; Habib, Nyberg, & Tulving, 2003; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Exceptions to this generalization have been found, and HERA tends to be most clearly observed for verbal materials, and more so during encoding than during retrieval (Fletcher & Henson, 2001). Other accounts have focused more on lateralization in the PFC according to the type of material involved in the memory task, with verbal material being more commonly linked to left-lateralized activation, whereas non-verbal material such as faces or visuo-spatial patterns are associated with right PFC activation (Buckner, Kelley, & Petersen, 1999).

The strength of frontal recruitment during memory processing has also been shown to be of relevance in functional neuroimaging studies. It has repeatedly been demonstrated that frontal regions are more strongly engaged during encoding of stimuli that are subsequently remembered, compared to stimuli that are later forgotten (e.g., Brewer, 1998; Wagner et al., 1998; for a review see Kim, 2011), linking PFC involvement specifically to successful encoding. More frontal involvement during episodic memory tasks thus seems to be beneficial. However, during other cognitive tasks such as working memory, it is sometimes observed that individuals who perform the task more proficiently have lower frontal activation (Neubauer & Fink, 2009). Given the substantial overlap between frontal brain regions, and hypothesized cognitive processes, mediating working and episodic memory (Cabeza, Dolcos, Graham, & Nyberg, 2002), this finding is somewhat puzzling. However, frontal involvement is sometimes thought to reflect higher effort, which does not need to be synonymous to good performance. In this sense, some believe that individuals with lower ability have lower neural efficiency (Neubauer & Fink, 2009), so that they have to employ more frontal resources at a lower level of difficulty. Relatedly, the dissociation between working and long-term memory tasks in terms of magnitude of frontal involvement could reflect the differential involvement of general cognitive control process networks and memory-specific brain networks. Lower performing individuals might rely more heavily on prefrontal cognitive control processes, when their memory-specific networks are inadequate (cf. Salami, Eriksson, & Nyberg, 2012). Still, the conflict between “less is more” and “more is more” of brain activity is a common issue in functional neuroimag-
ing studies, and is not restricted to the frontal cortex, which will be returned to later on.

Frontal – medial temporal interactions in memory processing

Thus far, MTL and frontal contributions to memory have been considered separately. However, it is generally agreed that these brain structures operate in concert during the formation and retrieval of declarative long-term memories. This notion is based on both the extensive anatomical connectivity between these regions, as well as their common co-activation during memory processing in functional imaging studies (Simons & Spiers, 2003). Although functional interaction, or connectivity, will not be a major topic of this thesis, it deserves mentioning. Knowledge of MTL-PFC interaction is still evolving, but one preliminary account was proposed by Simons and Spiers (2003). It was inspired by previous work, including lesion studies, functional neuroimaging and computer modeling. The model focuses on prefrontal top-down control during encoding, based on the current goals and demands. The processes are thought to guide, modify, and elaborate on representations of the to-be-remembered information that has been transmitted to the MTL from the cortical areas responsible for processing and representing the information. PFC is also proposed to be responsible for ensuring that the representations that underlie memory traces are sufficiently distinct, i.e., separable from one another. Different PFC regions are thought to be involved depending on the nature of the task, for instance the type of material or processing required, with dorsolateral PFC believed to be involved in organization and manipulation of representations.

Further, according to the framework of Simons and Spiers (2003), the interaction between PFC and MTL is even more important for retrieval, during which the ventrolateral PFC is suggested to be responsible for generating and specifying retrieval cues. The cue is then transmitted to the MTL where a matching process seeks concordance between the cue and stored representations. The results of this matching process are believed to be maintained in the ventrolateral PFC, while the dorsolateral PFC is responsible for verifying or rejecting the retrieved representations. To the extent that the retrieval operations involve internally generated or self-relevant information, the anterior and medial aspects of PFC are thought to be involved, respectively.

More recent developments in the study of MTL-PFC interactions include the application of functional connectivity techniques that investigate the functional coupling between brain regions during task performance or rest. For instance, it has been shown that the strength of functional coupling in a brain network encompassing the bilateral HC and left inferior frontal cortex during memory encoding, can predict intra-individual differences in recall ability.
That is, the functional coupling between regions in this network was stronger during encoding of test items that were subsequently remembered, compared to those that were later forgotten.

Other memory-relevant brain regions

Although the scope of this thesis is restricted to MTL and PFC due to their well-established connections to cognitive aging, it should be stressed that these are not the only regions relevant for memory processing. As already mentioned, memory formation and retrieval has been shown to engage large-scale brain networks (Cabeza & Nyberg, 2000; Nyberg et al., 2000), encompassing regions in all major lobes of the brain, as well as the cerebellum. In addition to the MTL and PFC, there are several other prominent regions in these networks. These include, for instance, midline diencephalic structures, specifically the thalamus and mammillary bodies, which are tightly coupled with the MTL memory circuits, and known to cause amnesia if injured (Aggleton & Brown, 1999). The parietal cortex also appears to contribute significantly to memory processing, particularly during retrieval, and its function has been proposed to relate to, for instance, attentional aspects of memory (Wagner, Shannon, Kahn, & Buckner, 2005). The lateral aspect of the temporal lobe is also involved in memory processing, perhaps by virtue of its role in stimulus perception, that is, the processing of the “content” of memories (Dickerson & Eichenbaum, 2010). Several additional brain structures could be added to this list, but a full review of the field is beyond the scope of this thesis.
Aging and memory

Before turning to the topic of brain aging and how it may affect memory functions, I will address some important issues regarding the nature of age-related memory decline, and some methodological disputes associated with its study. I will briefly cover issues such as the relation between memory decline and decline in other cognitive functions, the age of onset of age-related cognitive decline, as well as individual differences in age-related cognitive change. This brief review will mainly be concerned with findings regarding normal aging, in the absence of dementia.

Firstly, although this thesis deals predominantly with episodic memory change in aging, memory is just one of several interdependent mental abilities that tend to decline with age. It can be difficult to separate effects that are memory-specific from impaired performance due to other failing processes. For instance, in addition to mnemonic processing, performing an episodic memory task also requires sensory processing, holding information online in working memory, as well as various cognitive control functions. These are all functions with documented age-related decline (Braver & West, 2008; Lindenberger & Baltes, 1994). One major topic in the study of cognitive aging has therefore been to investigate whether certain failing abilities, such as general processing speed (Salthouse, 1996) or executive functions (Salthouse, Atkinson, & Berish, 2003) mediate decline in other cognitive abilities, such as memory. This can be demonstrated by showing that the relationship between chronological age and a specific mental ability is diminished when covarying for the hypothesized mediating variable. Such mediation analyses based on cross-sectional data have, however, been criticized on logical grounds (e.g., Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011). While there continues to be some support for the processing speed account, the estimated mediating effect has been shown to be weaker in longitudinal than in cross-sectional studies (Lemke & Zimprich, 2005; Sternäng, Wahlin, & Nilsson, 2008), and it has also been shown that processing speed differences in elderly might be more related to childhood intelligence than age-related changes (Deary, Johnson, & Starr, 2010). As for executive functions, there is some support for mediating effects, but interpretations are compromised due to problems with construct validity of the concept of executive functions itself (Salthouse et al., 2003). Nevertheless, the well-documented relationships between different cognitive variables are
important to keep in mind also when seeking neurocognitive explanations to age-related decline in specific cognitive abilities such as memory.

Another, related, issue in cognitive aging research has been the extent of covariation or independence of decline across different cognitive domains. Is it the case that when one ability begins to decline, the rest of them follow? On one hand it has been stated that “there is no uniform pattern of age-related changes in adulthood across all intellectual abilities” (Schaie, 1994, p. 306), on the other hand it has also been shown that up to two-thirds of the variance in age-related change across cognitive domains is shared (Ghisletta, Rabbitt, Lunn, & Lindenberger, 2012). One reason for this apparent discrepancy is whether one considers within-person or across-person trends. The data implies that within individuals there likely is both a general, unitary factor accounting for age-related cognitive decline across multiple domains, and several (somewhat smaller) factors allowing for domain-specific declines (Tucker-Drob, 2011; Wilson et al., 2002). Across individuals, some domains of cognition have typically been shown to be more resilient to the effects of age, with semantic knowledge, such as vocabulary, being one of the most prominent examples of relative sparing (Salthouse, 2004; Schaie, 1994).

Within the memory domain, there has been much focus on the differential aging trajectories of different memory systems. Some types of implicit memory measures, such as priming, have traditionally been thought to be spared, or at least significantly less affected by age than other memory measures, although the results are quite variable across studies (Fleischman & Gabrieli, 1998; La Voie & Light, 1994; Nilsson, 2003). Working memory ability has been shown to decline with age, although measures of short-term memory, which do not require manipulation of information, seem somewhat less affected (Nilsson, 2003; Park et al., 2002; Verhaeghen & Salthouse, 1997). As for the declarative memory systems, as already alluded to, semantic memory tends to be maintained longer in life than episodic memory (Rönnlund et al., 2005; Salthouse, 2004; Schaie, 1994). The relative preservation of semantic knowledge was acknowledged already in relatively early theories of human intellectual functioning (Horn & Cattell, 1967). Episodic memory, on the other, hand has been one of the most studied memory measures in relation to aging, and is held to be the one with the most consistent age-related decline (Nilsson, 2003). But there is also differentiation within the episodic memory domain. It is well known that different encoding and retrieval conditions can affect the magnitude of age-differences. For instance, tests of recall tend to produce more pronounced age-differences than tests of recognition (Craik & McDowd, 1987; Nyberg et al., 2003).
The average age of onset of episodic memory decline has also been an issue of disagreement, which to a large extent reflects methodological considerations. Early cross-sectional studies showed steep linear declines in memory and other cognitive functions, beginning as early as the twenties, whereas the emergence of large-scale longitudinal studies has shifted this age of onset to occur around age 60-65 (e.g., Rönnlund et al., 2005; Schaie, 1994). The discrepancy between cross-sectional and longitudinal estimates (see Figure 1) has been a major issue in aging research. One reason behind the divergent findings is that cross-sectional data may be contaminated by cohort effects, i.e., that older and younger age-cohorts differ with respect to a number of factors that are unrelated to aging per se, but associated with cognitive function, e.g., nutrition, sib-size and perhaps most importantly, education (Rönnlund & Nilsson, 2008). These, and other factors, have been thought to elevate cognitive levels in younger cohorts, making age effects in cognitive ability appear larger than they actually are. Longitudinal estimates have generally been considered to be more accurate, since they assess true, within-person change. However, longitudinal studies also face challenges, including selective attrition and practice effects. Attrition bias occurs if individuals who are initially lower-performing, or those who experience more than average cognitive decline, drop out of the study to a larger extent than average and high-performing individuals. This has often been shown to be the case (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Rönnlund et al., 2005), and can lead to an underestimation of age-related cognitive changes. Practice effects occur because individuals get better at performing cognitive tests due to repeated exposure to them, which biases estimates of average change in the same direction as attrition bias. Although measures have been

taken to control for these issues (Josefsson et al., 2012; Rönnlund & Nilsson, 2008), some claim that age-related changes begin much earlier than what is suggested by longitudinal studies (Salthouse, 2009). Nevertheless, in this thesis it will be assumed that, on average, age-related episodic memory changes begin in later life. However the major focus will be on individual differences in these changes, which will be described in the next section.

Individual differences and their determinants

While the foregoing paragraphs focused on cognitive declines in aging, it is generally agreed that there are significant individual differences in cognitive ability in late life, as well as in age-related trajectories of cognitive change (Christensen et al., 1999; de Frias, Lövdén, Lindenberger, & Nilsson, 2007; Mungas et al., 2010; Wilson et al., 2002). Individuals can differ substantially both in age of onset and rate of change over time, as can be discerned from Figure 2. Although aging research has traditionally focused more on age-related declines, there are also older individuals who maintain very high levels of cognitive performance into late life (e.g., Habib, Nyberg, & Nilsson, 2007). Successful aging (Rowe & Kahn, 1987) has in recent years become the topic of a growing research field. In this section I will briefly summarize some risk and protective factors for age-related cognitive decline.

Figure 2. Illustration of individual differences in episodic memory change across 15-20 years. Data is shown for 77 participants who completed the 5th test wave (T5) of the longitudinal Betula study (Nilsson et al., 2004) at the age of 80. The memory score is a composite of five episodic memory test variables, described in the Methods section of this thesis.
Most of the factors covered below have been found to distinguish major decline from normal decline, as well as successful cognitive aging from normal decline. There have also been suggestions that successful cognitive aging might be associated with a slightly different profile of predictors than cognitive decline (Barnes et al., 2007; Yaffe et al., 2009), but further validation is needed for such claims. Hence, the factors addressed here should tentatively be considered equally predictive of decline or preservation of cognition in aging. That is, the absence of a risk factor should be viewed as protective.

The most commonly identified risk and protective factors comprise primarily genetic, health and lifestyle factors, as well as educational or occupational attainment. In the genetic domain, the best established association between a genetic allele and cognitive function is that for the apolipoprotein E (APOE), with elderly carriers of the ε4-allele having lower cognitive function across a number of domains (Wisdom, Callahan, & Hawkins, 2011). Although this has been demonstrated also in healthy elderly, the association could be due to the acknowledged link between Alzheimer’s disease and APOE ε4 (Corder et al., 1993). Several studies have also shown associations between longitudinal cognitive decline rates and the ε4-allele (Caselli et al., 2009; Josefsson et al., 2012). Other genes, such as catechol-O-methyl transferase (COMT) and brain-derived neurotrophic factor (BDNF) have also been linked to cognitive function in aging (Payton, 2009), but the direction of effects has been somewhat inconsistent, and less reliable effects have been found in the few studies assessing actual cognitive change over time.

Health-related factors are also important for cognitive functions. Conditions such as cardiovascular disease, hypertension, diabetes, and obesity (Barnes et al., 2007; Yaffe et al., 2009) have all been associated with poorer cognitive outcomes. It seems safe to assume that physical health is related to brain health and integrity in aging, which in turn translates to cognitive outcomes. Related to this, a number of health-promoting lifestyle factors have also been linked to better cognitive function, including physical exercise, being a non-smoker, as well as better nutrition (Barnes et al., 2007; Josefsson et al., 2012; Plassman & Williams, 2010; Yaffe et al., 2009). Another lifestyle factor that has often been linked with better cognitive function in aging is social engagement (Fratiglioni, Paillard-Borg, & Winblad, 2004; Plassman & Williams, 2010), which includes factors such as the size of an individual’s social network, marital status, and frequency of participation in social activities. Collectively, several genetic, health, and lifestyle factors could act to preserve the brain’s grey and white matter integrity in aging, resulting in a sparing of cognitive functions. This is captured in the concept of brain maintenance (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012).
Another factor that has consistently been linked to better cognitive performance in elderly is educational attainment. However, although some studies have found associations between educational attainment and preservation of cognitive functions in aging (Habib et al., 2007; Yaffe et al., 2009), evidence also suggests that it might be more linked to level of cognitive performance rather than change in cognition over time (e.g., Lövdén et al., 2004; Zahodne et al., 2011). Educational or occupational attainment has also been used as a proxy for the hypothesized construct of cognitive reserve, which is thought to moderate the impact of brain pathology on cognitive function (Y. Stern, 2009). According to the cognitive reserve account there are inter-individual differences in the brain’s processing capacity that allow some individuals to cope better with brain pathology. These differences are thought to be driven by lifetime experiences such as physical and mental stimulation, which includes, but is not limited to, educational attainment. In essence, the reserve concept captures some of the lifestyle factors that have previously been associated with cognitive outcomes in aging. But in contrast to the brain maintenance hypothesis (Nyberg et al., 2012), the cognitive reserve account instead focuses on how individuals might continue to be cognitively high-functioning despite accumulating brain pathology. As reviewed by Stern (2009), there is fairly ample support for the notion of cognitive reserve in the epidemiological literature. There is also a similar notion of brain reserve (Satz, 1993), which is a more passive account that focuses on individual differences in brain characteristics such as neuronal count, as an explanation to why some individuals have more resistance to brain pathology.

Both cognitive and brain reserves could be associated with (partially) heritable individual differences in general intelligence, which have also been suggested to buffer against cognitive decline. That is, age has been suggested to be kinder to the initially more able (Thompson, 1954), so that individuals with high intellectual abilities in youth are less vulnerable to age-related cognitive decline. Some studies seem to support this notion (Richards, Shipley, Fuhrer, & Wadsworth, 2004), whereas others fail to find such connections (Salthouse, 2012), and still others report different results for different study samples (Gow et al., 2012). Hence, as of now the results are inconclusive regarding the existence of a protective effect of high initial cognitive ability level, and the mechanisms by which it would operate.

But there is also another, more methodological, reason why individual differences in cognitive ability in youth are important for research on cognitive aging. It is well established that individual differences in cognitive ability, including memory (Bors & MacLeod, 1996), are large also in early adulthood. In the past decade it has come to knowledge that that such individual differences tend to be relatively stable across large portions of the human lifespan (Deary, Whalley, Lemmon, Crawford, & Starr, 2000). Correlations
in the magnitude of $r = 0.6-0.7$ have been reported between cognitive ability in childhood, and that in the eight decade of life (Deary, Whiteman, Starr, Whalley, & Fox, 2004; Gow et al., 2011). These findings were obtained with cognitive tests assessing general intelligence, which is likely to be a somewhat more stable trait than episodic memory. Still, similar stability estimates cannot be ruled out for episodic memory measures as well. Since studies with cross-sectional designs lack information on the individuals’ cognitive ability prior to the onset of aging, the presence of such stability could cause individual differences from early life to be confused for differential age-related decline. For instance, one could erroneously conclude that a low-performing individual has experienced aggravated cognitive decline, when in fact he or she has always been low-performing. Thus, the need to consider both initial level and change in cognition when studying cognitive aging should be stressed.

In summary, the literature suggests that there are substantial individual differences in how cognitive abilities change in aging, and several genetic, health, and lifestyle factors have been associated with better or worse cognitive outcomes. These factors could serve to protect cognitive functions either through maintaining brain integrity or buffering brain function against pathology through a cognitive or brain reserve. On a methodological note, it should be remembered that prior cognitive ability level could be a confound in cross-sectional studies on individual differences in aging.
Brain aging

The aging brain undergoes many changes to its structure and function. Sometimes these changes have been found to relate to decline in cognitive functions, such as memory, but other times no observable links can be established. In this chapter, I will provide a brief overview of some important findings regarding the aging brain. The main focus will be on brain structures associated with episodic memory function, i.e., the MTL and the frontal cortex, which have also consistently been shown to be afflicted by aging. Relatively more attention will be given to functional than structural findings relating to brain aging. In the following paragraphs I will consider structure and function separately, although there is much reason to believe that functional age-related changes, at least in some instances, reflect underlying changes in brain structure. Both local gray and white matter reductions have been linked to alterations in functional neuroimaging measures (Kalpouzos, Persson, & Nyberg, 2012; Nordahl et al., 2006; Nyberg et al., 2010). However, since the majority of studies thus far have not addressed this possibility, it is difficult to consider them together. It should also be mentioned that many important age-related brain changes will not be covered in this review. These include, for instance, changes in the brain’s neurotransmitter systems. A prominent example is the dopaminergic system, that has been firmly linked to memory function in aging (Bäckman, Lindenberger, Li, & Nyberg, 2010). Nor will this review go into detail regarding deposition of β-amyloid protein in the brain, which is strongly linked to Alzheimer’s disease (Hardy & Selkoe, 2002), but also known to affect cognitive function in normal aging (Rodrigue et al., 2012).

Structural brain changes in aging

Changes to brain structure in aging can occur on both macro- and microscopic levels. This review will focus on larger-scale volumetric changes that are observable with MRI, as well as microstructural white matter changes observable with DTI. On the global level, total brain volume has an average annual decrease of about 0.2 - 0.5% across the adult lifespan, as assessed in a recent review (Salthouse, 2011). Other salient features of the aging brain include enlargement of the ventriciles and the appearance of white matter insults observable with DTI, or as so-called white matter hyperintensities on
structural MRI images (Raz, 2000). It is generally agreed that different brain structures are differentially affected by age, with the frontal cortex (together with the parietal cortex) consistently showing one of the steepest rates of age-related change in both cross-sectional and longitudinal studies (e.g., Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Frontal lobe volume is estimated to decline 0.9-1.5% per year (Dennis & Cabeza, 2008). It is important to note that longitudinal estimates of change have generally been shown to be more sensitive to changes in brain structure, exceeding those from cross-sectional studies. This is thought to result from the fact that cross-sectional studies contain noise from inter-individual differences in brain volume from youth (Raz et al., 2005). Frontal volume changes have been shown to affect both gray and white matter, with some indications that white matter may be more sensitive (e.g., Salat, Kaye, & Janowsky, 1999). Microscopic white matter changes observable with DTI have also been shown to be more prominent in the frontal cortex, compared with more posterior brain regions (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Head et al., 2004).

Volumetric reductions in the HC are also consistently demonstrated in aging, although they are not as pronounced as for the frontal cortex, see Figure 3. For instance, annual decrease in HC volume has been estimated to 0.79 - 0.84% in representative longitudinal studies (Fjell et al., 2009; Raz et al., 2005; Seahill et al., 2003). Further, there is evidence that the relationship between HC volume and age is non-linear, with atrophy rates increasing with age (e.g., Du et al., 2006). There are some indications that the different substructures within the MTL show different rates of volumetric change in healthy aging, with the HC proper being more affected than the entorhinal cortex (Raz et al., 2005). However, the entorhinal cortex does not seem to be

![Figure 3](image.png)

Figure 3. Longitudinal change in adjusted prefrontal and hippocampal volumes as a function of baseline age. Reproduced with permission from Oxford University Press, from Raz et al., (2005) Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex, 15*(11), 1676-1689.
altogether spared (e.g., an annual decrease of 0.55% was reported by Fjell et al., 2009).

The above cited findings pertain to average rates of decline in structural brain indices, but there are also substantial inter-individual differences in rates of volumetric change over time. For instance, Raz et al. (2005) reported significant individual differences in volumetric change in 11 out of 12 regions that they investigated (the only exception was the inferior parietal lobe). Further, Resnick et al. (2003) found attenuated rates of gray and white matter volume change over a four-year interval in a subsample of elderly individuals that were particularly healthy in terms of medical conditions and cognitive impairment. But even within this group, significant reductions were found across the frontal, parietal, temporal, and occipital lobes. A more recent study specifically probed the neuroanatomical differences between elderly individuals with maintained versus declining cognition during the past 10 years, and found that spared gray matter volume in the MTL region, as well as microstructural integrity of the cingulate cortex, were particularly characteristic for those with maintained cognitive functions (Rosano et al., 2012).

Structure-cognition relations

Although both brain structure and cognition correlate negatively with age, the literature suggests that structure-cognition relationships are more mixed than what would be expected (Raz & Rodrigue, 2006; Salthouse, 2011). Most studies have reported positive correlations between regional or global brain volume and cognition in aged individuals, that is, bigger is better, with the assumption being that smaller volume implies more age-related atrophy (Salthouse, 2011). However, the opposite pattern has also been found. Memory performance in healthy older adults has for instance been shown to correlate negatively with regional volume in the frontal cortex (Duarte et al., 2006; Van Petten et al., 2004) and in the HC (Van Petten, 2004). That is, smaller volume has been found to be associated with better cognitive performance. The reason for these discrepancies might be that in cross-sectional studies of brain structure, one might confuse pre-existing inter-individuals differences with age-related change. It has for instance been speculated that in younger age, smaller regional brain volume might be associated with better cognitive function due to more efficient pruning processes during brain development in youth (see discussion in Van Petten et al., 2004; Van Petten, 2004). Thus, negative associations between volume and cognition might be remnants from younger years in older adults without pathological conditions. On the other hand, correlations in samples of elderly with pathological conditions such as Alzheimer’s disease tend to show somewhat more consistent
positive correlation between regional volume and cognition (e.g., Duarte, Henson, & Graham, 2008; Köhler et al., 1998).

When considering correlations between longitudinal changes in brain structure and changes in cognition, there have been some reports of HC volume decline correlating with memory decline (Kramer et al., 2007; Murphy et al., 2010). Smaller HC volume at baseline has also been found to predict subsequent memory decline (Golomb et al., 1996; Woodard et al., 2010). Furthermore, HC volume has been found to differ between individuals with prior cognitive decline, compared to individuals with stable memory over the same time period (Persson, Nyberg, et al., 2006). However, it should be noted that there are also longitudinal studies that have failed to observe correlations between MTL change and memory change in healthy aging (Ylikoski et al., 2000). The discrepancy might reflect that the previously mentioned study samples were more cognitively impaired, for instance, 30% of the sample had converted to mild cognitive impairment, MCI (a transitional state between normal aging and dementia) at follow-up in the study by Golomb et al., (1996). Thus, it remains to be firmly established if the relationship between MTL decline and memory decline exists in healthy elderly samples without individuals that may be in early stages of pathological conditions.

Although longitudinal studies that have specifically studied frontal volume and cognition are hard to find, total cortical gray matter volume decline has been associated with decline in executive functions (Kramer et al., 2007), which might also mediate memory decline. Total brain volume change also correlated with memory change in another study (Schmidt et al., 2005). Further, a longitudinal voxel-based morphometry study found associations between frontal volume and prior cognitive decline on at least two out of six cognitive measures assessing memory, processing speed or executive function (Tisserand et al., 2004).

White matter integrity assessed with DTI or as white matter hyperintensities on MR images has also been found to correlate with cognitive functions, including memory, in several studies (Gunning-Dixon & Raz, 2000; Sullivan & Pfefferbaum, 2006). More damage to the white matter is usually related to lower cognitive function. Again, however, findings relating cross-sectional measures of white matter integrity tend to be somewhat mixed (Salthouse, 2011), and longitudinal studies are rare. Changes in DTI measures over a two-year period have been demonstrated to correlate with decline in working memory scores in an elderly sample (Charlton, Schiavone, Barrick, Morris, & Markus, 2010), but evidence regarding long-term memory is lacking. One study found that individuals with prior decline in episodic memory had reduced white matter integrity in the anterior corpus callosum (Persson, Nyberg, et al., 2006), but a recent large-scale cross-sectional study found
DTI measures to mediate age-differences in processing speed, but not in episodic memory (Salami, Eriksson, Nilsson, & Nyberg, 2012). Thus, although the importance of white matter integrity for cognitive functions should be acknowledged, it is still somewhat unclear how white matter integrity measures relate to episodic memory change over time.

Functional brain changes in aging

This section will attempt to briefly summarize the vast literature on age-related changes that has been derived from functional neuroimaging studies, predominantly employing fMRI and positron emission tomography (PET). The current summary will mainly deal with changes that have been observed while the study participants perform cognitive tasks, that is, changes in the so-called task-positive network. The specific focus will be on memory tasks and the memory-relevant structures in the frontal cortex and the MTL. Aging also entails significant changes to the default mode network of the brain (Hafkemeijer, van der Grond, & Rombouts, 2012), which is more engaged during periods of inactivity or rest; as well as to the functional connectivity between brain regions as they interact during task performance (Steffener, Habeck, & Stern, 2012). These types of changes, however, will not be addressed further here.

Three general patterns of age-related changes have emerged from the many studies conducted in this field. First, to a large extent older adults tend to engage similar brain regions as young while performing memory-tasks (e.g., Duverne, Motamedinia, & Rugg, 2009). But elderly are also often reported to significantly under- and overactivate certain brain regions compared to young adults. Many of these differences between older and young adults tend to occur across different task domains. Hence, they do not only pertain to memory processing, although memory has been one of the most studied topics in these studies. For instance, a common pattern is that elderly have less activation than young in the occipital cortex together with increased engagement of the frontal cortex. This pattern has been observed during perceptual matching tasks (Grady et al., 1994), visual attention, working memory, and episodic memory tasks (Cabeza et al., 2004), as well as across a number of other task domains, as shown in a quantitative meta-analysis of the literature (Spreng, Wojtowicz, & Grady, 2010). The pattern has been denoted the Posterior to Anterior Shift in Aging; PASA (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). While the decrease in occipital cortex activation has generally been attributed to deficient processing of sensory stimuli (e.g., Cabeza et al., 2004; Davis et al., 2008), the nature of the increased frontal activation has been a subject of debate, as will be addressed later.
Frontal cortex

As described, the frontal cortex is commonly observed to be more engaged by elderly than young across many cognitive tasks, including episodic memory ones. Another common pattern in functional neuroimaging studies of episodic memory is underrecruitment of the PFC in elderly, most frequently during episodic encoding, but also during retrieval (Cabeza et al., 1997; Grady et al., 1995; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Schacter, Savage, Alpert, Rauch, & Albert, 1996; Stebbins et al., 2002). In a review of the literature, Dennis and Cabeza (2008) note that the most consistent finding during episodic memory encoding is an age-related reduction in left-sided frontal activation. There is also longitudinal imaging evidence for reduced memory-related frontal activation over a 6-year period in an elderly sample (Nyberg et al., 2010). Such patterns are typically interpreted as impaired frontal function in the elderly, leading to poorer performance (Persson & Nyberg, 2006). The observations of both increased and decreased frontal activation in elderly during episodic memory tasks do not need to be incompatible, considering that the frontal cortex is a large structure, associated with many heterogeneous functions. One possibility is that elderly underrecruit task-specific memory networks, while displaying increased activity levels in regions not significantly engaged, or less strongly engaged, by young individuals. The alternative regions could include those associated with general cognitive control processes (cf. Salami, Eriksson, & Nyberg, 2012). Other possibilities for the discrepant findings will be discussed below, but first I will describe the various interpretations that have been attributed to higher frontal activation in elderly compared to young individuals.

There have been two common explanations for relatively increased frontal activation in elderly individuals. According to one account, it reflects compensatory processes (Cabeza, Anderson, Locantore, & Mcintosh, 2002; Reuter-Lorenz, Stanczak, & Miller, 1999). The alternative account states that increased activation reflects an age-related impairment in engaging the most efficient set of brain regions to perform a specific task, which is commonly referred to as non-selective recruitment or dedifferentiation (Grady, 2008; Li & Lindenberger, 1999; Logan et al., 2002). The compensation hypothesis has often been evoked in association with bilateral frontal recruitment in elderly while performing tasks associated with relatively more lateralized activation in young participants, a pattern denoted as the Hemispheric Asymmetry Reduction in OLDer adults; HAROLD (Cabeza, 2002). If the contralateral frontal activation is found in high-performing elderly, and/or correlates with successful task performance, it is usually interpreted as compensatory. Such patterns have been observed in many studies (e.g., Cabeza et al., 2002; Grady, McIntosh, & Craik, 2005). However, in some cases in-
creased frontal activation has also been found in low-performing elderly (Miller, Celone, et al., 2008) and negative performance-correlations have also been observed (de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011). That is, increased frontal recruitment associated with poorer performance. Relatedly, increased frontal recruitment has also been found in participants with cognitive decline over the past decade, compared to elderly with stable cognition during the same time (Persson, Nyberg, et al., 2006). Such additional frontal activation in lower performing elderly has sometimes been explained as unsuccessful or attempted compensation. Another term that has been suggested is partial compensation (de Chastelaine et al., 2011), indicating instances when the increased activation is beneficial for performance, but less effective than being able to perform the task by only recruiting the standard task-specific network.

The dedifferentiation account and related theories proposing that additional frontal activation in elderly is detrimental or dysfunctional, have also received empirical support. For instance, sometimes increased frontal activation is seen in elderly when task performance is equivalent to that of young individuals (Morcom, Li, & Rugg, 2007), which would imply less efficient use of neural resources in elderly compared to young individuals. Also, some studies have shown that older adults tend to engage the frontal cortex in a more non-selective manner than young individuals (e.g., Logan et al., 2002), which has been interpreted as a failure to use the most efficient set of brain regions in performing the task at hand. A similar pattern has also been observed in a study that demonstrated right frontal activation in low-performing elderly during memory encoding, but not in young individuals or higher-performing elderly (Duverne et al., 2009). A more recent study also favored a dedifferentiation, rather than a compensatory, account in explaining higher retrieval-related activation in elderly individuals, which was also less sensitive to task conditions and did not contribute to task performance (McDonough, Wong, & Gallo, 2013). So despite claims that more evidence is consistent with the compensation hypothesis than the dedifferentiation account (Dennis & Cabeza, 2008), the latter is still a viable candidate for explaining neuroimaging patterns observed in elderly (Grady, 2012).

In addition to the compensation and dedifferentiation explanations of increased frontal activity in elderly, a third possibility is that it is an artifact associated with the cross-sectional nature of most neuroimaging studies of healthy aging. This was suggested by a study in which both cross-sectional and longitudinal analyses were performed on the same data set (Nyberg et al., 2010). Cross-sectional analyses showed apparent age-related increases in frontal activation during episodic memory encoding, which were driven by a subset of high-performing elderly who were not representative of the full sample. When considering the longitudinal data, the same frontal region
showed decreased activation over time. However, another longitudinal imaging study demonstrated that longitudinal increases in frontal activity during memory tasks are possible (Goh, Beason-Held, An, Kraut, & Resnick, 2013). Here, increased activity was found to be related to declining cognitive functions, specifically those pertaining to executive control. In this study, participants with stable or improved neuropsychological scores tended to have decreased activity in several frontal regions, which the authors attributed to reduced processing needs owing to learning from repeated testing. However, Nyberg et al., (2010) tested specifically for effects of repeated testing, and did not observe any such. Hence, longitudinal evidence concerning frontal cortex function in aging is still inconclusive.

A number of other factors could be responsible for the discrepant findings across studies. One such is the nature of the task. It has been shown that older adults can overrecruit the frontal cortex compared to young individuals during relatively easy task conditions, when performance is equivalent between the groups, while displaying less activation during difficult task conditions, coupled with a performance decrement. To put it another way, older adults tend to reach their maximum level of neural activation faster than young, as task difficulty increases. This pattern has been referred to as CRUNCH, compensation-related utilization of neural circuits, and is consistent with many findings in the aging literature (Reuter-Lorenz & Cappell, 2008). Similar ideas have also been expressed as reductions in neural capacity and efficiency in older adults (Prvulovic, Van de Ven, Sack, Maurer, & Linden, 2005; Y. Stern, 2009). More recent data also suggest that the previously mentioned HAROLD model, pertaining to functional asymmetry reductions in elderly, might be a special case of CRUNCH (Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013). While the original formulation of CRUNCH referred to working memory tasks, in which it is easy to manipulate memory load, CRUNCH-like patterns have been observed during episodic memory tasks as well. In one study, young participants recruited bilateral frontal regions only during a difficult version of an episodic memory task, while elderly had bilateral frontal activation during both easy and difficult conditions (Spaniol & Grady, 2012). In summary, the CRUNCH model could thus explain some inconsistent findings regarding frontal under- versus over-activation in elderly compared to young, if differences in task difficulty are present between studies.

Another factor that can account for discrepant findings is the characteristics of the sample. For instance, if convenience sampling is used, there is a risk of recruiting individuals who are not representative of the elderly population as a whole. This is more likely to involve individuals with higher cognitive function than average (Dennis & Peterson, 2012), but inclusion of individuals in preclinical phases of dementia could also bias results (Buckner, 2004).
The composition of individuals in any given sample likely influences the brain activity patterns that are observed since high- and low performing elderly would be expected to suffer different degrees of functional impairment or dedifferentiation, as well as possessing differential capacities for compensation. However, it is not well understood how performance differences relate to frontal activation, since higher frontal activation has been demonstrated in both higher performing, or successfully aged, individuals (Cabeza, Anderson, et al., 2002; Rosen, Prull, & O’Hara, 2002) as well as in individuals who have experienced cognitive decline (Persson, Nyberg, et al., 2006). Due to possible differences in study design, task difficulty, and functional localization it is not easy to reconcile these findings. Further discussion of sample composition and other reasons for discrepant findings in neuroimaging studies of aging will follow after first reviewing evidence regarding MTL function in aging.

Taken together, the picture of memory-related frontal cortex function in aging is complex. Both decreased and increased activation patterns can clearly be observed in elderly compared to young individuals. Decreased activation is usually interpreted as a functional impairment, but as of yet, there is no consensus regarding age-related increases in frontal activation in aging (Grady, 2012). A number of factors, such as the functional heterogeneity of the frontal cortex, study design (cross-sectional or longitudinal), task difficulty, and sample characteristics need to be considered when interpreting findings.

Medial temporal lobe

In contrast to the frontal cortex, which has been associated with numerous cognitive functions, MTL activity can be assumed to reflect more memory-specific processing. This somewhat facilitates interpretations of age-related effects observed in the MTL, compared to the literature on frontal cortex findings. For the MTL, one prevalent outcome is that elderly fail to activate the MTL or HC proper during memory processing, or have significantly lower MTL activation than younger individuals (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003b; Dennis, Daselaar, & Cabeza, 2007; Grady et al., 1995; Gutchess et al., 2005). These reductions in MTL activation have most consistently been observed during memory encoding, leading to the suggestion that the age-related episodic memory deficit is mainly an encoding failure (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003a). However, age-related decline in MTL function, specifically in the HC proper, has been observed during retrieval as well (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Grady et al., 2005). In several of the reports of reduced MTL activation in elderly, it was coupled with increased frontal recruitment. Some studies also report significant negative
correlations between frontal and MTL activation, both during encoding (Gutchess et al., 2005) and retrieval (Grady et al., 2005). This could support the notion that increased frontal activation in elderly compensates for reduced MTL function.

Although the above cited studies reporting MTL impairment have found age-related activity reductions in both the HC proper (e.g., Dennis et al., 2007) and the parahippocampal gyrus (Gutchess et al., 2005), another line of research has found a pattern of decreased HC activation coupled with increased activation in the parahippocampal gyrus during retrieval (e.g., Cabeza et al., 2004; Daselaar et al., 2006). These observations have been attributed to an increased reliance on the familiarity-based retrieval processes governed by a substructure in the parahippocampal gyrus, the rhinal cortex, when the recollection-based mechanisms in the HC proper begin to fail. These findings are in line with behavioral research indicating that elderly are more impaired at recollection than familiarity-based memory retrieval (e.g., Mäntylä, 1993; Parkin & Walter, 1992), as already alluded to in the section on aging and memory.

HC impairment does not, however, seem to be an inevitable consequence of aging. There have also been several reports of preserved HC activation in healthy elderly during episodic memory tasks (Düzel, Schütze, Yonelinas, & Heinze, 2011; Miller, Celone, et al., 2008; Persson, Kalpouzos, Nilsson, Ryberg, & Nyberg, 2011; Rand-Giovannetti et al., 2006; Schacter et al., 1996). As discussed in relation to the frontal cortex, this finding could derive from the sample composition of the specific studies. Perhaps the samples of the studies that have not detected MTL impairment have been healthier and more high-performing than average, that is, mainly comprised successfully aged individuals. Another relevant factor in this context is the age of the participants, which can vary substantially across studies. However, there have also been suggestions that normal aging does not affect MTL function, and that the memory impairment in normal aging derives from failures of cortical processing (e.g., Rand-Giovannetti et al., 2006), such as the frontal cortex alterations discussed in the previous section. According to this account, one reason why some studies show a decrement in HC function in aging is that they fail to account for the lower task performance of the older participants (Rand-Giovannetti et al., 2006), that is, lower HC recruitment is seen as a consequence rather than a cause of low task performance. Relatedly, it has also been suggested that unintentional inclusion of individuals in the early, undiagnosed, stages of Alzheimer’s disease could be responsible for the observations of MTL impairment in some studies of healthy aging (Buckner, 2004). Another possibility that has to be considered is that most studies have used cross-sectional designs when investigating MTL function in aging. Longitudinal estimates have been shown to be more sensitive to
true age effects with regard to brain structure (Raz et al., 2005), which could also apply to functional aging studies, potentially explaining the failure of some studies to observe functional decline in the HC in healthy aging.

In addition to preserved MTL activation in healthy elderly, a different picture has also emerged from studies of individuals with MCI. Several studies have shown paradoxically increased HC activation in individuals in early stages of MCI, compared to healthy elderly and individuals diagnosed with Alzheimer’s disease (reviewed by Dickerson & Sperling, 2008). Elevated HC activation has also been found to predict subsequent cognitive decline in individuals who were diagnosed with MCI at baseline (O’Brien et al., 2010). In these studies, the HC hyperactivation has been hypothesized to reflect a time-limited compensatory mechanism, which later on fails, as the disease progresses. It is unclear how these findings relate to the findings of impaired HC function in healthy aging, but a possible explanation is that the mechanisms that underlie memory failure in normal aging are different from pathology that causes dementias such as Alzheimer’s disease (Buckner, 2004).

To summarize, while many studies report a functional MTL impairment in healthy aging, there is still some disagreement over whether this is the norm, or whether it is caused by performance confounds or samples contaminated by preclinical Alzheimer’s disease. Some studies have also found spared HC function in elderly samples, and yet others have observed paradoxically increased activity in the HC in persons who later experience cognitive decline.

**Synthesis and summary of MTL and PFC function in aging**

To summarize, the literatures on both MTL and PFC function in aging are characterized by inconsistent findings. For the MTL, many studies report decreased function with age, particularly in the HC, but there are also several demonstrations of spared function, and a few studies that have found increased BOLD signal in individuals who later experience cognitive decline.

For the frontal cortex, both increases and decreases are commonly seen in elderly relative to young, and it is not established whether it is good to have a high frontal BOLD-signal (compensation) or whether it is dysfunctional (decreased neural efficiency or dedifferentiation). Such inconsistencies can stem from differences in task paradigms, task difficulty, choice of contrast, or other methodological issues involved in neuroimaging research, and for the PFC from the functional heterogeneity of the structure itself. Still, when reviewing the literature a few shortcomings become evident. Firstly, many studies have neglected the variability in cognitive status within the older group, and when it has been taken into account, the elderly have oftentimes been considered high- and low-performing relative to the mean performance of the sample. This mean can be quite different from the mean of the aging
population as a whole, especially when small convenience samples are used. Alternatively, performance is compared to that of young participants, in which case it can be biased by cohort effects (as discussed in the section on aging and memory). Thus, functional neuroimaging studies of aging have generally had a quite poor characterization of their samples. Divergent results are unsurprising if some elderly samples are contaminated by participants in preclinical stages of dementia, while other samples are mainly characterized by individuals who are successfully aged. For this reason it is very important to characterize what distinguishes successfully and less successfully aged individuals from average ones. While the most part of the aging literature has focused on cognitive decline, relatively little systematic investigation has been done of successful aging, especially longitudinally defined successful aging.

The relative scarcity of longitudinal data in general, both on the behavioral and neural levels, is another shortcoming in the literature on neurocognitive aging. On the behavioral level, the best way to avoid some of the problems discussed in the previous paragraph is to characterize participants relative to their own ability level prior to the onset of age-related changes, by using longitudinal observations. Without this information, there is a risk of confusing variability associated with individual differences from youth with variability arising from age-related changes. That is, mistakenly inferring that a low-performing older individual has experienced cognitive decline when he or she has in fact been low-performing from youth, or vice-versa. Given the relative stability of individual differences in cognition over the adult lifespan (Deary et al., 2000, 2004; Gow et al., 2011) such concerns are highly relevant. A specific gap of knowledge in the neuroimaging literature is whether cross-sectional observations of performance-related individual differences in brain activity of elderly also reflect differences that were already present before the onset of aging.

On the neural level, it is clear that longitudinal and cross-sectional imaging data can produce substantially different results (Nyberg et al., 2010). Also, one of the few truly longitudinal studies showed a complex pattern of increasing and decreasing brain function across five scanning sessions during a nine-year period (Beason-Held, Kraut, & Resnick, 2008), in a sample that was cognitively stable during that time. By considering that cross-sectional imaging data only provide a snapshot of brain function at one point in time, it is easy to realize that this picture might appear quite different depending on the specific time-point one looks at. Thus, more studies with longitudinal imaging data are called for to confirm and qualify findings from previous cross-sectional studies.
Aims of the thesis

The overarching aim of this thesis was to investigate how information on individuals’ cognitive histories, that is, longitudinal behavioral data, can advance knowledge of inter-individual differences in neurocognitive aging. Focusing on memory-relevant structures in the medial temporal lobe and the frontal cortex, the specific aims were to investigate:

i) The relationship between cognitive decline and neural changes over time (Study I).

ii) The neural characteristics of longitudinally-defined successful cognitive aging (Study II).

iii) The relative contributions of cognitive status in middle-age, and age-related cognitive decline, on individual differences in memory-related brain activation in older age (Study III).
Methods

The Betula study

All data underlying the current thesis was derived from the Betula study (Nilsson et al., 1997, 2004), which is a longitudinal population-based study that started in 1988. The aims of the Betula study include investigating how memory and health develop across the adult age-span, mapping early cognitive and biological markers of dementia, and finding determinants for successful aging. To date, there have been five data collection waves in Betula (T1: 1988-90, T2: 1993-95, T3: 1998-00, T4: 2003-05, T5: 2008-10), with a sixth beginning in the fall of 2013. At each wave, participants undergo extensive cognitive and health-related testing. Data is also collected on a number of social, medical, and life-style variables. In total, approximately 4500 participants, distributed across six samples, have been tested throughout the years. However, all participants were not tested at each test wave, see Table 1. At each test occasion, a new sample was recruited to control for retest effects on the cognitive test battery.

Several subsamples of Betula participants have undergone structural and functional brain imaging with MRI. For the current thesis, data from three brain imaging collections was used. The first took place before T4, in 2002-2003, and was followed up in connection with T5, in 2008-2009. The second one was performed in parallel with T5, in 2009-2010. These samples will be described in detail below.

Table 1. Recruitment and testing of samples in Betula. Bold fonts indicate samples that were included in this thesis.

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>Sample 1</td>
<td>Sample 1</td>
<td>Sample 1</td>
<td>Sample 1</td>
</tr>
<tr>
<td>Sample 2</td>
<td>Sample 2</td>
<td>Sample 2</td>
<td>Sample 3</td>
<td>Sample 3</td>
</tr>
<tr>
<td><strong>Sample 3</strong></td>
<td><strong>Sample 3</strong></td>
<td>Sample 3</td>
<td><strong>Sample 3</strong></td>
<td><strong>Sample 3</strong></td>
</tr>
<tr>
<td>Sample 4</td>
<td>Sample 4</td>
<td>Sample 5</td>
<td>Sample 5</td>
<td>Sample 5</td>
</tr>
<tr>
<td><strong>Sample 6</strong></td>
<td><strong>Sample 6</strong></td>
<td><strong>Sample 6</strong></td>
<td><strong>Sample 6</strong></td>
<td><strong>Sample 6</strong></td>
</tr>
</tbody>
</table>
Study samples and selection procedures

The Betula study is population-based, which means that participants are recruited randomly from the population registry. This is valuable since it increases the generalizability of the results derived from the study. However, during the course of the study some participants drop out, and this is more common among older participants, and participants with a lower performance at initial testing (Rönnlund et al., 2005). This compromises sample representativeness, and can be an issue when interpreting the results, as will be discussed later in this thesis. Therefore, sample characteristics and selection procedures for the samples used in this thesis will be thoroughly described in the following paragraphs.

Data from three samples of the Betula study were used in this thesis, namely samples 1, 3 and 6. At the time of recruitment sample 1 comprised 1000 individuals evenly distributed across 10 age-cohorts, 35-80 years of age. Sample 3 originally consisted of 966 individuals, who were age-matched to sample 1, i.e., aged 40-85 at their first testing at T2. Betula has a narrow age-cohort design, in which the cohorts are recruited with five year intervals; i.e., 35, 40, 45 year olds, and so on. For samples 1 and 3, there were approximately 100 individuals in each age-cohort, except the oldest cohort in S3, which comprised 70 individuals. Sample 6 consisted of 357 participants aged 25-80 at T5, with approximately 30 individuals per cohort. Gender proportions in the samples were roughly even across the age-cohorts, with overall slightly more females in samples 1 and 3 (53 % and 57% female, respectively), while sample 6 contained slightly more males (51% males).

At the fifth test occasion in Betula, 366 individuals from sample 1 and 390 individuals from sample 3 completed cognitive testing, i.e., just over a third of the original samples. At this time sample 1 had been part of the study for 20 years and had five measurement points, while sample 3 had participated four times during 15 years. The remaining participants in these two samples, as well as those from sample 6, who were recruited at T5, formed the basis for recruitment into the brain imaging samples described next.

The ImAGen cohort

In connection with the fifth test occasion, a large brain imaging data collection was performed in the Betula study. We called this project ImAGen, which is an acronym for Imaging Aging and Genetics. A total of 376 individuals were scanned with structural and functional MRI, and a follow-up of this sample will begin in the fall of 2013. The ImAGen cohort formed the basis for Study II and III of this thesis, as well as many other studies (e.g., Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011; Salami, Eriksson,
Nilsson, & Nyberg, 2012; Salami, Eriksson, & Nyberg, 2012). Participation in the imaging study was offered to participants from samples 1, 3 and 6, who had completed the cognitive testing in Betula at T5, and agreed to be contacted for potential participation in an imaging study. Selection of participants was stratified by age and gender, but blind to their cognitive performance and other personal characteristics. An initial screening was made to exclude participants who had MR contraindications, such as metal implants, pacemakers, and/or were pregnant. Also, participants who had had strokes or heart/brain surgery were excluded at this point, as were participants who reported severe visual impairments or motoric problems that could interfere with response collection.

The characteristics of the scanned participants can be seen in Table 2. As the scanning took place on average 266 days (range: 35-552) after their memory assessment in Betula, the participants were slightly older than what is suggested by their age-cohort.

Table 2. Description of the ImAGen cohort

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>n</th>
<th>Gender (f/m)</th>
<th>Samples (1/3/6)</th>
<th>Education (years)</th>
<th>Age at MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>10</td>
<td>5 / 5</td>
<td>- / - / 10</td>
<td>15.0</td>
<td>25.9</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>5 / 4</td>
<td>- / - / 9</td>
<td>16.0</td>
<td>31.0</td>
</tr>
<tr>
<td>35</td>
<td>10</td>
<td>5 / 5</td>
<td>- / - / 10</td>
<td>15.5</td>
<td>35.9</td>
</tr>
<tr>
<td>40</td>
<td>8</td>
<td>4 / 4</td>
<td>- / - / 8</td>
<td>16.2</td>
<td>41.0</td>
</tr>
<tr>
<td>45</td>
<td>9</td>
<td>4 / 5</td>
<td>- / - / 9</td>
<td>14.2</td>
<td>45.7</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>6 / 4</td>
<td>- / - / 10</td>
<td>13.3</td>
<td>50.9</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
<td>27 / 28</td>
<td>26 / 24 / 5</td>
<td>14.5</td>
<td>56.4</td>
</tr>
<tr>
<td>60</td>
<td>54</td>
<td>27 / 27</td>
<td>24 / 25 / 5</td>
<td>14.2</td>
<td>61.1</td>
</tr>
<tr>
<td>65</td>
<td>54</td>
<td>27 / 27</td>
<td>25 / 26 / 3</td>
<td>13.9</td>
<td>66.0</td>
</tr>
<tr>
<td>70</td>
<td>67</td>
<td>37 / 30</td>
<td>33 / 28 / 6</td>
<td>11.5</td>
<td>71.1</td>
</tr>
<tr>
<td>75</td>
<td>61</td>
<td>34 / 27</td>
<td>24 / 33 / 4</td>
<td>10.2</td>
<td>75.9</td>
</tr>
<tr>
<td>80</td>
<td>28</td>
<td>15 / 13</td>
<td>11 / 13 / 4</td>
<td>8.9</td>
<td>80.5</td>
</tr>
<tr>
<td>95</td>
<td>1</td>
<td>1 / -</td>
<td>- / 1 / -</td>
<td>7.0</td>
<td>96.9</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>197/179</td>
<td>143/150/83</td>
<td>12.8</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Study I participants

The 26 participants that were included in Study I were a subsample of 60 Betula participants, originally recruited for a brain imaging study in 2002-2003 (Lind, Ingvar, et al., 2006; Lind, Larsson, et al., 2006; Lind, Persson, et al., 2006; Persson et al., 2008; Persson, Lind, et al., 2006). A follow-up imaging study was conducted in 2008-2009, for which 41 participants returned.
Two of these were only scanned structurally, and out of the 39 with complete data, 13 were excluded for the purposes of Study I. Reasons for exclusion were: missing behavioral data (6 participants), misunderstanding or not performing scanner task correctly (2 participants), corrupt MR-data (1 participant) and more than ± 10 points change in memory scores up to the baseline scanning session (4 participants). The requirement of stable memory scores until the baseline scanning was a specific inclusion criterion, implemented to avoid inclusion individuals who had already experienced prior cognitive decline. Since one of the objectives of the baseline study in 2002-2003 was to investigate the effects of the APOE gene on brain structure and function, there was an overrepresentation of ε4-allele carriers in the study sample. Since APOE ε4 is a known risk-factor for Alzheimer’s disease (Corder et al., 1993), this factor was controlled for in the analyses of Study I and I also report the number of ε4-carriers here.

The final sample of participants comprised 26 individuals, 18 females and 8 males. All were from Betula sample 1. They were aged 55-79 (mean: 69.7, SD = 8.3) at the time of the follow-up scanning. The mean level of education was 10.9 years (SD = 3.7). Seventeen were carriers of the APOE ε4 allele, 12 homozygotes and 5 heterozygotes. However, all participants were free from signs of dementia at the time of the follow-up study, and scored ≥24 on the Mini-Mental State Examination, or MMSE, (Folstein, Folstein, & McHugh, 1975), which is a screening test for dementia.

Study II participants

All participants in Study II were part of the ImAGen cohort, described above. For the purposes of this study, selection was based on a classification of participants into groups of cognitive maintainers, decliners, and average performers, according to statistical procedures that will be described below (see also Josefsson, De Luna, Pudas, Nilsson, & Nyberg, 2012). The classification was based on prior cognitive change across 15-20 years. Since the aim of Study II was to investigate the neural correlates of successful aging, the main analysis contrasted a group of maintainers, who had a better cognitive development over time than their peers, with a carefully selected control group of average participants. All participants in the ImAGen cohort, who were classified as maintainers and did not meet any of the exclusion criteria (see below), were included in the successful aging group of Study II. The final group consisted of 51 individuals, described in Table 3. A total of 24 maintainers were excluded for the following reasons: not meeting performance criteria on the scanner task (at least 10 correct responses out of 24; and less than 50% missing responses, n = 9), problems with the structural image preventing normalization procedures (e.g., missing data or outlier status, n = 6), health-related issues or remarks from the radiologist screening
the structural scans for abnormalities \( (n = 5) \), and problems with visual acuity \( (n = 4) \). All exclusions were made prior to imaging analyses.

The control group of average performing participants in Study II was age-matched, person by person, to the included successful agers. Also, to ensure that the most representative of the average participants were selected into this control group, we chose those individuals who were closest to the average baseline memory score, and slope of memory change, for each cohort in the full Betula samples 1 and 3. Thus, we calculated the shortest Euclidian distance to the mean baseline score and slope for each participant, and included those with the shortest distances in each age-cohort. Whenever an average participant met an exclusion criterion, this person was omitted from the control group, and the person with the next shortest Euclidian distance was included instead. In total, 29 average participants were omitted for the following reasons: not reaching performance criteria on the scanner task (same as for maintainers, \( n = 26 \)), problems with visual acuity (\( n = 2 \)), and misunderstanding the scanner task (\( n = 1 \)). An additional participant was excluded after preliminary imaging analyses, due to outlier status across all voxels in the brain. The final selection of 51 average participants in the control group can be seen in Table 3. Note that the control group was not gender-matched to the maintainers. This was because female gender was found to be one of the predictors of being classified as a maintainer (Josefsson et al., 2012). Instead, we controlled whether the observed group differences were driven by gender in retrospect.

Study II also had a young control group, to help interpret brain activation differences between the successful and average older participants. This group comprised all individuals in ImAGen who were 45 years or younger at the time of scanning (Table 3). Only one participant was excluded due to technical problems with response collection during scanning. All young participants were from Betula sample 6, which did not have longitudinal behavioral data. Therefore these individuals were not classified as maintainers, average, or decliners.

---

\(^1\) Any one participant could have several reasons for exclusion, e.g., failing to reach performance criteria due to neurological illness. However, for simplicity, screening for health issues was performed only in those participants who were not already excluded for other reasons.
Study III participants

A total of 203 ImAGen participants from Betula samples 1 and 3, who had not met any of the exclusion criteria, were included in Study III. Mean age was 65.7 years, and other sample characteristics are given in Table 4. In total, 90 participants were excluded due to: not having performed, misunderstood, or not reached performance criteria (same as above) on the scanner task (n = 67), corrupt functional data, severe movements and/or outlier status (n = 3), missing structural data, or outlier status on structural scans (n = 8). With these participants removed, the remaining ones were screened and 12 additional participants excluded after being found to have structural abnormalities in the brain, or self-reported health issues (e.g., stroke, multiple sclerosis, or epilepsy).

Table 4. Sample description Study III

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>n</th>
<th>Percent female</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>43</td>
<td>56%</td>
<td>15.0 (3.3)</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
<td>43%</td>
<td>14.5 (3.3)</td>
</tr>
<tr>
<td>65</td>
<td>45</td>
<td>47%</td>
<td>14.4 (4.5)</td>
</tr>
<tr>
<td>70</td>
<td>39</td>
<td>59%</td>
<td>12.4 (4.2)</td>
</tr>
<tr>
<td>75-80*</td>
<td>34</td>
<td>62%</td>
<td>10.4 (3.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>203</td>
<td>53%</td>
<td>13.5 (4.2)</td>
</tr>
</tbody>
</table>

* Four 80-year olds (two female) were included. Standard deviations in parentheses.

Assessing selection effects

The representativeness of the brain imaging samples could be compromised by selective attrition across the 20 years of the Betula study, as well as selection bias resulting from applying exclusion criteria in selecting which participants should be included in the final analyses, as described in the preceding...
paragraphs. However, since the Betula study is population-based from outset, the representativeness of the included samples can be quantified. Calculating a measure of representativeness compared to the full population-based samples can help interpretation and validity-assessments of the results derived from the studies in this thesis, as well as other studies using Betula and ImAGen data. In the following paragraph I have attempted to quantify sample representativeness by computing a standardized measure of memory performance at the first measurement occasion for each participant, compared to his/her full age-cohort in the Betula samples. This z-score was computed through the standard formula \( (x - \mu) / \sigma \), where \( x \) is the raw memory score for each participant, \( \mu \) is the mean memory score for the age-cohort the participant belongs to, and \( \sigma \) is the standard deviation in that age-cohort. A selection/attrition effect is demonstrated if a subsample has a higher than average memory already at the first measurement occasion in Betula. The memory score will described in detail below.

First, I quantified the attrition effect for the remaining participants from sample 1 and sample 3 at the latest measurement occasion in Betula (366 out of 1000 from sample 1, and 390 out of 966 from sample 3). This subset of participants had performed on average 0.13 standard deviations (SDs) above the mean of the full population-based samples at recruitment to Betula. The selection effect had a small, but positive correlation with age \( r = 0.11, p < 0.01 \), indicating that attrition was more biased for older individuals. Regarding the imaging samples used in this thesis, the 26 participants included in Study I had performed on average 0.28 SDs above the mean at first testing. This can be compared to all 38 participants who completed follow-up in the longitudinal imaging study, who were slightly more representative; 0.24, and the full sample of 60 participants who were selected for the baseline study in 2002, who had a mean z-score of 0.16. For the 293 individuals from sample 1 and 3 that were scanned in the ImAGen cohort, the selection effect was only slightly stronger than for all sample 1 and 3 participants tested at T5. The ImAGen participants had performed on average 0.19 SDs above the mean of their peers at first testing in Betula. Again the selection effect was related to age, becoming apparent for participants aged 55 and older at first testing, as can be seen in Figure 4. After applying exclusion criteria to this sample, leaving the 203 participants who were included in Study III, the mean z-score was 0.20. Thus, the exclusion criteria had only a marginal effect above the selection effects into the imaging cohort. As for the successfully aged and average participants who were selected for Study II, the successful had scored 0.92 SDs above the mean, while the participants in the average group were indeed average and scored 0.07 SDs below the mean.
Longitudinal memory measure

The main measure of memory performance used in all three studies of this thesis was a composite of five episodic memory test scores from the Betula test battery. Hence, whenever I refer to memory performance, ability or scores of the participants included in thesis, this is the measure that was used. This measure was also used to assess memory change over time, as change scores in Study I, and as a slope estimated by ordinary least squares linear regression in Studies II and III. The composite score for each participant consisted of the raw number of items recalled in each task condition, with a maximum of 76 points. The included test variables were the following:

![Figure 4. Selection effects for ImAGen participants compared to full samples 1 and 3 from the Betula study. The y-axis shows the raw memory scores, and the x-axis shows the age at first testing. Actual age at scanning was 20 years older for sample 1 participants and 15 years older for sample 3. Error bars represent 95% confidence intervals.](image-url)
1. Immediate free recall of 16 short verbal commands that were enacted by the participants using objects provided by the experimenter (e.g., point at the book, lift the apple). Each command was presented for 8 seconds, and the participants were given 2 minutes for recall.

2. Immediate free recall of 16 short verbal commands that were studied without enactment. Instead, the experimenter read the commands aloud while also showing them in written form. Presentation time was 8 seconds per item, and 2 minutes was given for recall.

3. and 4. Delayed cued recall of nouns from the 16 enacted and 16 non-enacted commands, using 8 noun categories as recall cues (e.g., “fruits”). Three minutes was given for recall.

5. Immediate recall of 12 verbally presented, unrelated, nouns. Presentation rate was 2 seconds per word, and participants were given 45 seconds for recall.

For tasks 1 and 2, presentation order was counterbalanced across participants and test occasions, so that half of the participants performed the non-enacted condition first. There were two different lists of commands, with eight list-order variations each, which were also counterbalanced across participants. Further, counterbalancing was done across test occasions, so that for each participant, the list studied with enactment at first testing was studied without enactment at the next test occasion five years later, or vice versa. The delayed cued recall test (tasks 3 and 4) was performed after completion of the second immediate free recall condition. Task 5 was a part of a more extensive test which addressed learning and recall of words during divided compared to focused attention conditions. Three conditions of this task had concurrent card-sorting as a manipulation of attention, but only the fourth condition without concurrent card sorting was used for the current purposes. The presentation order of the different conditions of task 5 was counterbalanced across participants and across test occasions. In total there were two sets of four word-lists for this test that varied across participants and test occasions. By and large, all other testing procedures were kept as similar as possible across test occasions in the Betula study. Counterbalancing and switching of item-lists across test occasions served to reduce practice effects.

Finally, a few words should be mentioned about the reliability of the memory composite score. The pairwise correlation coefficients between the tests included in the composite ranged from $r = 0.38$ to $r = 0.73$, all significant at the $p < 0.001$ level (based on 1000 sample 1 subjects at T1 in Betula). This yields a Cronbach’s alpha of 0.83, which can be considered a good level of internal consistency, i.e., an indication that the different tests measure the same construct. Test-retest reliability of the memory composite was estimated to 0.79 (Pearson correlation coefficient) between the first and sec-
ond Betula test occasion. This calculation was based on 838 participants (age-range: 40-85 years) from sample 1 that returned for retest at T2.

Statistical classification for Study II

In Study II, successful and average agers were identified using a statistical classification model including all Betula participants from samples 1 and 3, with two or more memory assessments. Participants were classified as maintainers, average, or decliners based on how their memory performance over time compared to the average of their age-cohort in Betula. The statistical classification model has been described in full detail by Josefsson et al. (2012). However, a slight modification of the model was implemented for Study II, namely that separate models were estimated for sample 1 and 3 participants because of the different number of available measurement points. A brief description of the classification procedures will be given here. The classification model was based on 1954 participants’ baseline memory scores, and 1561 participants’ linear slopes of memory change across 15-20 years of participation in the Betula study. The 1954 participants were the full samples 1 and 3 from Betula, and 1561 of these had at least two measurement points, which was required for estimating a slope of change. The baseline score was from each participant’s first memory assessment in Betula. The slopes were estimated with ordinary least squares regression of the episodic memory composite scores on time. Using these data, the average memory development over time was estimated for each of the 10 age-cohorts in the full samples. A key feature of the classification model was that it corrected for non-ignorable attrition (drop-out) by using random-effects pattern-mixture modeling (Little, 1995). This technique makes use of all available data to factor in the scores of the participants who drop out during the course of the study.

We wanted to define a cognitive maintainer as a person with a moderate to high baseline memory, combined with a better than average slope for a given baseline score. To obtain a measure that took into account both the baseline score and the slope, we used the predicted score for the last measurement point as an outcome measure. Each person’s predicted final score is a linear combination of his/her baseline, score plus the rate of change multiplied by the time in the study (i.e., 15 or 20 years). This final score was compared to the average final score in each respective age-cohort, which was derived from the pattern-mixture model. All participants with predicted final scores higher than 1 SD from the average were classed as cognitive maintainers, whereas all participants with predicted final scores lower than 1 SD from the mean were classed as decliners. Everyone in-between was considered as average. As previously mentioned, we only considered maintainers and av-
verage individuals in Study II. The decliners could hold potentially relevant information, but were too few in the ImAGen cohort to form a group (n = 7, after exclusions). However, the identification and exclusion of decliners likely served to minimize the risk of inadvertently including individuals in preclinical phases of dementia, which could bias the results.

Scanner tasks

During functional neuroimaging the participants usually perform a cognitive task to elicit task-related brain activation. Two different episodic memory tasks were used for the studies in this thesis.

Study I: Incidental encoding of words

During scanning participants performed a semantic categorization task in which they indicated whether nouns that were presented to them were abstract (e.g., truth) or concrete (e.g., book). This task served as an incidental encoding condition for a later recognition test. In total, 160 words were presented to the participants during the categorization task, one at a time. Half of the words were familiar to the participants from having categorized them twice before, once before scanning, and once in the scanner during collection of structural scans (with shifted word order). However, for the purposes of Study I, the data were collapsed across novel and previously presented words. The categorization task was presented in a blocked manner, alternating between categorization blocks (30 seconds) and fixation blocks (21 seconds). The fixation blocks were used as a baseline, during which participants merely focused on a fixation cross in the center of the screen. In total there were four identical functional runs, each run starting and ending with a brief fixation block (12 seconds), with four categorization blocks in between. Each categorization block contained 10 words.

The recognition test was performed after the scanning at the baseline study in 2002-2003, but during the follow-up study in 2008-2009 a portion of the words was tested in the scanner. During the recognition tests, participants made old/new judgments on a total of 240 words, of which 80 were new.

Study II and Study III: Face-name paired associates

The face-name task consisted of alternating blocks of encoding, retrieval, and an active baseline task. During encoding, participants viewed photographs of unfamiliar faces, presented one by one, together with common first names, see Figure 5. They were instructed to encode the face and indicate with a button press that they had seen each face. The button press was in-
cluded to equate the motoric components during encoding, retrieval, and baseline. During the retrieval blocks, participants were presented with the previously viewed faces, presented together with three letters (Figure 5). One of the letters corresponded to the first letter of the name encoded for that face. Participants indicated the correct letter with a button press. When unsure, they were instructed to guess. During the baseline blocks, a simple perceptual discrimination task was presented, in which participants were instructed to indicate with a button press whenever a fixation cross was replaced by a circle.

Presentation time was 4 seconds per face in the encoding and retrieval blocks, with 1.5 - 4.5 seconds randomized inter-stimulus intervals (allowing for both event-related and blocked imaging analyses). Mean duration between the encoding and retrieval of a given face was 85.1 seconds (SD = 26.1). A total of 24 face-name pairs were presented throughout the task, which lasted approximately 10 minutes. Block and stimulus order was pseudo-randomized and constant across all participants. Prior to scanning, participants were familiarized with the task by completing a short practice version.

In the same scanning session that the face-name task was given, the participants also performed a short visuo-motor task with the purpose of assessing individual hemodynamic response functions for each participant, as well as a working memory task. The face-name task was given after the visual task, which lasted approximately 4 minutes, but before the working memory task.

Brain imaging

All brain image acquisition was performed at the Norrland’s University Hospital in Umeå, Sweden. For Study I, a 1.5 tesla Philips Intra scanner was used. The data for Studies II and III were collected on a 3 tesla Discover MR750 scanner from General Electric. In all three studies of this thesis, both functional and structural MRI data were used, as well as diffusion tensor imaging (DTI) in Study II. For the functional MR-data, standard echo-planar imaging pulse sequences were used, while the structural data were collected.
with T1-weighted sequences. The DTI data were acquired with a single shot, spin-echo planar T2-weighted pulse sequence. All details regarding the pulse sequence parameters are found in each respective study’s methods section.

Preprocessing and analysis of imaging data

Functional data

Preprocessing

Before one can statistically analyze functional MRI data, a number of computational procedures need to be performed on it to remove uninteresting variability inherent in the data. For the work presented in this thesis, the preprocessing procedures and subsequent statistical analyses were performed with versions 5 and 8 of the Statistical Parametric Mapping (SPM) software (Wellcome Department of Imaging Science, Functional Imaging Laboratory). Some of the analysis steps, however, were performed in an in-house developed software, DataZ, which is based on SPM.

The first step in the preprocessing is to correct for differences in slice acquisition times. Since the entire volume of the brain cannot be sampled at once, MR-images are acquired in slices. For instance, 33 slices were acquired during 3 seconds to cover the entire brain in Study I, whereas 37 slices were acquired in 2 seconds in Study II and III. Therefore there is a slight temporal displacement between subsequent slices, which is corrected for using a temporal interpolation procedure known as slice timing. In the second step of the preprocessing, a correction for head motion is performed by rigidly aligning each image volume to the first volume of the series. An unwarping procedure is also used to correct for image distortions caused by interactions between head movement and inhomogeneities in the magnetic field.

In order to perform group analyses, the images of all participants need to be spatially normalized to a common space. There is large individual variation in the shape, size, and morphology of the human brain, and in group analyses one needs to assure that the same anatomical location is sampled for each person. Therefore, all participants’ images are transformed into a common template in the third step of preprocessing. For Study I this was a standard template of the Montreal Neurological Institute (MNI), which is provided in SPM8. For Study II and Study III a slightly more sophisticated normalization procedure was used. The motivation behind this was that the MNI template is not optimally representative of the variation in brain morphology caused by aging. Therefore, a sample-specific template was created from
292 individuals (51% female, aged 25-81 years) from the ImAGen sample. These were individuals selected for having performed the face-task according to performance criteria, and not being structurally deviating according to the sample homogeneity function in the voxel-based morphometry (VBM) toolbox in SPM8. The template was created using an algorithm called Diffeomorphic Anatomical Registration using Exponentiated Lie algebra, or DARTEL (Ashburner, 2007). In brief, this was done by first segmenting each individual’s structural T1-image into gray and white matter components, which were then imported into DARTEL space. Next, all subject-specific gray/white-matter images were averaged into one initial template. Each participant’s deformations from this template were subsequently computed, and the inverse of these applied to his/her segmented gray/white-matter image. Thereafter a new template was created from the mean of the deformed subject-specific images. This procedure was iterated six times to create the final template, which was then rigidly aligned to MNI standard space. The functional MRI data, which had been co-registered to each person’s structural T1-image at the beginning of the template-creation process, were then non-linearly normalized to the final template. This was done using the subject-specific flow fields derived from the creation of the template.

The final step of the preprocessing is smoothing. This is done on the normalized images, by averaging data over adjacent voxels with a Gaussian spatial filter. In the current studies, the size of this filter was 8 millimeters at full-width-half-maximum. There are several reasons for smoothing fMRI data. It removes noise, and can also correct for remaining between-subject variability after normalization. Thereby the functional signal-to-noise ratio is improved. Smoothing also improves the validity of the statistical tests performed on the data, by making parameter errors more normally distributed.

**Statistical analyses**

There are several methods for analyzing fMRI data. Perhaps the simplest and most commonly used is to treat the BOLD signal time-series from each voxel in the brain as a separate dependent variable, and modeling the effects of experimental manipulations with multiple regression. This approach is known as a mass-univariate analysis (Friston et al., 1994), and was used in all studies of this thesis. In this approach, one models the expected time-series of each voxel by using a general linear model (GLM). Specifically, one defines a set of regressors (i.e., predictors) that one believes explains change in signal intensity during the experimental run. Each condition from the experimental task is included as a regressor, and convolved with the hemodynamic response function (in order to account for the relatively sluggish response of the vascular system, compared to neural activity). In blocked tasks, for instance, the regressors take the form of a box-car waveform. One
can also add nuisance regressors, such as the realignment parameters derived from the motion correction procedure during preprocessing, to remove unnecessary variance from the data. When the model is specified, the parameter weights ($\beta$s) of each regressor are estimated to find the combination of parameter weights that minimizes residual unexplained variance (the error term), compared to the measured time-course of the voxel. Subsequently, one can statistically test the effects of the regressors at the voxel-level.

Individual-level contrasts are usually set up, for instance, contrasting an experimental condition (e.g., memory encoding) with a baseline condition (e.g., visual fixation). Since fMRI does not assess absolute levels of activation, hypothesis testing usually involves contrasting two conditions in a subtractive logic. The subject-level contrast is represented in a contrast image containing, for each voxel in the brain, an estimated difference in parameter weights between the conditions. These contrast images can subsequently be used to test hypothesis on the group-level, typically using random-effects analyses that allow the effects of the experimental manipulation to vary across participants. For instance, in Study II, a two-sample t-test was used to compare successful and average agers. In Study III, a different form of second-level analyses was employed. Here, the effect of memory performance was used as a covariate in a one-sample t-test to identify voxels in the brain that correlated with memory performance. The results from second level analyses are represented in statistical maps, containing a t-statistic for each voxel in the brain. These maps are thresholded at a predetermined alpha-level (e.g., $p < 0.001$) to determine which, if any, voxels that express statistically significant effects (e.g., group differences or correlations with memory performance).

Structural data
Both Study I and Study II investigated aspects of how the brain’s structural, or anatomical, properties related to differences in cognition. In Study I, the volumes of the hippocampi for each participant were assessed using Freesurfer software. This is an automated tool for anatomical labeling of voxels in the brain, based both on signal intensities from the MR image, as well information of brain anatomy contained in an anatomical atlas (Fischl et al., 2002). This software generated raw hippocampal volumes for each participant, which were then adjusted for differences in head/body size using a covariance approach. This adjustment removes variance associated with individual differences in head size, that otherwise could confound volumetric comparisons. The following formula was used: adjusted volume = raw volume $- b \times (\text{height} - \text{mean height})$, where $b$ is the slope of regression of the raw volume on height in the sample. This procedure redefines the data points as the difference between an individual’s volume, and that of others of
similar height in the sample. The choice of body height instead of a direct measure of brain, or intracranial, volume in the formula, was motivated by wanting to use the same procedure as in previous studies on the same sample (Persson, Nyberg, et al., 2006). An alternative correction with intracranial volume instead of height was run, but did not change the results substantially.

As mentioned in the section on brain aging, variation in BOLD-signal in elderly samples could be driven by differences in gray matter volume, due to, for instance, differential age-related atrophy. To control for such potential confounding effects, the Biological Parametric Mapping (BPM) toolbox (Casanova et al., 2007) was used to co-vary for gray matter volume in the functional analyses in Study II and Study III. BPM uses a similar voxel-wise general linear model approach as SPM, but allows adding an additional image as a regressor. In this way, each voxel gets a different design matrix depending on the gray matter value of that voxel. If group differences in BOLD signal that are observed in standard SPM analyses are replicated when using the BPM approach, it is reasonable to conclude that differences in gray matter volume were not driving the observed effects (Casanova et al., 2007). To be able to use BPM on our data set, each individual’s structural T1-weighted image was segmented, normalized, and coregistered to the fMRI data. Thereafter, the gray matter image was used as a covariate of no interest in an ANCOVA model in Study II, and in a multiple regression model in Study III, with the functional data as the primary modality. Study II investigated whether the differences in functional activation between successful and average older participants were driven by differences in brain structure. In Study III, it was investigated whether the associations between BOLD-signal and memory scores (or memory slopes) were driven by differential gray matter volume.

**Diffusion Tensor Imaging**

In Study II possible group differences in the integrity of the brain white matter was investigated using DTI. From diffusion weighted contrast images one can calculate measures of fractional anisotropy (FA), which is a scalar quantity reflecting the tendency of water molecules to diffuse in a preferred direction. The FA value is bounded by 0 and 1, with values near 0 indicating that the molecules are equally likely to diffuse in any direction and values near 1 indicating highly consistent diffusion orientation. High FA values are thus indicative of a high integrity of the local white matter.

The DTI data used in Study II were obtained from another study on the ImAGen cohort (Salami, Eriksson, Nilsson, et al., 2012), in which all details regarding preprocessing and analyses are described. In brief, the analyses
were carried out using software from the University of Oxford’s Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL), specifically the Tract-Based Spatial Statistics method (Smith et al., 2006). Preprocessing steps included averaging data from the three diffusion acquisitions that were collected during scanning, correcting for head movement and eddy-current distortions, creation of three dimensional FA maps and normalizing these to a template (the most typical participant of the sample). Then, the individual FA images were averaged to a mean FA image for the sample, from which a white matter skeleton was extracted. Each participant’s aligned FA image was subsequently projected onto this skeleton to account for residual misalignments from the normalization. Finally, individual-specific mean FA values were extracted from regions of interest (ROIs) defined on the group skeleton. The ROIs were defined according to JHU ICBM-DTI-81 white matter labels which are part of the FSL software package. FA values for each participant were averaged along the length of each of 12 white matter tracts, and across hemispheres. The following tracts were included in the analyses: genu, body, and splenium of the corpus callosum, cingulum, corona radiata, cortico-spinal tract, external and internal capsules, superior/inferior fronto-occipital fasciculus, superior longitudinal fasciculus, sagittal striatum, and the uncinate fasciculus. The extracted FA values were entered into IBM SPSS statistics software and tested using a MANOVA to investigate possible differences in white matter integrity between the successful and average older groups in Study II.
Overview of empirical studies

Study I

The aim of Study I was to use longitudinal data to investigate relationships between change in memory performance and changes in structural and functional brain characteristics. Most previous studies have used cross-sectional designs for investigating the involvement of the HC and lateral PFC in cognitive decline in aging. As described in previous sections of this thesis, cross-sectional and longitudinal data have been shown to generate diverging findings on both the behavioral and neural level (Nyberg et al., 2010; Raz et al., 2005; Rönnlund et al., 2005). Longitudinal data are commonly held to have better sensitivity in detecting age-related changes, so it is well motivated to investigate whether longitudinal observations converge with the cross-sectional literature.

By correlating memory change scores across a 6-year period with change in brain activation during the same time, a significant association was found in the left HC. Individuals with more functional decline in the HC also displayed more memory decline (Figure 6A). With regard to brain structure, an analogous correlation between right HC volume and change in memory performance was also observed. This suggests that both structural and functional alterations of the HC contribute to age-related memory decline. However, there was no significant correlation between HC volume change and change HC activation, indicating that the observed functional decline was not directly related to atrophy of gray matter.

Figure 6. Relationship between memory change and HC activation change. Panel A displays the continuous relationship between memory change and HC activation change in the full sample (n = 26). Panel B displays HC signal change in stable and declining subgroups, defined by a median split.
An incidental observation was that the subsample of individuals with declining memory \((n = 13\), defined by a median split) had increased HC activation at the baseline MR session compared to the group with stable or improved memory over time (Figure 6B). In fact, higher HC activation at baseline predicted more memory decline over the following 6 years \((r = -0.41, p = 0.037)\). Although this was an incidental finding, it is in line with previous observations (O’Brien et al., 2010), and suggests that cognitive decline could be preceded by a period of paradoxically increased HC recruitment.

Brain activation change was also correlated with memory change in the bilateral parahippocampal gyrus (PHG). However, in contrast to the HC proper, the relationship in these regions was negative, indicating that individuals with declining memory increased their activation over time. It has previously been demonstrated that aging can affect substructures in the MTL differentially. For instance, during episodic retrieval, an increased reliance on the PHG and/or the rhinal cortex has been demonstrated in combination with functional reductions in the HC (Cabeza et al., 2004; Daselaar et al., 2006). This has been related to the increased reliance on familiarity-based recall processes in older individuals, since these processes seem less affected by aging than recollection-based ones (Mäntylä, 1993; Parkin & Walter, 1992). Since the current effects were found during episodic encoding this explanation is not directly applicable. However, half of the blocks in the incidental encoding task contained previously seen words, which could have triggered recognition-related processes.

It was further investigated how the reported findings were related to APOE ε4 status. There were no statistically significant differences in MTL activation or memory performance change, but ε4 carriers had a numerically larger memory decline than non-carriers \((-4.9\) points compared to +0.7 for the non-carriers). The ε4 carriers also had a significantly larger reduction of HC volume over time. Thus, it cannot be ruled out that APOE status was one of the driving forces behind the observed results. However, there was a significant correlation between hippocampus volume and memory change even after controlling for APOE status, and age. As well, APOE status and age were included as covariates of no interest in the functional whole brain analysis that identified the MTL clusters. So although APOE status could have partially explained the findings, other underlying factors likely exist.

In conclusion, the results of Study I corroborated previous cross-sectional results by showing a longitudinal association between memory change and structural and functional decline in the HC. The study also contributed tentative new findings regarding increased recruitment of PHG regions with cog-

\*\*2 This finding was not reported in the published version of the paper.\*\*
nitive decline. However, contrary to expectations, no significant relationships were observed between memory change and activation change in the lateral PFC in Study I.

Study II

The objective of Study II was to investigate structural and functional brain characteristics that differentiate successfully aged individuals from those with an average age-related cognitive change. In contrast to the extensive literature on neural correlates of age-related cognitive decline (Buckner, 2004), relatively little is known about the brain characteristics of successful agers and no study has thus far investigated functional brain characteristics of longitudinally defined successful agers. In Study II, successful and average individuals were defined relative to the average attrition-corrected memory development in a sample of 1561 participants from the Betula study, as described in the Methods section. Figure 7 displays the longitudinal memory change in the resulting groups, which differed in both initial memory level and memory change over time. When comparing memory-related brain activation between the groups, it was found that successful participants had higher encoding-related activation than average participants in the bilateral PFC and the left HC. In order to better characterize these findings, the activation levels were compared to those of a young reference group. For the HC it was found that the activation of average, but not successful, older participants was significantly lower than for young individuals (Figure 8). The activation pattern across the frontal clusters was more mixed. In a left inferior frontal cluster (cluster a, Figure 8) successful older had higher activation than young participants, while the activation levels in the remaining frontal clusters were comparable between the groups (Figure 8).

![Figure 7. Longitudinal memory scores for successful and average groups.](image)
The average older participants did not differ significantly from young individuals in any frontal cluster, but a trend was seen in the anterior cingulate cortex (cluster c).

The observed functional effects were not directly driven by differences in gender proportions or educational attainment between the groups. Neither could the differences be explained by differences in gray or white matter integrity. The activation in the HC correlated with scanner task performance, but no such relationship was observed for the frontal clusters.

As the successful and average older groups differed both in initial memory level and slope of memory change, a number of control analyses were performed in order to try to tease apart the effects of level and slope. The results were first replicated in subgroups matched on initial memory levels, indicating that the effects were not only driven by differences in initial level. Further, hierarchical regressions using initial level and slope as predictors of BOLD-signal in the clusters from the main analysis showed that, in these groups, slope was the only significant predictor of BOLD-signal in the HC and anterior cingulate cortex, while both initial level and slope were significant predictors of the frontal effects.

The HC activation differences were interpreted as reflecting a relative sparing of HC function in the successful agers, which likely also contributed to the sparing of memory functions over time. The decrease in HC function in the average elderly is also noteworthy, since these individual’s memory per-
formance change was comparable to the average in the full population-based sample. Regarding the frontal activation differences, they could not easily be attributed to compensatory processes, since no correlations were observed between activation and performance, nor activation and age. Rather they were interpreted as mainly reflecting higher frontal functionality since youth, and perhaps a higher neural capacity (Y. Stern, 2009), which is the capability to recruit more neural resources in order to cope with a challenging cognitive task. This brain characteristic in turn could be a manifestation of cognitive reserve (Y. Stern, 2009), which could contribute to the preservation of cognitive abilities through the course of aging. In summary, the findings of Study II illustrate that successful cognitive aging could be accomplished by preservation of a youth-like HC recruitment in combination with a high frontal function. Also, successful aging was found to be driven mainly by functional, rather than structural brain characteristics.

Study III
Study III aimed at investigating the relative influences of prior level of memory function on the one hand, and memory change over time, on the other, on brain activation differences in elderly participants. Although there is an average decline in cognitive functions with age, large-scale longitudinal studies have reported that individual differences in cognitive ability are remarkably stable across the lifespan. Correlations in the magnitude of \( r = 0.6-0.7 \) have been reported between childhood cognitive performance and performance in the 8th decade of life (Deary et al., 2004). Further, it has also been shown that childhood cognitive ability differences can account for associations between cognitive ability and brain structure in older age (Karama et al., 2013). This prompts the question of whether individual differences in cognitive ability, established in youth, also account for a significant portion of variability in cross-sectional assessments of functional brain activation in elderly.

First, we demonstrated that in our sample, midlife memory scores, assessed 15-20 years earlier, accounted for approximately three times as much variance (\( R^2 = 0.37 \)) in current memory performance, as did estimates of prior memory change (\( R^2 = 0.12 \)). Then, current memory scores were correlated with brain activation during the Face-Name task to identify brain regions that were differentially engaged as a function of performance level. During episodic encoding, the bilateral HC and four clusters in the left PFC were found to correlate positively with memory performance (Figure 9A). Parameter estimates were extracted from these clusters and used as dependent variables in hierarchical regressions, with midlife memory performance and memory slope as predictors. In clusters with significant age-correlations, age
Figure 9. Differential encoding-related activation as a function of current memory performance is displayed in panel A. Panel B shows effects of slope in green and midlife memory in blue. In panel C overlapping effects are shown for midlife and current memory as well as slope (color scale is the same as in previous panels).
was controlled for by entering it first in the regression. It was found that both midlife memory and slope were significant predictors of activation in the left HC cluster, as well as the largest left inferior frontal cluster (cluster 4, Figure 9A). This was found regardless of order of entry into the regression, i.e., midlife memory before slope, or vice versa. Midlife memory explained numerically more variance than slope in these clusters. For a left superior cluster (no. 6 in Figure 9A), slope was the only significant predictor, while the opposite was true for an inferior frontal cluster (no. 3), and for the right HC, i.e., these effects reflected only differences in midlife memory. Finally, in the last of the frontal clusters (no. 5), age was the only significant predictor, whereas both midlife memory and slope failed to reach significance.

To assess the replicability of these findings, midlife memory scores and memory slopes were regressed directly onto encoding-related brain activation. For midlife memory, a pattern similar to that of current memory performance was seen, with prominent overlap in the left inferior frontal cortex and the bilateral hippocampus (Figure 9C, in blue). Thus, memory scores assessed 15-20 years prior to scanning reliably predicted brain activation in memory-relevant brain areas. Regressing memory slopes directly onto encoding-related activation identified clusters overlapping the bilateral HC and left inferior frontal clusters from the current memory analysis (Figure 9B-C, effects of slope in green). Additionally, the slope analysis identified a right-sided PFC cluster (Figure 9B, left), which was not found in the contrast using current memory as a covariate. The slope analysis also resulted in a substantially increased extent of the left superior frontal cluster from the current memory contrast (Figure 9B, right-hand side). This points to the increased sensitivity of longitudinal estimates in identifying brain regions indicative of actual cognitive change. Hierarchical regressions confirmed that slope, but not midlife memory ability predicted significant variance in these two frontal clusters. Control analyses were also performed, showing that these functional results were not primarily driven by differences in gray matter volume.

In summary, the findings of Study III highlighted that individual differences in cognition, established early in life, can account for a substantial share of variability in memory and brain activation of healthy elderly. In the absence of longitudinal data, this variability can be misinterpreted as differential age-related changes. These findings have implications for interpretations of results from cross-sectional studies of neurocognitive aging, specifically for approaches that seek to use BOLD-signal variability in elderly as a neural marker for forthcoming cognitive decline. The results of Study III also identified regions in the right inferior and left superior PFC that were specifically indicative of that age-related cognitive change had occurred. The importance of these regions would have been underestimated, or altogether missed, if only cross-sectional memory performance data were available.
Discussion

The main aim of the work presented in this thesis was to explore how longitudinal observations of aging individuals can advance knowledge of neurocognitive aging.

The major contributions of this thesis to the cognitive neuroscience of aging can be summarized as follows:

i) Substantiating the role of hippocampal structure and function in age-related memory decline
ii) Shedding light on the relatively neglected topic of neural underpinnings of successful cognitive aging
iii) Contributing new evidence for the role of the prefrontal cortex in age-related memory decline and stability.
iv) Emphasizing the influence of prior memory ability behind cross-sectional brain activation differences in elderly.

In the following paragraphs I will discuss the findings relating to the MTL and the frontal cortex separately. Then I will summarize the contribution of longitudinal assessments to the field of neurocognitive aging, before addressing some limitations of the current work, as well as some avenues for future work.

The hippocampus and the medial temporal lobe

The fact that significant effects were found in the HC across all three studies strongly underscores its importance for heterogeneity in age-related memory change. Not only was encoding-related left HC activity found to decline in parallel with episodic memory decline across 6 years (Study I), it was also spared in a group of individuals who had maintained high levels of memory performance across 15-20 years (Study II). Moreover, left HC activation during memory encoding was found to correlate with memory decline over the past decade in Study III. Collectively the findings from all three studies converge to show that HC function is impaired in healthy aged individuals with memory decline in the normal range, but spared in those who have maintained memory function up to older age. Although these findings were
obtained with fMRI, which is a correlational method, when considered together with related findings from brain injured patients and animal studies, they strongly suggest that HC function is an important factor in age-related memory decline or preservation.

Although a low HC function has previously been found in elderly compared to young participants (Daselaar et al., 2003b; Dennis et al., 2007; Grady et al., 1995), and particularly for low performing elderly (Daselaar et al., 2003a), longitudinal evidence has been scarce. Evidence has also been somewhat inconsistent, with several studies on healthy aging failing to find functional HC reductions in elderly (Miller, Celone, et al., 2008; Persson et al., 2011). Some have also suggested that memory impairment in healthy aging might predominantly be caused by frontal rather than MTL dysfunction (Buckner, 2004). Thus, the longitudinal finding of decreased HC function correlating with decline in memory performance in Study I is strong evidence in establishing HC failure in healthy elderly with age-related memory decline. Further, our findings are strikingly similar to a previous longitudinal study that showed that decreased HC activation correlated with change in a global dementia rating scale (O’Brien et al., 2010). Our study extends these findings by demonstrating this longitudinal HC-cognition link in individuals free of clinical cognitive impairment (MMSE > 24 at follow-up). Because in contrast to our study, several of the fastest declining individuals progressed to MCI or probable Alzheimer’s disease at the follow-up (8 out of 13 participants) in the previous study. The reason that we were able to detect earlier signs of cognitive decline was likely the use of sensitive episodic memory measures instead of a global dementia rating scale.

Although Study II and III did not have longitudinal imaging data, the findings from both these studies are consistent with decreasing HC function in healthy aging, as long as the participants are experiencing some degree of memory decline. The finding of lower HC activation in the average older group compared with the young participants in Study II speaks strongly for this. This group had very close to average memory performance when recruited to the Betula study 15-20 years ago (0.07 SDs below the mean of their population-based age-cohort), and also were the ones with the most average rate of change compared to the population-based sample. Having this information probably makes this one of the most well-characterized cross-sectional imaging samples to date. Thus, observing a decrease in HC function in these individuals strongly corroborates the notion of a functional HC impairment also in age-related memory loss within the normal range. Although one can never be completely certain that no individuals in preclinical stages of dementia were included in the samples, in this case it seems unlikely. First of all, all individuals with more than average decline were excluded in the statistical classification procedures (Josefsson et al., 2012),
and secondly, we applied rather strict exclusion criteria to the ImAGen sample (see Methods section). Thus, it is more likely that the observed effects are underestimation of the true age effects, rather than caused by inclusion of individuals with prodromal dementia.

The demonstration that longitudinally-defined successful aging is associated with spared HC function is novel, although cross-sectional studies have provided such indications previously (e.g., Daselaar et al., 2003a; Düzel, Schütze, Yonelinas, & Heinze, 2011). However, in the light of the findings from Study III, cross-sectional definitions might produce results that are mainly caused by differences in cognitive ability from youth. This was not the case in Study II, however, since we carefully controlled for differences in memory performance at the beginning of the Betula study and found that the differences in brain activation between successful and average agers remained. A previous longitudinal PET study (Beason-Held et al., 2008), also concluded that HC function was spared in healthy elderly with preserved cognition over time (although here an increase in HC signal over time was actually observed). In general, successful aging has been somewhat neglected topic in the functional neuroimaging literature, with very few studies explicitly aimed at investigating it. Several studies have, however, classified elderly individuals as either high- or low-performing. In a review of this literature (Eyler, Sherzai, Kaup, & Jeste, 2011), nine studies were identified in which successful performers had more HC/MTL activation than normal performers, whereas the opposite pattern was found in eight studies (26 studies reported no significant relationship, and one study provided mixed findings). Whereas the nine studies with successful > normal patterns are consistent with the results of Study II, it is unclear how the opposite pattern could have emerged. Since no information is given regarding how normal and successful were defined, or during which task conditions this pattern was observed, it is difficult to speculate on this matter (but see discussion on increased HC activation in cognitively impaired individuals below). Nevertheless, the findings in Study II were robust and suggest that one reason why some studies fail to demonstrate age-related HC decline in healthy elderly (e.g., Persson et al., 2011) could be that the study sample is biased towards successfully aged individuals. Also, the finding that successful agers had spared HC function is in line with the brain maintenance account (Nyberg et al., 2012).

Another novel contribution regarding HC function in aging was provided by Study III, in demonstrating that a low HC recruitment in elderly does not necessarily imply age-related decline, but can also reflect a low memory performance from midlife - when no substantial age-related memory decline is expected to have occurred (Rönnlund et al., 2005). The finding that memory scores assessed 15-20 years prior to scanning reliably predicted
activity in brain areas that have been implicated in age-related memory decline is quite striking. This finding further underscores the importance of longitudinal data for investigating neurocognitive aging, and has implications for interpretation of results from cross-sectional studies, in which age-related memory decline is inferred from low performance at one point in time. The findings from Study III do not imply that cross-sectional studies cannot detect true age-related changes in HC function, only that on an individual level it is not possible to conclude functional decline or risk for impending dementia merely from observing a low HC BOLD-signal at one point in time. This mainly has implications for approaches that attempt to use BOLD-signal as a stand-alone biomarker for cognitive decline. However, it is still possible that BOLD-signal reductions, in combination with other biomarkers, such as HC volume and APOE-status, could be useful in predicting cognitive decline (Woodard et al., 2010).

The relative influences of midlife cognitive ability and age-related cognitive change on HC activation in elderly are likely dependent on the sample characteristics. In the relatively healthy and high-performing sample in Study III, midlife ability accounted for numerically more variance. It is, however, likely that age-related change would have more influence in older samples, and in samples with clinically relevant cognitive impairment. Still, it is acknowledged that the majority of cross-sectional neuroimaging studies of aging mainly include high-functioning and healthy individuals (e.g., Dennis & Peterson, 2012), which highlights the widespread implications of the findings in Study III. Due to the cross-sectional design in this study, the exact causal chain of events linking midlife memory ability and current brain activation patterns cannot be resolved. It could be the case that the brains of initially high-and low performing individuals still function in the same manner as they did 15-20 years ago, i.e., that the brain processing differences observed in Study III are a stable trait. Alternatively, they could reflect differential trajectories of age-related brain changes. The “age is kinder to the initially more able”-hypothesis (Gow et al., 2012; Richards et al., 2004; Thompson, 1954), as well as the cognitive and brain reserve hypotheses (Satz, 1993; Y. Stern, 2009), would predict the latter, that is, differential impact of detrimental age-related processes.

Structural findings

With regard to HC volume, both Study I and Study II provided complementary evidence to the already extensive literature on structural brain changes in aging. First, in Study I, converging evidence was found for the notion that HC volume loss is associated with memory decline over time in healthy elderly (Kramer et al., 2007). Interestingly, however, the functional findings in Study I did not appear to be directly driven by HC volume reduction, indi-
cating that volumetric and functional loss might be at least partially independent contributors to memory decline in aging. Also, in Study II, the differences in HC activation between the successful and average agers were not driven by more atrophy in the average individuals, as demonstrated in a BPM analysis. Rather, it appeared as though successful agers had smaller proportions of gray matter within the functional ROIs, which was partially but not fully accounted for by the higher proportion of females in the successful group. This is in line with the notion that bigger is not always better when it comes to HC volume, which seems to be the case in younger adults (Foster et al., 1999; Van Petten, 2004). Thus, in the face of this evidence, the smaller gray matter volumes of successful agers are likely remnants from younger years, and it remains to be clarified with longitudinal imaging data whether successful agers experience HC volume loss or whether they are relatively spared of such losses. However, in the light of previous findings it could be the case that functional, rather than structural, brain imaging measures are more predictive of cognitive variability within the range of healthy aging (Walhovd et al., 2010).

Incidental findings

A few incidental findings relating to the MTL also deserve mentioning. One such is the observation of increased PHG activation over time in individuals with declining memory in Study I. Although this was not an expected finding, similar observations have been reported in cross-sectional aging studies (Cabeza et al., 2004; Daselaar et al., 2006), as well as in a longitudinal fMRI study from our own lab (Nyberg et al., 2010). Both Cabeza et al. (2004) and Daselaar et al. (2006) found older age to be related to decreased HC activation coupled with increased activation in the PHG during episodic retrieval, and interpreted this shift as an increased reliance of familiarity-based processing when recollective processing in the HC proper begins to fail. The findings in Study I were obtained during episodic encoding, and although I am not aware of any studies reporting age-related increases in encoding-related PHG activation, the distinction between familiarity and recollection in the MTL has been found during memory encoding previously. For instance, Ranganath et al., (2004) reported that BOLD-signal in the rhinal cortex during encoding predicted familiarity-based recognition, while BOLD-signal in the HC predicted recollection in young participants. In our study there is also a possibility that the study design, in which half of the items in the encoding condition were repeated, could have elicited recognition processes in the PHG. Also, although no direct evidence was reported to support it, the increased PHG activity could potentially have served a compensatory role in our study. This is suggested by the fact that episodic memory scores from the offline Betula test battery did not correlate with the change in recognition scores from the scanner task (p = 0.76). Nor did the stable and
declining subgroups differ significantly in recognition performance on the scanner task at follow-up \((t = 0.46, p = 0.63)\), although the difference was significant on the offline Betula composite score \((t = 6.76, p < 0.001)\) which mainly consisted of free recall measures. Thus, the declining individuals did not show deficits in recognition memory performance comparable to their impairment on the recall tasks that were used as outcome measures, much in line with notion that recognition processes are relatively spared in aging (Craik & McDowd, 1987). It is not impossible that the relative sparing of recognition memory performance was due to elevated PHG processing, although more systematic investigation is certainly needed before any firm conclusions can be drawn.

Another incidental finding in Study I was that HC activation at baseline was increased in individuals who subsequently experienced memory decline. These types of observations have been made previously, most commonly in individuals with MCI (Dickerson et al., 2005; Miller, Fenstermacher, et al., 2008; O’Brien et al., 2010), but also in low-performing healthy elderly (Miller, Celone, et al., 2008). On the basis of these observations, it has been suggested that HC hyperactivation is indicative of forthcoming dementia or Alzheimer’s disease (Dickerson & Sperling, 2008). According to this account the increased HC activation is some form of attempted compensatory response that is possible only as long as there is no severe structural pathology to the MTL structures. Once such pathology becomes manifest, HC hypoactivation is seen instead. This hypothesis has been qualified by a multimodal study that found increased HC activation to be associated with beta-amyloid burden (i.e., Alzheimer’s-related pathology) in healthy elderly (Mormino et al., 2012), but at the same time positively correlated with memory performance. Conflicting evidence was however provided by a study in which HC hyperactivation in MCI participants was reduced pharmacologically, resulting in better memory performance during scanning (Bakker et al., 2012).

While a clear consensus cannot currently be reached regarding the nature of HC hyperactivation preceding cognitive decline, in the light of the work presented in this thesis it seems paradoxical to find higher HC activation in both successfully aged individuals and individuals who will experience future cognitive decline. However, it needs to be considered that the mechanism behind higher BOLD-signal can be quite different in these two groups. While the successfully aged individuals in Study II likely had preserved HC activation levels since youth, the individuals who experienced decline in Study I might have increased their activation levels in response to accumulating pathology. Also, the increased activation in the decliners in Study I

---

3 These statistics are from post hoc analyses not reported in the published paper.
was observed at a younger age than in the successful individuals in Study II, i.e., the supposed hyperactivation preceded decline. It might therefore be the case that these individuals have had elevated HC-activation levels since youth, which could cause subsequent decline due to an increased metabolic burden (cf. Jagust & Mormino, 2011). This would be consistent with the fact that brain-behavior correlations are sometimes observed to be negative in younger individuals (less activation is better), while they are positive in older individuals (Eyler et al., 2011). These and other possible explanations will need further examination in larger scale longitudinal imaging studies, with more cognitively diverse samples.

In summary, a few important points pertaining to the hippocampal findings in this thesis should be highlighted. Firstly, the longitudinal assessments used here confirmed prior cross-sectional findings suggesting that HC function and structure underlies individual differences in cognitive aging. Secondly, functional reductions were found also in well-characterized healthy elderly samples, with little risk of inclusion of individuals in preclinical phases of dementia. This speaks strongly for HC impairment also in normal aging. However, successfully aged individuals were shown to be spared from such detrimental changes. Hence, a third take-home message is that HC impairment does not seem to be an inevitable consequence of aging, or at the very least that the course of HC change with aging can vary markedly between individuals. Another noteworthy observation in the current work was that the absolute level of HC activation at one point in time might not be a reliable indicator of age-related changes in cognitive function, partially since it might reflect individual differences unrelated to aging processes. In contrast, reduction in HC activation over time is thus far undisputed as a marker of age-related cognitive decline.

Frontal cortex contributions to memory in aging

Frontal effects were found both in Study II and Study III. In Study II, successful agers had higher frontal recruitment during encoding than average elderly, predominantly in the left hemisphere. The findings of Study III illustrated that encoding-related frontal activation is partially driven by pre-existing memory differences from midlife, but that longitudinal data on actual memory change can identify different frontal brain regions that are uniquely diagnostic of age-related decline in memory ability. Possible reasons for lack of lateral frontal findings in Study I will also be discussed further below.

In general, the findings from Study II and Study III converge on the notion that more frontal activation is beneficial for elderly individuals, much in line
with a recent review on cross-sectional imaging markers of successful cognitive aging (Eyler et al., 2011). The current studies found no evidence for higher brain activation in lower performing elderly, or in those displaying cognitive decline (de Chastelaine et al., 2011; Miller, Celone, et al., 2008; Persson, Nyberg, et al., 2006). Due to the lack of longitudinal data in these two studies, it is not possible to conclusively determine whether the observed higher frontal activation is a result of a functional reorganization, so that spared memory function goes together with increased frontal function over time; or whether individuals who have maintained high levels of frontal function have preserved memory function, while individuals with declining memory have decreased their frontal function over time. The first scenario would be predicted by the compensation hypothesis (Cabeza, Anderson, et al., 2002; Reuter-Lorenz, 2002), whereas the second is in line with the brain maintenance account of successful aging (Nyberg et al., 2012). In the following paragraphs I will discuss the possibility of these scenarios, and others, in relation to three prominent frontal regions in which findings from Study II and Study III converged: i) the left inferior frontal cortex (LIFC), ii) the right inferior frontal cortex, and iii) the left superior frontal cortex.

**Left inferior frontal cortex**

Largely overlapping clusters in the LIFC (around xyz = -42, 34, 4) were identified in both Study II and Study III. This area was more engaged by the successful than average older participants during encoding in Study II. But it was also significantly related to memory performance when only considering data for those with declining slopes in Study III (n = 106; r = 0.35, p < 0.001), indicating that it is also sensitive for memory performance differences in the lower ability range. Further, the results in both Study II and Study III indicated that activity in this region was predicted by both midlife memory scores, and slope of prior memory change. Thus, older individuals with low activation in this area tend to have lower memory, and a low activation/memory could be a static trait since youth, or a result of age-related decline.

The exact function performed by the LIFC during memory encoding is still not fully established (cf. section ‘Frontal cortex contributions to memory’), but it should be noted that it is the brain region that most strongly displays subsequent memory effects, i.e., stronger activation for later remembered compared to forgotten study items in neuroimaging studies (Kim, 2011). However, another study that investigated both encoding effort and encoding success, found that the LIFC activation was more predictive of effort than success (Reber et al., 2002). Nevertheless, the LIFC region is known to be one of the most consistently underrecruited regions in older individuals compared to young, during memory encoding (Dennis & Cabeza, 2008).
The compensation account

The LIFC cluster is interesting because it is the only cluster in which a sub-group of elderly, namely the successful agers in Study II, had significantly higher BOLD-signal than young individuals (cluster A in Figure 8). This could be interpreted as a compensatory response in the elderly group. However, a few facts speak against this interpretation. Firstly, activation in this cluster did not contribute directly to successful performance on the scanner task, although the same inferior left PFC region did correlate with memory performance on the offline Betula composite score in Study III. Secondly, the observed pattern of findings goes against a central premise of the compensation hypothesis, namely that compensation should be most prominent in those who need it the most (Cabeza & Dennis, 2012). Not only did the successful agers have spared memory function relative to the average elderly, they also had spared HC function. Given that additional frontal recruitment is often thought to compensate for failing MTL processing (Grady et al., 2005; Gutches et al., 2005), the obtained pattern of results seems to contradict the traditional view of compensation. There is of course a possibility that the activation in this cluster compensated for failing processing in some other brain region, such as the occipital cortex. Since we did not directly compare young and older participants on whole-brain activation it cannot be ruled out that even successful older had lower activity than young in some other brain region. Also, since no longitudinal data were available for HC activation there is no way of knowing whether the successful older had decreased their HC-activation relative their own levels in youth, and therefore were in need of compensatory processes.

Another fact could possibly speak for a compensation account, namely that the successful agers in Study II, like their average counterparts, did perform the scanner task more slowly and less accurately than young participants, indicating that some neural processes might be failing also in the successful group. This entails the possibility that the task was perceived as more difficult by the older groups, and that their brains might need to “work harder” to perform the task at an optimal level. So, could the increased activation of the successfully aged reflect increased effort, or decreased neural efficiency, relative to the young individuals? If this were the case, the most effortful processing, and highest frontal activation, would have been expected in the group of average older, with the lowest memory performance. But it could also be the case that the average individuals lacked the resources, or neural capacity (Y. Stern, 2009) to recruit additional neural populations in the frontal cortex in order to cope with the task demands. In other words, it

---

4 This behavioral decrement could also reflect that the elderly in general were more distracted or hindered by the scanner environment, the response mode, and/or the more speeded nature of the task compared to the Betula episodic memory tasks.
could be that aging had caused reduced neural efficiency in both older groups, but only the successful agers had the capacity to increase frontal activation in response to the challenging cognitive task. Such individual differences in capacity have been demonstrated for frontal cortex activation during working memory tasks, in both younger and older individuals (Nagel et al., 2011). This line of reasoning would also be consistent with a higher cognitive or brain reserve in the successful agers (Y. Stern, 2009), which has also been referred to as compensatory potential (Reuter-Lorenz & Cappell, 2008).

Are there any other grounds than lower scanner task performance for assuming reduced neural efficiency also in the successful elderly? Since we did not quantify structural integrity of the older groups relative to young individuals in Study II, we cannot determine whether this could be a cause for reduced efficiency. We only noted that the functional activation differences between successful and average older were not caused by differences in gray matter, and that the two older groups did not differ in white matter integrity. Thus, as far as can be discerned from these data, the successful and average older participants seemed equally spared from, or equally afflicted by, age-related structural degradation. This would entail an equal need for compensation, but possibly different capacities to do so. The need to consider differing efficiency, capacity, and reserve has previously been proposed when accounting for BOLD-signal patterns in elderly, and individuals with dementia (Prvulovic et al., 2005). This account, however, assumed capacity to be limited by age-related neurodegeneration. In the light of Study III, individual differences from youth are also an important determinant of brain activation patterns in elderly. Specifically, individual differences in innate intellectual ability, educational/occupational attainment, or other lifestyle factors could potentially contribute to higher baseline neural capacity in the successfully aged individuals (Y. Stern, 2009). So although the current findings on LIFC activation do not clearly fit with a traditional account of compensation, a compensatory explanation cannot be ruled out.

**The case for brain maintenance**

Perhaps the most parsimonious account of the higher left PFC activity of the successful agers in Study II would be to assume that their activation levels have not increased over time, but remained at a stable high level since youth. This would be in line with a brain maintenance account of successful aging (Nyberg et al., 2012). The reason that the successful agers had higher LIFC activation than the young individuals could be that they, the successfully aged, were such a highly select group. In fact, they performed on average one SD above their peers on the memory composite score when they were first recruited to the Betula study. The young individuals in the control group in Study II likely had memory abilities closer to the average (cf. Table 1 in
Study II). Until longitudinal data exists that can confirm this pattern, the plausibility of this account rests on whether it can be expected that individual differences in memory or general intellectual ability are reflected in a high LIFC BOLD-signal in youth. To date, this has not been well established. Subsequent memory studies do consistently show that more activation in the left inferior frontal region during encoding of later remembered than forgotten items (Kim, 2011), but is unclear how this relates to individual differences in ability. And since the successful older performed worse than young on the scanner task, the obtained pattern is not likely to be a subsequent memory effect. As well, the literature on individual differences in general intellectual ability (which is likely to also include memory) suggests that higher-ability young individuals often display less brain activation, particularly in the frontal cortex (Neubauer & Fink, 2009). This pattern has, however, been less consistently demonstrated for long-term memory tasks.

In summary, activation in the LIFC distinguished between high and low performing elderly. This was partially due to individual differences from midlife. Also, high-performing successfully aged individuals appeared to have higher LIFC BOLD-signal than young individuals, a pattern that could be consistent with both brain maintenance and compensatory accounts. However, the traditional compensatory account did not fit well with the data.

Right inferior frontal cortex

Both Study II and Study III observed effects in overlapping clusters in the right inferior frontal region (around xyz = 54, 36, 12). In Study II, the successful agers had higher activation than the average individuals in this region. The successful older also had slightly, but not significantly, higher activation than young in this right-sided frontal cluster. Further, in Study III this right-sided effect was shown to be driven only by differences in prior slope of memory change, as opposed to individual differences in midlife memory performance, a pattern that also differs from the left inferior cluster.

Although the right PFC is not thought to be as strongly engaged by episodic memory encoding as the left (Tulving et al., 1994), young individuals typically also engage this right frontal region when encoding face-name pairs (Persson et al., 2011). This indicates that this region likely is a part of the normal encoding-network, and one that begins to fail in elderly with memory decline, as indicated in Study III. Successful older adults, however, seemed to be spared from this decline, or at least significantly less affected by it, according to the results from Study II. Although this pattern does not provide strong evidence for the HAROLD model (Cabeza, Anderson, et al., 2002; Cabeza, 2002), it is at least not inconsistent with it, considering that those elderly with the most spared memory performance have the most involve-
ment of right PFC during encoding. But there is still no direct evidence for functional reorganization, that is, increased right frontal involvement over time, which is assumed in the HAROLD model.

On the other hand, the fact that lower performing individuals with a negative memory slope over time tended to have lower right frontal activation in Study III converges with the finding of decreased encoding-related right frontal activation across a 6-year interval by Nyberg et al., (2010). So although a decrease in right frontal function over time cannot be concluded based on the cross-sectional data in Study III, the findings from Nyberg et al. (2010) suggest that this is a likely scenario. Interestingly, left frontal activation decreases during encoding is most commonly observed in cross-sectional aging studies (Dennis & Cabeza, 2008), but as seen in Study III, activation in the left frontal cortex can also reflect individual differences from midlife. Thus, collectively, Study III and the findings in Nyberg et al. (2010) suggest that a decreased right frontal encoding-related activation in elderly is more diagnostic of actual memory decline.

The lack of lateral frontal findings in Study I seems to contradict this pattern, however. Why wasn’t memory decline associated with longitudinal change in right frontal activation, if cross-sectional imaging data (Study III) suggest that this should be the case, and a main effect of time was observed in this region in the full sample from which the individuals in Study I were drawn (Nyberg et al., 2010)? The discrepancy between Study I and Study III could be due to sample size. In Study I the sample comprised 26 participants, while the results in Study III were based on 203 participants. Considering that the PFC likely is a heterogeneous structure across participants, the relatively small sample size could have made it difficult to detect effects that were inconsistent across participants. Nyberg et al. (2010) found a frontal activation decrease in the full sample of participants (n = 38) that completed follow-up in the same longitudinal imaging study that Study I was based on. In other words, the 26 participants included in Study I were a subsample of these individuals (exclusions are listed in the Methods section, and mainly comprised individuals with missing behavioral data and those with substantial memory decline before the baseline scanning session). The fact that Study I failed to pick up the effect observed in Nyberg et al., (2010) could be due to lack of power, or that the effect was driven by the excluded participants. Alternatively, the frontal activation decrease could be a general phenomenon, not restricted to individuals with declining memory. In this case the contrast used in Study I might not have detected it due to the presence of individuals with zero or positive slopes. Thus, the phenomenon of decreased right frontal activation during encoding will need to be investigated further in larger-scale longitudinal data sets.
Left superior frontal cortex

An effect in the left superior frontal cortex (peak xyz = -22, 20, 64) was only observed in Study III, and this effect was driven selectively by differences in slope. Thus, like the right inferior frontal cluster it was independent of individual differences from midlife. In contrast to the right inferior cluster, however, the left superior cluster was not found in the contrast between successful and average elderly in Study II, which could suggest that it might be more sensitive to the more impaired end of the performance distribution, specifically those individuals who have experienced cognitive decline. This left-sided cluster was also the only one to show a trend (p = 0.056) towards an interaction effect between slope and initial memory level in Study III, so that a low initial level combined with a more negative slope tended to result in the lowest activation levels. Many previous studies have also shown reduced activation in elderly compared to young in this region during memory encoding, both according to a comprehensive literature review (Rajah & D’Esposito, 2005), and prior findings from our own lab (Salami, Eriksson, & Nyberg, 2012). In combination with the current findings, the left superior frontal region appears to be a specifically diagnostic region for memory decline over time.

Synthesis and summary of frontal cortex findings

To summarize the findings regarding frontal cortex function, it should first be noted that the studies in this thesis indicated that high frontal recruitment during memory encoding is beneficial for older individuals. This was true for all frontal regions that were identified. Another noteworthy observation is that although the left inferior frontal region differentiated between high and low performing elderly, activation differences in this region appeared to offer less diagnostic value than those in the right inferior and left superior regions. This was because midlife memory differences explained significant BOLD-variability in the left inferior region. Although this pattern of results needs to be replicated, this observation could be of potential value for imaging studies that lack longitudinal data. That is, knowing that low activation levels in the left superior or right inferior frontal cortex during memory encoding, coupled with low performance, are more reliably indicative of age-related decline than low activation in the left inferior frontal cortex.

Relatively higher frontal activation was found for higher performing and successfully aged individuals, but this does not necessarily need to be a reflection of compensatory processes. The findings could also be consistent with the notion of brain maintenance rather than age-related increases in activation over time (Nyberg et al., 2012). Only longitudinal imaging data can resolve this issue, and current longitudinal evidence points to both re-
ductions (Nyberg et al., 2010) and increases (Goh et al., 2013) in frontal activation over time. Of course, successful cognitive aging could also be a result of relative brain maintenance (compared to average elderly), in combination with some forms of compensatory neural processes. There are likely multiple routes to successful aging, and the relative amount of maintenance and/or compensation probably varies on the individual level. In line with this idea, results from a recent study showed that preserving a youth-like brain activation pattern during memory encoding was associated with successful cognitive aging, but a subgroup of elderly with a high degree of deviation from the youthful pattern were still high-performing, presumably thanks to their higher recruitment in, for instance, the left frontal cortex (Düzel et al., 2011).

Another factor that cannot be ignored in this context is pre-existing ability or capacity differences between individuals, especially in the light of the results from Study III. Individual differences in frontal cortex capacity, or responsiveness to cognitive demands, have been demonstrated in both young and elderly individuals, and are reflected in individual differences in performance levels (Nagel et al., 2011). To a large degree, variability in frontal cortex activation in aging is likely to reflect such stable individual capacity differences from younger age. But it is also likely that individual capacities are decreased by detrimental age-related changes (Prvulovic et al., 2005), of which an individual could be more or less afflicted. Further, situations when elderly, even high-performing ones, have higher frontal recruitment than young individuals, possibly reflect increased effort in performing the task, which is more or less equivalent to the concept of decreased neural efficiency (Y. Stern, 2009). However, elderly that for various reasons have lower frontal capacity may not be able to modulate frontal activation to meet task demands. Increased neural recruitment of this type could be considered compensatory, as long as task performance is maintained at a relatively high, or youthful, level. This type of compensation does not, however, need to be unique to elderly individuals, but is likely an expression of the same mechanism as when young individuals increase frontal recruitment in response to elevated task demands (Callicott et al., 1999).

In summary, it is tempting to conclude that both compensation and brain maintenance can explain frontal cortex function in aging, and future studies with longitudinal data will be able to better tease apart their relative influences. As the preceding discussion highlighted, the nature of frontal cortex involvement in age-related changes is complex, and many factors need to be considered in interpreting the results.
Contributions of longitudinal data

One methodological motivation behind the current thesis was to investigate what is gained from knowing a person’s cognitive history, that is, having access to longitudinal data. Firstly, as I have argued throughout this thesis, longitudinal behavioral data provide a better characterization of samples. The aging population is heterogeneous and as sampling rarely is random or population-based, the risk for skewed and non-representative samples is substantial. Longitudinal data eliminates the need for inferring age-related decline or maintenance from a low or high cognitive performance at one point in time. By extension, this allows for a better apprehension of the sample characteristics, that is, whether one is dealing with a successfully aged sample or individuals who have experienced cognitive decline. Given that such inter-individual differences are linked to specific brain characteristics, it is not surprising that the findings from neuroimaging studies of normal aging provide such divergent results. Better characterization of samples with longitudinal data, or through other means, will be essential to get to the bottom with what normal neurocognitive aging is, and what characterizes successfully and less successfully aged individuals.

Longitudinal assessments might be even more important for neuroimaging measures. Age-related change in brain function is likely a dynamic process, with a continuous interplay of structural, functional, neurochemical, and cognitive/strategic alterations causing increased and decreased BOLD-signal over time. A glimpse of this complexity can be gained from one of the only truly longitudinal functional imaging studies of aging, with multiple follow-ups across 9 years (Beason-Held et al., 2008). This study demonstrated linear increases and decreases in brain function across the whole measurement period, as well as step decreases and increases at various time-points in between. Further, the study demonstrated that increases and decreases over time can co-occur within a single brain region, as was found for the middle frontal gyrus. Considering that cross-sectional studies provide merely a snap-shot of such dynamic processes, it is easy to come to erroneous conclusions. This was elegantly demonstrated in the study by Nyberg et al. (2010), in which cross-sectional analyses alluded to age-related increases in frontal activation over time, but longitudinal analyses of the same data set showed a decrease in frontal activation. Another illuminating example is the longitudinal change in HC activation in Study I. Consider the left panel of Figure 6 (p. 63), which shows that the subgroups of declining and stable individuals have equivalent HC activation at the follow-up scan. If the baseline measurement was lacking, it would have been easy to conclude that prior memory change had no relation to HC activation.
Limitations and future directions

Two limitations of the work presented in this thesis were the small sample size in Study I, as well as the lack of longitudinal imaging data in Study II and Study III. Both of these limitations will be addressed with the upcoming follow-up of the ImAGen sample. The resulting data set can be used to better address remaining questions about, for instance, the nature of frontal activation change or stability over time, which has relevance for distinguishing between compensation and maintenance accounts of frontal brain function in aging. Another question that can be addressed is the paradox that higher HC activation is both associated with successful aging, and predictive of subsequent cognitive decline. The current work is also limited in that there is, as of yet, no follow-up data on the cognitive status of the participants. Such data would be valuable since it would make it possible to, in retrospect, exclude participants who later go on to develop dementia or other pathological conditions. Although all participants were thoroughly assessed with a comprehensive cognitive test battery in connection with the fifth measurement point in Betula, there is always a risk that such individuals could have gone undetected. Since brain pathology can be manifest before the onset of cognitive symptoms of dementia, the inclusion of individuals in preclinical stages could influence the imaging results. However, as will be discussed below, the samples used in this thesis are more likely to be healthier and more high-functioning than average.

The studies in this thesis were also relatively modest in the use of structural indices of brain aging, which are known to influence the BOLD-signal (Kalpouzos et al., 2012). One major avenue for future research on neurocognitive aging will certainly be multi-modal imaging, not only combining structural and functional MRI, but also considering PET-markers of, for instance, dopaminergic function and amyloid burden. Such methods can provide both converging and complementary information on the aging processes in the brain. This is also important because the BOLD-signal in itself has some limitations that need to be considered, for instance that it only provides a correlative measure of neural activity. Converging evidence from alternative imaging modalities and experimental procedures, such as transcranial magnetic stimulation and pharmacological studies, would therefore be reassuring. There are also many known complications when attempting to probe the aging brain using fMRI. These include age-related alterations in the vascular response of the brain, differences in resting cerebral blood flow, and a decreased signal-to-noise ratio (D’Esposito, Deouell, & Gazzaley, 2003; Kannurpatti, Motes, Rypma, & Biswal, 2010). Such confounds are likely to have the largest influence when directly contrasting young and elderly individuals. For that reason, the main analyses throughout all three studies of this thesis were comparisons within the elderly age-span (with the
exception of the comparisons with the young control group in Study II). This should have served to lessen the impact of such concerns, although there are likely individual differences in vascular factors within the older population as well, which might influence the results.

While the merits of longitudinal data have been stressed throughout this thesis, they are also associated with their own sets of challenges. One such is that sample representativeness can be compromised by higher attrition of lower-performing individuals, and those who experience accelerated decline (Josefsson et al., 2012; Rönnlund et al., 2005). Although such effects are hard to avoid altogether, measures were taken to correct for attrition in Study II (cf. section ‘Statistical classification for Study II’), which helped to improve the representativeness of the control group of average elderly. In general, for Study II as well as Study I, an attrition effect would not compromise the validity of the obtained results, but rather make it harder to detect effects in the first place, i.e., increase the risk for type II errors (false negatives). Possible attrition effects are, however, more troublesome for Study III since having a more healthy and cognitively stable sample might overestimate influences of midlife memory ability on brain activation patterns 15-20 years later. This was acknowledged in the discussion of the paper, and I argue that the findings of the study still are of relevance for the field, since our sample likely is at least as representative as those used in the majority of cross-sectional neuroimaging studies with convenience sampling. Also, I have tried to be very thorough in describing the characteristics of the samples used in this thesis, as well as the selection procedures applied to them. By doing this, I hope that the possible impact of attrition on the presented results can be better appraised.

Another issue in longitudinal research is the existence of practice effects on cognitive scores over time, which results in positive slopes of memory change over time. Positive slopes can also result from regression to the mean effects, or rebound effects from temporary cognitive declines caused by factors such as depression or stress. Finding positive slopes in elderly samples does not need to be undesirable in itself, since a practice effect can signal the presence of an intact memory system. In Study II, for instance, finding improved memory scores over time further supports that a truly successfully aged group of individuals has been identified. However, to the extent that positive slopes result from rebound effects, they may interfere with detecting effects in correlative approaches such as the ones in Study I and Study III.

Finally, I will briefly touch upon two future directions related to the findings in this thesis, that I would find particularly interesting to pursue. Firstly, the finding that midlife memory predicted brain activity 15-20 years later (Study III), is worth investigating with longitudinal imaging data. Only by doing
this, one can uncover in what way midlife memory ability is related to brain activation in older years. Is it because higher-ability individuals have high activation levels and maintain them over time, while lower-ability individuals maintain low activation levels from youth? Or do high- and low-ability individuals show different rates of neural changes, so that age is kinder to the initially more able? Or is it possible that high-ability individuals in fact increase their activation over time in a compensatory manner? Another interesting path to pursue would be individual-level characterization of hippocampal function, especially with longitudinal imaging data. The major advantage of doing this characterization on the individual level is to avoid loss of sensitivity when averaging data across participants, as is done in standard imaging analyses (Vandenbroucke et al., 2004). Also, by only considering group analyses there is a loss of some information, such as the opportunity to assess the proportion of individuals who have spared HC function. For instance, by using individual characterization of hippocampal function at rest it was found that 13 out of 30 healthy elderly from a longitudinal study had a HC signal that was comparable to that of young individuals (Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002). Such a characterization would be interesting to implement in a larger sample, such as the ImAGen cohort, although it would likely present some methodological challenges.

Concluding remarks

This thesis investigated how longitudinal observations of cognitive change and neuroimaging measures can advance our knowledge of neurocognitive aging. Based on the work presented in the preceding sections, I would like to highlight the following points:

i) Higher frontal cortex activation was found to be beneficial in aging, but the pattern of frontal findings could not conclusively distinguish between prevailing theories of frontal function in aging. Studies with longitudinal imaging data will be needed to elucidate the dynamics behind frontal cortex contributions to memory in aging.

ii) Tentatively, the results indicated that frontal cortex regions might be differentially indicative of age-related cognitive decline. Activation levels in the left superior and right inferior frontal cortices during memory encoding were exclusively related to memory change over time, while activation levels in other regions could reflect individual differences unrelated to aging.
iii) Functional decline in the hippocampus was found to be present in healthy elderly with memory decline in the normal range, but it is not a necessary consequence of aging since successfully aged individuals were found to be spared from, or at least substantially less afflicted by, such changes.

iv) Hippocampal activation levels at a given point in time might be unreliable indictors of age-related cognitive decline, but reduction in hippocampal activation over time has consistently been associated with declining cognitive functions.

v) Finally, longitudinal data is imperative in the study of neurocognitive aging since it makes it possible to better characterize elderly samples, and eliminates the need to infer decline from low performance or brain activity at one point in time.
Acknowledgements

Firstly, I would like to thank my supervisors, Jonas Persson and Lars Nyberg, for their excellent scientific guidance and all their patience and support during the past few years. I am also deeply grateful to Lars-Göran Nilsson for welcoming me to the Betula project, and for giving me access to such an exceptional and high-quality data set. I have been truly privileged to be working with such data.

Many people have made substantial contributions to the work presented in this thesis. Maria Josefsson and Xavier de Luna at the statistics department at Umeå University provided the statistical classification model for Study II, and Maria has patiently helped me many times since. Micael Andersson taught me all I know about fMRI data analyses, and has been immensely helpful with all technical issues and questions I’ve had. Alireza Salami provided great assistance with methodological aspects of MRI analyses, and Anders Lundquist was very helpful in answering all my statistical questions. I sincerely thank all of you.

Thanks also to the lab group at UFBI for providing such an educational and stimulating work environment, and particularly to my former roommates Karolina, Urban, and Fredrik for all the discussions about work-related (and not so work-related) matters. Special thanks to Karolina, my closest collaborator during these years, for all the thoughtful feedback, rewarding discussions, and for your ceaseless positivity.

Many thanks to my co-workers in the Betula project, especially to Mikael Stiernstedt, for all the assistance during (and after) the data collection. Thanks also to the nurses at MR for all their help during that time, and, of course, to all the research participants!

I am also very grateful to my family for all the support you have given me throughout the years.

Last but not least, my deepest gratitude to my grandmother, Viola, to whom I have dedicated this thesis. Thank you for all your concern, encouragement, and support throughout my life. And for being such a prime example of a successful ager! Tack fammo!
References


reduction in older adults a special case of compensatory-related utilisation of neural circuits? Experimental Brain Research, 224(3), 393–410. doi:10.1007/s00221-012-3319-x


temporal activity. *Journal of Cognitive Neuroscience, 17*(1), 84–96. doi:10.1162/0898929052880048


Rönnlund, M., & Nilsson, L.-G. (2008). The magnitude, generality, and determinants of Flynn effects on forms of declarative memory and


