STRUCTURAL AND FUNCTIONAL CHANGES UNDERLYING COGNITIVE AGING

EVIDENCE FROM NEUROIMAGING STUDIES

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Le bonheur de l'homme n'est pas dans la liberté, mais dans l'acceptation d'un devoir.

André Gide

CONTENTS

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INTRODUCTION: AGING AND THE BRAIN

Advancing age is associated with impaired cognitive functioning, such as slower mental processing and a decrease in the capacity to learn and remember new information. Although many factors may have an impact on cognitive abilities, the most direct cause of age-related cognitive impairments comes down to a change in brain structure and/or function. Due to the neuronal activity in the brain, events in the world outside the organism can be perceived, and behavior in response to these events can be initiated and executed. From this perspective, the brain can be considered as the substrate of all cognitive processes.

Aging is accompanied by a large number of changes in the brain, such as cerebral atrophy (Raz, 2000), reductions in blood flow and metabolism (Newberg and Alavi, 1997), and neurochemical changes (Strong, 1998). Nevertheless, it is still not known exactly how brain changes and cognitive deficits in aging are related. In this thesis, age-related changes in the structure and function of the brain were investigated in an attempt to explain cognitive impairments in aging. Neuroimaging techniques, in particular magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), were used to study these cerebral changes.

This introductory chapter will start with a brief description of cognitive processes that are affected by normal, non-pathological aging. Subsequently, it will be argued that these cognitive impairments are particularly associated with age-related changes within the prefrontal cortex (PFC). Whereas the evidence for this theory was originally derived from patient studies, the development of neuroimaging methods has led to a large increase in research focusing on the neurobiological basis of cognitive aging, including the pivotal role of the PFC. Next, some methodological considerations in neuroimaging

research will be discussed. This chapter will end with a summary of the rationale behind the studies described in this thesis.

AGING AND COGNITION

There is ample evidence that advancing age is associated with decrements in a wide range of cognitive functions, such as difficulties to recall information, to keep attention focused, or to plan and execute complex behavioral sequences (e.g., Jolles, 1986; Moscovitch and Winocur, 1992; Verhaeghen et al., 1993; Prull et al., 2000; Zacks et al., 2000). An important question that has been the focus of much research is whether age-related changes are general across all cognitive domains, or whether they are restricted to particular types of function. For instance, it has been suggested that the cognitive deterioration as observed in aging can mainly be attributed to a single factor, such as a decrease in the speed of mental processing (e.g., Salthouse, 1994, 1996; Earles et al., 1997) or a reduction in attentional resources (Craik and Byrd, 1982; Stankov, 1988; Kirasic et al., 1996). Indeed, such general factors have been found to explain a substantial part of age-related variance in cognitive performance (Kirasic et al., 1996; Park et al., 1996; Salthouse, 1996). Hence, older individuals are generally slower at information processing and particularly compromised on attention-demanding tasks, which consequently leads to performance deficits in other cognitive domains.

The prevailing view, however, is that in addition to global factors, there are specific mechanisms that underlie the pattern of cognitive impairments in aging. One such mechanism is an executive control system that coordinates the distribution of the available resources, for instance in sustaining and dividing attention and in task switching (West, 1996; McDowd and Shaw, 2000). Higher age is generally associated with a strong reduction in the capacity to perform such executive control processes (Craik, 1986; Jennings and Jacoby, 1993; Moscovitch and Winocur, 1995). Another specific mechanism that has been put forward to explain age-related variance in cognitive performance is a reduction in inhibitory functioning (Hasher and Zacks, 1988; Burke, 1997). It implies that cognitive impairments in aging are considered to be the consequence of a failure to keep attention focused by inhibiting irrelevant information (Hasher and Zacks, 1988; McDowd, 1997; Zacks et al., 2000).

To conclude, it seems that age-related differences in performance can be attributed both to global (e.g., speed) and specific (e.g., executive control) cognitive mechanisms. Because, as argued, these cognitive deficits in elderly individuals are likely to reflect structural and/or functional changes in the brain, various theories have been proposed in an attempt to link these deficits to neurobiological factors. In the next

section, the most influential of these views, i.e., the frontal lobe theory of cognitive aging, will be discussed in more detail.

THE PREFRONTAL CORTEX IN AGING AND COGNITION

The frontal theory of cognitive aging suggests that age-related cognitive decline is the result of changes in the frontal lobes and, more specifically, the PFC (Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001). This theory was originally formulated on the basis of neuropsychological research and has been extended by neuroimaging studies in recent years. In neuropsychological literature, deficits in attention, memory and executive control functions have been reported since long to characterize individuals with prefrontal damage (Luria, 1973; Fuster, 1980; Cummings, 1993; Knight et al., 1999). Based upon this, it has been suggested that the PFC supports the formation, monitoring and execution of complex behavior, while keeping attention focused and inhibiting irrelevant information (Fuster, 1980; Cummings, 1995; Knight et al., 1999). In other words, the PFC operates at the highest level of cognitive organization, serving as the 'central executive' (Fuster, 1980; Baddeley, 1986; Miller, 2000) or the 'supervisory attentional system' of the brain (Norman and Shallice, 1986; Stuss et al., 1995). As pointed out in the previous section, it is especially with these prefrontal functions that older individuals have difficulties.

The neuropsychological evidence for frontal lobe involvement in these higher cognitive control processes is substantial and irrefutable. Also, there are remarkable similarities between cognitive deficits resulting from frontal lobe injury and those associated with aging. Nonetheless, these observations alone are insufficient to appoint the PFC a central role in age-related cognitive changes. A possibility to evaluate the importance of brain regions in normal cognitive functioning more directly is offered by neuroimaging techniques, such as computerized tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). Since these techniques started to be applied for scientific purposes around the 1980s, research on the neurobiological basis of cognitive processes has expanded enormously. However, despite the fact that neuroimaging facilities have become widely available in recent years, studies devoted to explore associations between cognitive performance and age-related changes in the structure and function of the brain are still rather scarce, and their results are often conflicting.

METHODOLOGICAL CONSIDERATIONS IN NEUROIMAGING STUDIES

Which factors can explain these inconsistencies in neuroimaging studies in aging? Besides the more obvious differences between experiments (such as sample size, and health criteria for inclusion), also the choice of a certain methodology for image acquisition and analysis may influence the findings of a study. For instance, the accuracy of measurements depends on the choice of imaging device (e.g., CT versus MRI), on the resolution of the images, as well as on the approach used to process and analyze the data. With respect to the latter issue, pertinent to both structural and functional neuroimaging, various methods can be applied to reduce the vast amount of data and to obtain objective measurements. A widely-used approach in MRI studies is to define a region of interest (e.g., hippocampus, regions of atypical white matter) and to determine its volume. This can be done by means of rating scales, or by manually tracing the region. Until recently, these measurements were generally carried out in only two dimensions (slice by slice), whereas today it is becoming more common to determine brain volumes in three dimensions (by simultaneously viewing each image orientation). Three-dimensional visualization may improve the accuracy of measurements, especially in the case of irregularly shaped brain structures (e.g., prefrontal regions). In the past few years, whole-brain analysis methods (such as voxel-based morphometry, VBM) have been developed, which allow the localization of anatomical differences between individuals or groups of individuals, irrespective of any predefined regions of interest (Ashburner and Friston, 2000).

With respect to functional neuroimaging experiments, a similar distinction can be made between region-based and whole-brain approaches. For instance, age-related differences in neural activity have been examined in specific PFC regions (e.g., Rypma and D'Esposito, 2000; Logan et al., 2002). Most PET and fMRI studies, however, have considered neural activity in regions across the entire brain. These whole-brain approaches either consider the signal in each individual voxel (image element) across task conditions or between groups of individuals, or identify clusters of brain regions that together covary with a task condition or between groups of individuals. The advantage of region-based approaches is that they allow testing of specific hypotheses. However, because much is still unknown about age-related changes in brain functioning (e.g., recruitment of additional regions by older individuals, Cabeza et al., 1997; Anderson et al., 2000) exploratory whole-brain analyses make up an important supplement.

Both structural and functional neuroimaging experiments provide a powerful means to investigate brain-behavior associations in humans. In this thesis, these two methodologies are used to study the brain as the mediating substrate in the relation between aging and cognition.

THESIS OUTLINE

The central question addressed in this thesis is: what brain mechanisms underlie cognitive impairments in normal, non-pathological aging? The focus of the research is on age-related changes in the morphology and function of brain regions involved in higher cognitive operations. To investigate this, neuroimaging techniques (MRI and fMRI) are used.

Chapter 2 provides an overview of the current knowledge of structural and functional changes in the aging brain. It is argued that the integrity of the frontal lobes as well as their cortical and subcortical connections is of particular importance for normal cognitive aging.

Chapters 3 to 6 examine whether differences in specific brain structures can be related to cognitive functioning. The central assumption in these chapters is that smaller brain volumes can be considered to reflect lower neural efficiency. The study described in *Chapter 3* starts off with a rather broad approach by taking head size (used as an estimate of brain size) as a potential predictor of cognitive performance in a population-based study of elderly individuals. In the two following chapters, experiments are described in which MRI scans were acquired in a group of healthy individuals across the adult age range (20-80 years).

Chapter 4 discusses age-related volumetric changes in limbic brain structures: hippocampus, parahippocampal gyrus, mamillary bodies, and the third ventricle as an estimate for the medial thalamus. Furthermore, since these structures are all involved in memory functioning, the relation between their volume and cognitive performance is investigated.

In *Chapter 5*, an experiment using VBM in healthy, non-demented elderly individuals is described. Two groups of older individuals participated in this study: a group that showed a decline in cognitive test performance after three years, and a group of control subjects whose performance remained stable over time. The relation between age and gray matter density across the brain is examined cross-sectionally in the control group. In addition, the association between gray matter density and longitudinal decline in performance on cognitive tests is studied by comparing the 'decliners' and the control subjects.

Chapter 6 focuses on the importance of the choice of measurement approach. Three different methods are applied to examine the effect of age on regional brain volumes: a manual tracing approach, a semi-automatic volumetric method, and VBM. The brain region of interest is the PFC, which (as already pointed out) plays a major role in cognitive functioning.

Chapter 7 describes an experiment in which functional MRI was used to compare the brain activity of young and old individuals during word processing. Brain activity associated both with the task conditions and with performance (i.e., reaction times) is evaluated.

Finally, *Chapter 8* provides a summary of the findings and suggestions for future research. In addition, possible extensions to the frontal lobe theory are presented.

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STRUCTURAL AND FUNCTIONAL BRAIN CHANGES IN AGING: AN OVERVIEW

This chapter is based upon
TISSERAND DJ and JOLLES J. On the involvement of prefrontal networks in cognitive ageing. *Cortex*, in press.

INTRODUCTION

It has been known for long from postmortem research that human aging is accompanied by a reduction in brain volume (e.g., Haug, 1985; Kemper, 1994; Morrison and Hof, 1997; Uylings et al., 2000). Until recently, this atrophy was thought to be the consequence of neuronal loss (Kemper, 1994). However, with the aid of more modern tools it has been shown that the reduction in total neuronal number is only slight, and atrophy may be rather the result of cell shrinkage, dendritic regression, and a reduction in synaptic density (Haug, 1985; Uylings et al., 2000). The functional significance of these neuronal changes is unclear. At present, there is no direct evidence for a relationship between regional neuronal number and cognitive performance in non-pathological aging (e.g., Uylings et al., 2000).

Nevertheless, because cognitive processes are dependent upon the integrity of the brain, it does seem likely that changes in brain morphology and/or brain functioning can (partly) account for age-related decreases in cognitive functioning. The neural basis of human cognitive aging has gained increasing interest since it became possible to study the structure and function of the brain in vivo, using techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

In this chapter we will provide an update of the most recent neuroimaging literature on structural and functional changes in normal, non-pathological brain aging, while specifically focusing on those regions involved in higher cognitive functioning. We will put forward the view that cognitive changes in normal, non-pathological aging are particularly associated with alterations within the prefrontal cortex (PFC). This hypothesis has been proposed since the eighties (e.g., Jolles, 1986; Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001). However, recent findings suggest that the 'frontal aging hypothesis' needs to be refined. We will elaborate on this notion by hypothesizing that: (1) age-related brain changes are greatest in specific subregions within the PFC and the neural circuits they are part of, (2) not only gray but also white matter integrity is of major importance for adequate cognitive functioning, and (3) neural networks and larger systems of interconnected brain regions may be more important than local gray or white matter condition as such to explain age effects on cognitive functioning.

BRAIN AGING: STRUCTURAL NEUROIMAGING

The limbic-diencephalic system

Both postmortem and in vivo neuroimaging studies have consistently shown that the total brain volume decreases as a function of age (e.g., Jernigan et al., 1991, 2001; Coffey et al., 1992, 1998; Pfefferbaum et al., 1994; Blatter et al., 1995; Raz et al., 1997; Courchesne et al., 2000; Resnick et al., 2000; Tisserand et al., 2000b). Just as age effects are not uniform across cognitive functions, regional differences in structural decline of the aging brain have been found. Because numerous neuropsychological studies have emphasized age-related deterioration of memory processes (e.g., Jolles, 1986; Craik and Jennings, 1992; Verhaeghen et al., 1993; Moscovitch and Winocur, 1995; Prull et al., 2000), the majority of neuroimaging research has focused on the neural substrate of memory. A number of brain regions, together making up the limbic-diencephalic network, play a key role in learning and memory. These include the hippocampal system, parahippocampal gyrus, anterior cingulate, medial thalamus, and mamillary bodies (Zola-Morgan and Squire, 1993; Petri and Mishkin, 1994). Atrophy of the hippocampus and related structures is consistently found in pathological aging (e.g., De Leon et al., 1989; Fox et al., 1996; Kaye et al., 1997; Jack et al., 1992, 1998, 1999; Visser et al., 1999; Laakso et al., 2000). Also in many studies on normal aging, a reduction in hippocampal and parahippocampal volume has been found (Murphy et al., 1996; De Leon et al., 1997; Raz et al., 1997; Jack et al., 1992, 1998; Mueller et al., 1998; Tisserand et al., 2000b; Ylikoski et al., 2000; Pruessner et al., 2001). However, several studies did not find evidence for age-related volume losses in the hippocampus (Lim et al., 1990; Sullivan et al., 1995; Bigler et al., 1997), or reported that the decrease was not disproportional when compared to tissue loss in other brain regions (Raz et al., 1997; Tisserand et al., 2000b). Most of these studies have been cross-sectional and therefore provide only indirect evidence for age-related atrophy. Several studies found a significant longitudinal decrease in medial temporal lobe (MTL) volume in individuals over 65 years of age (Kaye et al., 1997; Jack et al., 1998; Mueller et al., 1998), whereas in two studies in adult subjects across the age range, no evidence was found for longitudinal changes in the volume of the temporal lobes as a whole (Pfefferbaum et al., 1998; Resnick et al., 2000).

Whereas age effects on MTL regions have been fairly well documented, only a small number of studies have focused on other limbic-diencephalic structures, with conflicting results. A significant reduction in the volume of the thalamus has been reported by some (Murphy et al., 1996; Van der Werf et al., 2001), but not by others (Jernigan et al., 1991, 2001). Likewise, while we found an age-related decrease in anterior cingulate volume (Tisserand et al., 2001, 2002), others did not (Jernigan et al., 1991; Raz et al., 1997). Finally, with respect to the volume of the mamillary bodies, age-related

losses have been found in some studies (Raz et al., 1992; Sullivan et al., 1999), but not in other (Charness and DeLaPaz, 1987; Tisserand et al., 2000a).

Several studies with healthy elderly subjects have tried to relate these reductions in limbic-diencephalic volumes to cognitive performance, with mixed results. For instance, one research group reported that hippocampal volume predicted performance on word list recall (Golomb et al., 1994) and subsequent decline on memory tests after a period of four years (Golomb et al., 1996), while others failed to find a relationship with test performance after adjusting for age effects (Raz et al., 1998; Petersen et al., 2000; Tisserand et al., 2000b; Ylikoski et al., 2000) or even found an inverse relationship (Köhler et al., 1998; Foster et al., 1999). Interestingly, one study found an age-independent correlation between thalamic volume and speed of information processing (but not memory functioning) in young but not in older subjects (Van der Werf et al., 2001). This suggests that in healthy young adults, larger thalamic volume may be favourable for fast processing of information, while variance in volume associated with increasing age is not predictive for task performance. Perhaps in elderly subjects, volume decreases are linked to cognitive deterioration only when pathological mechanisms are involved, such as cardiovascular disease (DeCarli et al., 1994; Köhler et al., 1998; Foster et al., 1999; Kabani et al., 2002). Alternatively, a lack of associations between brain volume and performance in older subjects may be due to an increase in the variance of these measures with age (e.g., Blatter et al., 1995; Jernigan et al., 2001). This differential influence of age on the direction of brain-behavior associations may explain why most studies with subjects across the adult age range have not found a relation between brain volume and cognitive performance.

The frontal-striatal-thalamic system

Studies involving patients with focal brain damage (e.g., Janowsky et al., 1989; Stuss et al., 1994; Shimamura et al., 1995) and functional neuroimaging experiments with healthy individuals (e.g., Tulving et al., 1994; Kapur et al., 1996; Smith et al., 1996; reviewed by Fletcher and Henson, 2001) suggest that frontal regions may play an equally important role as the limbic system in certain memory domains, especially those involving active organization of the memory contents. The frontal cortex plays a crucial role in a second cognitive brain circuit, which is designated the frontal-striatal-thalamic network (Alexander et al., 1990; Cummings, 1993, 1995; Rubin, 1999). This network actually consists of five parallel circuits, three of which are involved in complex behavior and cognition, such as working memory and executive control. These circuits typically include a region within the frontal lobes, projecting to striatal structures, which are connected through the globus pallidus and substantia nigra to the thalamus. This structure in turn projects back to the frontal regions (Alexander et al., 1990; Cummings,

1993, 1995). In comparison to the literature on limbic-diencephalic structures, reports on age-related changes within the frontal-striatal circuit are still relatively limited in number. Nonetheless, there is evidence for disproportionate volume losses within the frontal lobes (Coffey, 1993; Cowell et al., 1994; Raz et al., 1997; Salat et al., 1999, 2001; Tisserand et al., 2001, 2002), the thalamus (Van der Werf et al., 2001) and the striatum (Gunning-Dixon et al., 1998; Rubin, 1999). In an extensive review of the literature on correlations between regional cerebral volume and age, Raz (2000) found that the brain regions most affected are the PFC and the striatum (caudate and putamen). Longitudinally, the cortical region with the greatest volume reduction over a 5-year period was found to be the PFC (Pfefferbaum et al., 1998). Unfortunately, no subcortical gray matter structures (such as the striatum or thalamus) were measured in this study.

Only few studies examined the association between atrophy in this circuit and cognitive decline. A weak relation was found between prefrontal volume and working memory performance (Raz et al., 1998) as well as cognitive flexibility (Hänninen et al., 1997), but this association was no longer significant when age effects were adjusted for (Raz et al., 1998). As mentioned earlier, in young individuals, the volume of the thalamus was found to be predictive for processing speed (Van der Werf et al., 2001).

White matter changes

Whereas an age-related decline in regional gray matter volume has been observed in most imaging studies (e.g., Jernigan et al., 1991, 2001; Pfefferbaum et al., 1994; Blatter et al., 1995; Raz et al., 1997; Courchesne et al., 2000; Resnick et al., 2000), starting already in young adults (Blatter et al., 1995; Gur et al., 1999; Courchesne et al., 2000), there is still debate as to the relative contribution of white matter to volume decreases in aging. Postmortem findings have suggested that white matter atrophy is even more extensive than gray matter loss (e.g., Kemper, 1994). Likewise, several MRI studies have reported age-related loss of white matter (Guttmann et al., 1998; Resnick et al., 2000; Jernigan et al., 2001), especially in the frontal lobes (Raz et al., 1997; Salat et al., 1999; Jernigan et al., 2001). However, other imaging studies have not found evidence for global white matter volume decreases (Jernigan et al., 1991; Pfefferbaum et al., 1994; Blatter et al., 1995; Raz et al., 1997). It has been suggested that white matter volume remains relatively stable until high age, after which a rapid decline occurs (Salat et al., 1999; Tisserand et al., 2002).

Regardless of the fact whether or not the overall white matter volume decreases, it is not to say that no structural changes take place within the white matter with advancing age. In fact, a very prominent feature noted in brain imaging is an age-related increase in white matter lesions: small damaged foci, which nevertheless can be quite readily observed on CT and MRI (e.g., Jernigan et al., 1991, 2001; Boone et al., 1992; Ylikoski et al., 1993; Breteler et al., 1994; DeCarli et al., 1995; Longstreth et al., 1996).

White matter lesions have been found to co-occur with, and to be even more common than, gray matter atrophy (Ylikoski et al., 2000; Jernigan et al., 2001). These lesions have been associated with cognitive deficits and may be implicated in the age-related decline in cognitive performance (Longstreth et al., 1996; Gunning-Dixon and Raz, 2000). The associations between severity of the lesions and cognitive decline are particularly evident on tests measuring attention and processing speed (e.g., Boone et al., 1992; Ylikoski et al., 1993; DeCarli et al., 1995; De Groot et al., 2000). Little is known about regional specificity, although there is some evidence that white matter lesions in older individuals are most frequent in the frontal lobes (De Leeuw et al., 2001; Jernigan et al., 2001).

Conclusion

To summarize, aging is associated with decreased gray matter volume, and the volume reductions are greatest for the frontal lobes and striatum. Changes within the limbic-diencephalic memory system appear to be relatively mild. Age-related changes within the white matter have also been observed, particularly as an increase of white matter lesions, with the highest frequency in the frontal lobes. It is plausible that volume losses within the frontal-striatal-thalamic circuit may contribute to age-related cognitive decline. Generally, however, volume decreases within gray matter structures have not been found to be predictive for deterioration in specific cognitive functions. On the other hand, lesions within the white matter have been associated with aspecific dysfunctions such as reduced information processing speed and attention. As the white matter contains the fibers which connect the various cortical and subcortical gray matter structures, these white matter lesions may disrupt the neural transmission in functional networks, resulting in performance decreases.

BRAIN AGING: FUNCTIONAL NEUROIMAGING

General findings in neuroimaging studies

The fact that only few associations have been found between structural brain changes and cognitive performance in normal aging, may be due to the fact that changes in brain structure as such do not have a straightforward relation with brain function. A more direct way to link brain and behavior is by using functional imaging methods. In contrast with the large number of studies of age-related structural brain changes, the field of research which investigates functional changes is still relatively young, although the number of publications is increasing rapidly (see for some recent reviews on functional imaging studies and aging: Cabeza, 2000, 2002; Grady and Craik, 2000; Raz, 2000). In this chapter we will mainly focus on changes within the PFC and the MTL.

Functional neuroimaging studies have examined the effect of age both at rest and during cognitive test performance. At rest, a moderate decrease in both regional cerebral blood flow and metabolic rate has consistently been found, with differential sensitivity of the frontal lobes (Kuhl et al., 1982; De Leon et al., 1987; Leenders et al., 1990; Martin et al., 1991; Loessner et al., 1995; Moeller et al., 1996; Petit-Taboué et al., 1998; Garraux et al., 1999), a pattern which is already evident in middle-aged adults (Schultz et al., 1999). Findings with respect to the MTL are inconsistent, but in general, no disproportionate change in activity has been reported (save by Martin et al., 1991).

The majority of activation studies on aging have focused on explicit memory and working memory. This is not surprising, given the evidence that age-related cognitive deficits are particularly evident in these domains (Jolles, 1986; Craik and Jennings, 1992; Moscovitch and Winocur, 1992; Verhaeghen et al., 1993; Salthouse, 1996; Parkin and Java, 2000; Prull et al., 2000). Experiments that have examined age-related differences in brain activation patterns during more basic cognitive functions such as visual perception (Grady et al., 1994; Horwitz et al., 1995; Ross et al., 1997), motor function (Calautti et al., 2001), and attention (Johannsen et al., 1997; Madden et al., 1997) are still relatively limited in number. Although in this chapter we will concentrate on higher cognitive functions, it is important to bear in mind that already at the lowest level of information processing age-related changes occur (due to real functional differences or a lower signal-to-noise ratio in older subjects, e.g., D'Esposito et al., 1999). Because in most functional imaging studies a certain experimental condition is compared to a baseline condition, baseline differences in activation can substantially influence the results of group comparisons.

Brain activity and memory tasks

Neuropsychological research has consistently found that working memory capacity, which involves the temporal storage and processing of information, is strongly reduced by increasing age (e.g., Kirasic et al., 1996; Park et al., 1996; Parkin and Java, 2000). During working memory tasks, young individuals tend to activate regions within the lateral and medial prefrontal and posterior parietal cortex, and this activity is asymmetrical depending on the stimulus material. Verbal tasks have been associated with predominantly left-hemisphere activity, whereas spatial tasks elicit mainly activity in the right hemisphere (Smith et al., 1996; Smith and Jonides, 1997; D'Esposito et al., 1998; Reuter-Lorenz et al., 2000). In elderly subjects, this lateralization in frontal regions is less outspoken and bilateral activity patterns during both spatial and verbal working memory tasks occur (Reuter-Lorenz et al., 2000; Cabeza, 2002). Furthermore, apart from such a hemispheric distinction, task-dependent differences in activity in ventrolateral versus dorsolateral PFC have been observed in young subjects (Braver et al., 1997; Cohen et al.,

1997; Manoach et al., 1997; Rypma and D'Esposito, 1999; Stern et al., 2000). According to the so-called two-stage model of working memory, the ventrolateral PFC is principally concerned with maintaining information in working memory, while the dorsolateral PFC is recruited when active manipulation of the stored items is required (Petrides, 1995; Owen et al., 1996, 1998). Because elderly are more impaired on tasks which require manipulation and executive control than those requiring only temporal storage in working memory (as reviewed by Verhaeghen et al., 1993), one might expect the greatest age-related differences in brain activity to be located within the dorsolateral PFC. Indeed, whereas task-related activity has been noted both in dorsolateral and ventrolateral PFC across groups, an age-related difference in activation during various working memory tasks has been found in the dorsolateral but not ventrolateral PFC (Nagahama et al., 1997; Esposito et al., 1999; Rypma and D'Esposito, 2000). In the experiment by Rypma and D'Esposito (2000) the effects of aging on the various stages of working memory (encoding, storage, and retrieval) were explicitly investigated. Differences between young and older subjects were found only at the retrieval stage, i.e. older individuals activated the dorsolateral PFC to a lesser degree. Other studies, however, did not find evidence for such a differential age effect on the dorsolateral PFC (Grady et al., 1998a; Mencl et al., 2000; Mitchell et al., 2000). Interestingly, in each of these latter reports an age-related difference was instead consistently observed in (the anterior part of) the ventrolateral PFC, as well as in the MTL, areas which the older subjects activated to a lesser degree than the young, or did not activate at all. To conclude, there is conflicting evidence as to whether aging reduces task-related activity in specific regions within the PFC.

Apart from a working memory decline, a considerable age-related deterioration can also be observed on tasks measuring explicit memory, i.e. the conscious recollection of past events and facts (Graf and Schacter, 1985). A number of studies have considered age-related changes in brain activity on explicit memory tasks. PET and fMRI experiments have shown that in young subjects, encoding tasks (either verbal or nonverbal) generally elicit left prefrontal, bilateral medial temporal and fusiform gyrus activation (e.g., Kapur et al., 1996; Nyberg et al., 1996a; Fletcher et al., 1998; Kopelman et al., 1998). The most consistent difference between young and older adults during encoding has been found in prefrontal activity. Older subjects either fail to activate the left frontal cortex (Grady et al., 1995), or exhibit reduced activity (Cabeza et al., 1997a, b; Grady et al., 1998b; Anderson et al., 2000). Findings with regard to age effects on posterior brain regions are less consistent. Medial temporal areas have been reported to be equally (Schacter et al., 1996; Madden et al., 1999), or less (Grady et al., 1995) activated during encoding in elderly.

Whereas during encoding prefrontal activity is mostly left-lateralized, the opposite hemisphere is activated during retrieval, a pattern described as the hemispheric

encoding/retrieval asymmetry, HERA (Tulving et al., 1994). Other regions involved in retrieval include the anterior cingulate, medial temporal and parietal lobes, and the cerebellum (e.g., Andreasen et al., 1995; Nyberg et al., 1996b; Rugg et al., 1997; Schacter et al., 1997; Wagner et al., 1998). Again, older adults differ from their younger counterparts particularly in prefrontal activity, that is, they show a more bilateral activation pattern (Schacter et al., 1996; Cabeza et al., 1997a, b; Madden et al., 1999; Anderson et al., 2000; Cabeza, 2002). With respect to the MTL, generally, no age-related difference in activity has been reported (Schacter et al., 1996; Madden et al., 1999; Cabeza et al., 2000; but see Bäckman et al., 1997).

Brain activity and effortful tasks

How can we interpret these findings, in particular, how can we explain the fact that prefrontal activity in elderly has been found to be decreased under some circumstances (e.g., Grady et al., 1995) and increased under other (e.g., Madden et al., 1999)? One explanation for age-related differences in left prefrontal activity is that it reflects recruitment of additional resources to cope with task demands, i.e. extra effort. That is, when task difficulty increases, an increase in prefrontal activation is likely to occur. This pattern has been found in studies with young subjects, using both working memory (Braver et al., 1997; Manoach et al., 1997; Rypma and D'Esposito, 1999; Tisserand et al., 2000a) and episodic memory tasks (as reviewed by Nolde et al., 1998). Moreover, practice (i.e., a decrease of conscious processing) has been associated with a decrease in frontal activity (Raichle et al., 1994; Garavan et al., 2000; Jansma et al., 2001). This 'prefrontal-effort hypothesis' may also apply to older individuals. On the neural level, it has been described in terms of compensation: by recruiting additional prefrontal regions older adults may prevent their performance from declining (e.g., Grady et al., 1994; Cabeza et al., 1997a; Grady, 2000; Mencl et al., 2000; Cabeza, 2002). This view is supported by a study by Anderson et al. (2000), who found that left prefrontal activity was reduced similarly by aging and by a divided attention task, suggesting that increasing age and effortful cognitive processing put an equal claim on the available attentional resources. Furthermore, in a study which compared performance on a dual-task with performance on either task alone (Smith et al., 2001) it was found that both older subjects and young poor performers activated the left PFC during a demanding dual-task, whereas young good performers did not. Additional evidence for the effort hypothesis comes from an experiment in which a simple (recognition) and difficult (temporal order) retrieval task were compared (Cabeza et al., 2000). It was found that during the difficult task version young subjects activated the right PFC more than the left, whereas the older subjects had stronger activity in the left PFC. No age differences were found in posterior regions. A final source of evidence for the effort hypothesis is

the finding that reduced frontal activity is often accompanied by poorer task performance and/or longer reaction times in older subjects (Grady et al., 1998a; Madden et al., 1999; Grady and Craik, 2000; but see Rypma and D'Esposito, 2000). These findings support the view that older adults make an extra effort to perform as well as young subjects on cognitive tasks, and this is reflected on the functional level as an increase in (left) prefrontal activity.

An alternative (albeit not incompatible) explanation is that age-related changes in frontal activity are part of a more general reduction in the efficiency of neural circuits, and recruitment of brain areas which are not essential to the task (e.g., Cabeza et al., 1997a; Esposito et al., 1999; Madden et al., 1999; McIntosh et al., 1999). This reduced neural efficiency has been attributed to a decline in frontal inhibitory control over posterior brain regions (Hasher and Zacks, 1988; Esposito et al., 1999; Grady, 2000; Cabeza, 2002). For instance, whereas young individuals were found to recruit a network in which there was strong inhibitory feedback from frontal to posterior regions during a short-term memory task, older subjects' neural connections were much weaker and hardly displayed such inhibitory influences (Della-Maggiore et al., 2000). According to this 'decreased neural efficiency' view, an increase in activity is not necessarily beneficial, as generally assumed, but rather may be detrimental for cognitive functioning. This interpretation can be tested by relating brain activation patterns to behavior. Reductions in the efficiency of a given neural circuit may lead to slowing of cognitive processes, which would be reflected as a positive correlation between brain activity and reaction times. Support for this hypothesis comes from a study which showed that in young participants, increases in activity within frontal as well as occipital and medial temporal regions were associated with shorter reaction times, whereas in older adults increased activity in these areas was related to slower performance (Grady et al., 1998a). Other evidence for reduced neural efficiency in the elderly is provided by the study by Madden et al. (1999) in which it was shown that both in young and old subjects, the best predictor of reaction times was a right prefrontal region, while in the old group several additional, non-frontal regions were found to also predict performance.

Conclusion

In sum, aging is - generally - accompanied by global decreases in brain activity, both at rest and during cognitive test performance. The most evident changes occur within the PFC. In addition to a general decrease in baseline activation, a particular pattern of task-related activation has been found in elderly where both decreased and increased frontal activity have been noted. Age effects on brain activity in posterior regions are less clear. An increase in frontal activity possibly reflects an extra effort to cope with task demands, whereas a decrease may be related to a reduction in neural efficiency.

OVERALL CONCLUSION: LINKING BRAIN AND BEHAVIOR IN AGING

In aging, most cognitive functions deteriorate, and it is likely that these impairments are a consequence of structural or functional losses in the brain. In this chapter, findings of age effects on the brain, provided by neuroimaging studies, have been summarized. Aging is associated with numerous cerebral changes, but the impact of these age effects is region dependent. The greatest age-related changes occur in the frontal lobes, in terms of structure (volume losses in gray and white matter, increase in white matter lesions) and function (decreased metabolism and perfusion, altered task-related activity patterns). These findings hence provide further support for the frontal lobe theory of aging. However, this view needs to be extended to include frontal projection areas and the fiber tracts interconnecting them. Only by considering such networks (both anatomically and functionally) will it be possible to fully understand the pattern of age-related cognitive decline.

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3

HEAD SIZE AND COGNITIVE ABILITY IN NONDEMENTED OLDER ADULTS ARE RELATED

This chapter is based upon
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ABSTRACT

In a cross-sectional analysis of 818 healthy older individuals (aged 50-81 years), head size was found to be related to performance on tests measuring intelligence, global cognitive functioning, and speed of information processing (but not memory). These relations were not confounded by educational level, socio-economic background, or height. Large head/brain size may protect elderly people against cognitive deterioration, supporting a 'reserve hypothesis' of brain aging.

INTRODUCTION

During childhood and adolescence, total brain mass increases and as a consequence so does head size. Already in the twenties the volume of the brain starts to decrease, whereas head size remains constant throughout life (Rushton and Ankney, 1996). Hence, head size is an indicator of maximal mature brain size. Larger brains may contain more neurons and synaptic connections and may therefore provide a greater 'reserve' against cognitive decline when tissue loss or brain damage occurs (Satz, 1993; Robertson and Murre, 1999). In elderly subjects, small head/brain size has indeed been found to be a vulnerability factor for cognitive dysfunctioning. Katzman et al. (1988) found at autopsy that the main difference between ten nondemented subjects who nevertheless had signs of Alzheimer brain pathology and subjects without such signs was that the former had heavier brains and more large neurons. The authors suggested that having a larger brain protected these subjects from developing Alzheimer symptomatology. Several studies have found evidence for such an association between head/brain size and cognitive ability (Graves et al., 1996; Mori et al., 1997; Schofield et al., 1997). These studies mainly focused on demented subjects. Only one large study (Reynolds et al., 1999) focused on a healthy elderly population (n = 825) and reported that smaller head size was associated with low Mini-Mental State Examination (MMSE) scores.

The goal of the present study was to investigate whether we could corroborate the finding that head size and cognitive performance are related in a healthy elderly population. Not only did we examine global cognitive functioning (with MMSE), but we also administered tests that assess the function of specific cognitive domains. Moreover, all associations were controlled for the potentially confounding influence of height, socio-economic background, and educational level. To test these hypotheses, we used data from 818 nondemented elderly subjects who participated in the Maastricht Aging Study (MAAS, Jolles et al., 1995).

METHODS

Subjects

Participants took part in the Maastricht Aging Study (MAAS), a longitudinal study into the determinants of cognitive aging (Jolles et al., 1995). In this study, 1869 subjects, initially nondemented and carefully screened for health problems, will be monitored for 12 years. For the present study, the data of participants 50 years and older (n = 818; 431 men, 387 women) were used.

Measurements

A standard neuropsychological test battery was administered to assess cognitive functioning. A full description of the tests used can be found elsewhere (Jolles et al., 1995). In short, global cognitive performance was examined with the Mini-Mental State Examination (MMSE, Folstein et al., 1975). The Stroop Color-Word Task (Stroop, 1935) was used to measure speed of information processing. The Word Learning Task was used to assess the ability to learn (WLT Total) and retrieve (WLT Recall) verbal information (Brand and Jolles, 1985). To estimate IQ, four subtests of the Groninger Intelligence Test (GIT, Luteijn and Van der Ploeg, 1983), comparable to the Wechsler Adult Intelligence Scale (Wechsler, 1991), were used: Arithmatic, Vocabulary, Mental rotation, and Analogies.

Head size (in mm) was determined twice with a tape measure placed around the subjects' head, 0.5 cm above the eyebrows and over the occipital protuberance. The mean of the two values was used for further analysis. Height was measured to the nearest millimeter. Educational level was measured on an 8-point scale, ranging from primary education to higher vocational training or university degree (De Bie, 1987). Likewise, socio-economic background was determined by asking subjects about their father's profession during their childhood, ranging from simple, unskilled work (1) to complex, scientific work (7) (DGA, 1989).

Statistical analysis

Head size was treated both as a categorical variable based on quartiles and as a continuous variable. In both instances, ordinary least-squares regression was used, adjusted for age and sex. Dependent variables included the intelligence and cognitive measures. To test whether the associations with head size still existed after correction for potential confounders, analyses were repeated after separately entering educational level, socio-economic background, and height into the regression model. Significance was defined as $p < 0.05$. Relations with p levels of < 0.10 were considered marginally significant.

RESULTS

The mean age of the participants was 63.2 years (SD = 9.0, range 50-81). The mean head size was 56.8 cm (SD = 2.0, range 50.7-62.2). Women had smaller heads than men (55.5 vs 58.0 cm, $p < 0.01$). Age and head size were not related (Pearson $r = -0.04$, $p = 0.32$). Head size and education were associated (Pearson $r = 0.15$, $p < 0.01$). Table 3.1 shows the association between head size and measures of intelligence and other cognitive functions, adjusted for age and sex.

Table 3.1. Association (unstandardized regression coefficients) of head size with cognitive test performance, adjusted for age and sex.

	Head size Categorical				Head size Continuous
	1 (58.2-62.2 cm)	2 (56.8-58.1 cm)	3 (55.4-56.7 cm)	4 (50.7-55.3 cm)	
GIT					
- Arithmatic	(reference)	-0.96†	-1.56‡	-1.33‡	0.21†
- Vocabulary	(reference)	-0.77†	-0.74*	-0.80*	0.14*
- Mental rotation	(reference)	-0.45	-0.82†	-0.56	0.16†
- Analogies	(reference)	-0.50	-0.46	-0.56	0.09
Stroop 1	(reference)	1.90†	2.66‡	1.41	-0.21
Stroop 2	(reference)	2.30†	3.59‡	3.29†	-0.54†
Stroop 3	(reference)	4.13	8.52‡	8.39†	-1.48†
WLT Total	(reference)	-0.34	-1.24	0.13	-0.09
WLT Recall	(reference)	-0.02	-0.08	0.12	-0.04
MMSE	(reference)	-0.35†	-0.28	-0.37*	0.07*

Note. GIT = Groninger Intelligence Test, WLT = Word Learning Test, MMSE = Mini-Mental State Examination.
*$p < 0.10$; †$p < 0.05$; ‡$p < 0.01$.

In the categorical analyses, head size was consistently related ($p < 0.05$) to performance on one GIT subtest (Arithmetic), whereas head size as a continuous variable was associated with performance on two intelligence subtests (Arithmetic and Mental rotation). In the other subtests, the relation was in the expected direction but did not reach significance. Furthermore, small head size (both categorical and continuous) was associated with decreased performance on the Stroop task ($p < 0.05$) and with lower

scores on the MMSE ($p < 0.10$). Head size and memory performance were not related. The influence of educational level, socio-economic background, and height were examined in separate analyses (Table 3.2).

Adjusting for educational level did not change the relation between head size and cognitive performance. Correcting for both socio-economic background and height only slightly weakened the associations.

Table 3.2. Association (unstandardized regression coefficients) of head size (continuous measures) with cognitive test performance, adjusted for age and sex (Model 1), with additional adjustment for either socio-economic background (Model 2), height (Model 3), or educational level (Model 4).

	Model 1	Model 2 (socio-economic background)	Model 3 (height)	Model 4 (educational level)
GIT				
Arithmatic	0.21†	0.18*	0.18*	0.19†
Vocabulary	0.14*	0.13*	0.07	0.12*
Mental rotation	0.16†	0.12*	0.12*	0.15†
Analogies	0.09	0.06	0.01	0.07
Stroop 1	-0.21	-0.10	-0.12	-0.18
Stroop 2	-0.54†	-0.42*	-0.36	-0.51†
Stroop 3	-1.48†	-1.24†	-1.18†	-1.37†
WLT Total	-0.09	-0.14	-0.16	-0.11
WLT Recall	-0.04	-0.05	-0.07	-0.04
MMSE	0.07*	0.06	0.04	0.06*

Note. GIT = Groninger Intelligence Test, WLT = Word Learning Test, MMSE = Mini-Mental State Examination.
*$p < 0.10$; †$p < 0.05$.

DISCUSSION

In this cross-sectional analysis, smaller head size was found to be associated with lower intelligence, lower general cognitive functioning (MMSE), and slower speed of information processing. No relation was found between head size and memory function. A large 'brain reserve capacity' (Satz, 1993) may protect older persons against cognitive decline. Head size, reflecting the maximum mature brain size, represents an indirect

measure of this concept. In studies with Alzheimer patients, smaller head/brain size was found to be associated with an increased risk of developing dementia (Graves et al., 1996; Mori et al., 1997; Schofield et al., 1997). A relation between head size and global cognitive functioning has also been found in healthy subjects (Reynolds et al., 1999). However, an alternative explanation is that the head size – cognition association is based on differences in educational level. In the present study, educational level and head size were significantly related (see also Graves et al., 1996; Rushton and Ankney, 1996, although others did not find such a relation, e.g., Schofield et al., 1997; Reynolds et al., 1999). This possibly implies that not large head size but high educational level protects against cognitive decline (Mortimer and Graves, 1993; Stern et al., 1994). Therefore, we investigated the head size – cognition relation both with and without adjustment for educational level. This did not alter the associations, indicating that educational level is not a (strong) mediator of the relation between head size and cognitive performance.

Several other factors may influence the relation between head size and cognitive ability. Small head size may reflect exposure during the process of brain maturation to detrimental factors, such as nutritional deficits or low socio-economic background. We investigated the effect of paternal profession (reflecting socio-economic background) and height (possibly reflecting nutritional and other developmental factors during early life) on the head size – cognition relation. Only a subtle decrease in the association was found when height or socio-economic background was included in the model. This implies that the association between head size and cognitive ability is not substantially confounded by the effects of socio-economic background or height.

Generally, examining the relation between anthropometric measures and mental abilities is a charged research topic. History has shown that associating intellectual abilities or personality characteristics with individual differences in physical appearance can lead to the discrimination of certain groups of people. However, the purpose of this study was to investigate the relationship between head size and cognitive performance in elderly subjects while explicitly *adjusting* for individual differences (e.g., age, sex, and education). Race was no issue here as all participants were Caucasian.

To conclude, a small but remarkably consistent relation was found between head size and performance on tests measuring intelligence, global cognitive functioning, and speed of information processing. These associations could not be attributed to the influence of possible confounding factors, such as educational level, socio-economic background, or height. These results support a brain reserve hypothesis, that is, larger brains may provide a buffer against cognitive deterioration later in life.

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4

THE RELATION BETWEEN GLOBAL AND LIMBIC BRAIN VOLUMES ON MRI AND COGNITIVE PERFORMANCE IN HEALTHY INDIVIDUALS ACROSS THE AGE RANGE

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ABSTRACT

The present study investigated the range of age-related changes in brain morphology and the relation with performance on memory and other cognitive tests in a healthy population. A group of 61 subjects (21 to 81 years old, mean = 55.7), free from cognitive and medical deficits, underwent MRI scanning and neuropsychological assessment encompassing memory and other cognitive tests. Volumetry of the hippocampus, parahippocampal gyrus, mamillary bodies, third ventricle and total brain matter was performed. The results indicate that in healthy individuals increases in ventricular volume and volume decreases in total brain matter, hippocampus and parahippocampal gyrus, but not mamillary bodies, are clearly apparent with increasing age. However, no relation could be established between the brain volumes and test performance when controlling for the effects of age. To conclude, variations in total and limbic brain volumes do not seem predictive for cognitive performance independent of age.

INTRODUCTION

Since the proportion of elderly people has increased considerably during the last century, there is growing interest in normal and pathological changes associated with the aging process. Neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have substantiated the findings from postmortem studies (see Selkoe, 1992, for a review) that nonpathological aging is associated with considerable morphological brain changes. Widening of the ventricular and sulcal liquor spaces is clearly evident in elderly persons (Jernigan et al., 1990; Coffey et al., 1992; Kaye et al., 1992; Murphy et al., 1992; Blatter et al., 1995; Coffey et al., 1998), and studies that directly measured brain volume have found age-related reductions in total and gray (but not white) matter volumes (Jernigan et al., 1990; Coffey et al., 1992; Pfefferbaum et al., 1994; Raz et al., 1997). This atrophy seems to occur particularly in the frontal and temporal lobes (Coffey et al., 1992; Raz et al., 1997), and also in subcortical regions (Jernigan et al., 1991).

With respect to cognitive functioning, especially speed of mental processing and the ability to learn and retrieve new information tend to decrease with advancing age (La Rue, 1992; Birren and Schroots, 1996). Since cognitive processes are dependent upon the integrity of the brain, it seems probable that changes in brain morphology (partly) account for these decreases in cognitive functioning. Studies examining patients with neurodegenerative disorders (e.g., Alzheimer's disease and Korsakoff's syndrome) have demonstrated that damage to specific brain structures is indeed related to deterioration of

cognitive functions. In these studies memory impairment is often associated with atrophy of limbic structures, including hippocampus, parahippocampal gyrus (Jack et al., 1992), thalamus (Victor et al., 1989) or third ventricle (Visser et al., 1999a), and mamillary bodies (Squire et al., 1990). Global cognitive deficits such as slower mental processing is related to more general cerebral atrophy (Seab et al., 1988; Shear et al., 1995).

Despite a considerable number of patient studies, relatively few studies with healthy volunteers have examined the relation between age-related changes in brain structures and neuropsychological test performance. No clear associations have emerged, which might be caused by a lack of adequate image analysis methods. For instance, several studies have relied only on global atrophy measures such as ventricular dilatation (Kaye et al., 1992; Breteler et al., 1994), whereas others focused on specific brain regions but used qualitative rating scales to assess severity of atrophy (Golomb et al., 1993; De Leon et al., 1997). Only two studies have investigated the relation between regional brain atrophy and cognitive deterioration using quantitative (i.e., volumetric) analysis methods in a large sample (Golomb et al., 1994; Raz et al., 1998). A relation was found between limbic structures and memory in subjects over 55 years of age.

In the present study a group of healthy subjects with a wide age-range was examined using both MRI and a number of neuropsychological tests. The aim of this research was twofold. First, we wanted to establish the range of nonpathological changes in brain regions known to be involved in memory across the adult age spectrum. Volumetry of the hippocampus, parahippocampal gyrus, mamillary bodies, third ventricle and total brain matter was performed. Secondly, we investigated whether normal age-related cognitive decline can be explained by volume changes. The general hypothesis was that volume reductions in limbic structures (hippocampus, parahippocampal gyrus and mamillary bodies; and dorsomedial thalamus as indexed by the third ventricle, Jacobson and Lishman, 1990) are especially related to lower scores on memory tests, whereas decreases in total brain volume are related to slower performance on timed tasks. Furthermore, although advancing age is accompanied by decreases both in brain volumes and in test performance, it was expected that the volume-performance associations were only partially mediated by age.

METHODS

Subjects

The study sample comprised 61 healthy and cognitively normal persons, aged 21 to 81 years (mean ± SD = 55.7 ± 16.1). The group consisted of 35 men (mean ± SD = 53.5 ± 16.2) and 26 women (mean ± SD = 58.6 ± 15.8). Mean educational level, as measured on

a five-point scale (1= primary school, 5 = university degree), was 2.6 (SD = 1.1). Subjects were rigorously screened and excluded if there was a history of cerebrovascular (e.g., stroke) or chronic neurological disease (e.g., dementia, epilepsy, head trauma), systemic disorders (e.g., diabetes mellitus), or major psychiatric illnesses using health questionnaires and interviews.

MRI acquisition and analysis

All subjects were imaged using a 1.5 T Gyroscan ACS-II MRI scanner (Philips, Best, The Netherlands). T1 weighted images were acquired in the coronal plane (perpendicular to the anterior commissure – posterior commissure line). A 3D gradient fast field echo (FFE) sequence was applied with TR=23 msec and TE=7 msec, and a flip angle of 30°. Slice thickness was 1.5 mm with no interslice gap. The image matrix was 256 × 256 and the field of view 230 mm.

Intracranial volume (including the cerebellum) was automatically determined (in mm^3) on all slices using custom software developed at the Department of Medical Informatics of the Universiteit Maastricht, The Netherlands, running on a G3 MacIntosh workstation (Apple, Cupertino, California). This procedure generates a contour around all neural tissue, excluding the meninges and bone structures. All structures below the pons were manually excluded from the measurements. After that, using the program BrainImage (Kennedy Krieger Institute, Baltimore, MD) the total brain volume was determined (in mm^3) with an automated segmentation algorithm (Otsu, 1979). This algorithm calculates the mean gray-level intensity of white matter, gray matter and liquor, and the cut-off value between liquor and gray matter was used to separate brain from non-brain.

The other brain volumes were determined using custom software developed at the Department of Clinical Physics and Informatics of the Vrije Universiteit Amsterdam, the Netherlands, running on a SUN workstation (SUN Microsystems, Mountain View, California). All brain structures were manually traced. In all cases, demarcation criteria (see below) were determined by consulting anatomical atlases (Nieuwenhuys et al., 1981; Duvernoy, 1991). The criteria that were applied for measurement are described in detail elsewhere (Visser et al., 1999a). In short, the hippocampus was measured every other slice in both hemispheres (range of measurements: 8-13) and included the hippocampus proper, dentate gyrus, alveus and subiculum. Left and right surfaces were calculated separately as well as together. Measurements were started anteriorly on the first slice where the hippocampus and amygdala were clearly separated, and the last slice was the slice before the crura of the fornices became visible. The parahippocampal gyrus was measured every other slice in both hemispheres, on the same slices on which the hippocampus was measured. The upper boundary was formed by the hippocampus or

transverse fissure, and the lateral boundary consisted of the collateral sulcus. Left and right surfaces were calculated separately as well as together. The mamillary bodies were seen on three or four slices, and were measured on each of those. The third ventricle was measured on each slice on which it appeared (range: 15-19) using a threshold pixel value. The anterior border was defined as the first slice where the optic chiasma was clearly connected to the diencephalon. The last slice was the slice before the posterior commissure became visible. Surfaces of the measurements were calculated automatically (in mm^2), and volumes were computed by multiplying the surfaces with the slice thickness, or twice the slice thickness in case of the hippocampus and parahippocampal gyrus. Figure 4.1[1] shows a typical image with various brain regions outlined.

Each brain structure was assigned to only one rater. Measurements were performed blind, i.e., raters were unaware of subject characteristics. To establish that measurements were sufficiently reliable, on ten scans all volumes of interest (VOIs) were remeasured after several weeks by the same investigator. The Pearson correlation coefficient between the first and second measurements was 0.91 for the hippocampus, 0.91 for the parahippocampal gyrus, 0.86 for the mamillary bodies, 0.98 for the third ventricle, 1.0 for the total brain matter, and 1.0 for the intracranial volume. These correlations indicate a high level of intrarater agreement for all measurements.

Neuropsychological assessment

Tests were aimed at measuring memory (Word Learning Test) on the one hand, and speed of mental processing (Memory Scanning Test, Stroop Color-Word Test) on the other.

In the Word Learning Test a list of 15 monosyllabic words is auditorily presented to the subjects five times and after each trial they are asked to recall as many words as possible. The total score of all trials is taken as a measure for learning ability (WLT total). After a time interval of 20-30 min subjects are asked again to recall as many words as possible (WLT recall) (Brand and Jolles, 1985).

The Memory Scanning Test is a paper and pencil cancellation test that consists of 12 rows of 12 letters and numbers, randomly interspersed with a target symbol or letter that subjects have to cross out. The cognitive load can be enhanced by increasing the number of targets that need to be memorized (Brand and Jolles, 1985). In the present study, two target sets were used: one with one target symbol (MST%) and one with three letters (MST3), and the time needed for completion was recorded.

In the Stroop Color-Word Test a sheet is presented consisting of a 10 □ 10 matrix with colored patches and subjects have to name them as fast as possible (Stroop Card 1). Subsequently, a sheet is presented consisting of a 10 □ 10 matrix with color names

[1] This Figure and the ones following can be found in the Appendix.

printed in a different color of ink. Subjects have to name the color of ink as fast as possible, which requires the inhibition of reading the words themselves (Stroop Card 3) (Houx et al., 1993). Time needed for completion was recorded.

Statistical analysis

To take intersubject variation in head size into account all VOIs were regressed on the intracranial volume. These adjusted volumes were then used for further analysis. Age was regressed on the adjusted brain volumes to investigate linear or higher order correlations. The contribution of a quadratic age component was examined by means of the R^2 change when age and age^2 were entered into the model successively (while correcting for collinearity between those variables, according to the method described in Earles et al., 1997). To test whether the regional volume changes exceeded that of the total brain, total brain volume and age were entered successively into a model with regional brain volume as the dependent variable.

Furthermore, hierarchical regression models were created with the neuropsychological test results as dependent variables. Sex and educational level were treated as covariates and were entered in the first step. In one model, the adjusted VOIs were entered in the second step. In another model, the second entry consisted of age, or age+age^2 (beneficial in the case of speed tests), while in the final step the adjusted brain volumes were entered.

RESULTS

Relations between VOIs and age

Men had significantly larger intracranial volumes than women (1071 vs. 957 cm^3, $p < 0.001$). Because of this difference, and because brain structures and intracranial size are related (Gould, 1981), all VOIs were adjusted for intracranial volume. In none of the cases did either sex or education add significantly to the model, so these variables were not considered any further. Associations between the adjusted brain volumes and age were assessed in hierarchical regression analyses. A summary of the measurements and their relation with age is presented in Table 4.1 and in Figure 4.2.

A quadratic effect of age was found for the total brain volume ($r = -0.80$, $p < 0.001$). A similar quadratic pattern was found for the total volume of the parahippocampal gyrus
($r = -0.54$, $p < 0.001$). This volume reduction was significant for both the left ($r = -0.57$, $p < 0.001$) and the right hemisphere ($r = -0.38$, $p < 0.01$). A linear relation was found between volume of the hippocampus and age (total: $r = -0.35$, left: $r = -0.35$, right: $r =$

-0.30; $p < 0.05$). The third ventricle volume also increased linearly with age ($r = 0.61$, $p < 0.001$). Finally, the volume of the mamillary bodies showed no age-related changes ($r = 0.17$, n.s.). In addition, it was investigated whether the regional volume changes were disproportional compared to the global atrophy. This was the case for none of the regions, which indicates that regional volume reductions were not greater than expected given the decrease in total brain volume.

Table 4.1. Brain volumes (mm^3), adjusted for intracranial volume, and their relation with age (Pearson product-moment correlations).

	Mean	(SD)	min - max	*r* (age)
Total brain matter	821743	(35281)	735722 - 870930	-0.78‡
Hippocampus	2929.4	(372)	2112 - 3805	-0.32*
left	1427.1	(205)	975 - 1969	-0.33*
right	1501.4	(189)	1135 - 1899	-0.28*
Parahippocampal gyrus	4629.4	(595)	3426 - 5802	-0.42‡
left	2395.8	(328)	1741 - 3184	-0.42‡
right	2339.3	(309)	1738 - 3115	-0.36†
Mamillary bodies	67.5	(10)	51 - 90	0.17
Third ventricle	874.7	(362)	314 - 1711	0.61‡

Note. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Relations between VOIs and neuropsychological test performance

To account for possible influence of sex and educational level on test performance, these variables were treated as covariates in all models. The relation between VOIs and cognitive functioning was examined in two models. In a model without accounting for the effects of age (Table 4.2) highly significant relations were found between all brain volumes (except mamillary bodies) and various tests of processing speed, all in the predicted direction (i.e., smaller brain volumes and larger ventricular volumes were related to poorer test scores).

Table 4.2. Results of hierarchical regression analysis. Sex and education were entered in the first step, followed by the brain volumes. Displayed is the proportion of explained variance (R^2) and the significance of the R^2 change after each step.

	step 1	step 2				
	gender + education	hippo-campus	parahippo-campal gyrus	mamillary bodies	third ventricle	total brain matter
MST %	0.08	0.22†	0.29‡	0.08	0.39‡	0.55‡
MST 3	0.12*	0.19*	0.25†	0.14	0.25†	0.43‡
Stroop 1	0.09	0.22†	0.23†	0.11	0.20†	0.24†
Stroop 3	0.09	0.13	0.15	0.14	0.29‡	0.34‡
WLT total	0.18*	0.18	0.24*	0.18	0.28†	0.33‡
WLT recall	0.06	0.06	0.10	0.07	0.13*	0.17†

Note. MST = Memory Scanning Task, WLT = Word Learning Test.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Volumes of the hippocampus and parahippocampal gyrus were related to performance on both subtasks of the Memory Scanning Test and Card 1 of the Stroop Test. Total brain and ventricular volumes were related to performance on both subtasks of the Memory Scanning Test and the Stroop Test. With respect to memory, a significant association was found between learning ability (WLT total) and volumes of total brain matter, parahippocampal gyrus and third ventricle. Delayed recall was only correlated with total brain volume. Other associations were not significant.

To investigate to what extent age obscured this relation between brain volumes and test performance, a second model controlling the effects of age was examined (Tables 4.3 and 4.4).

As expected, after controlling for sex and education, age explained a large proportion of the variance, varying between 8% ($p < 0.05$) for the WLT recall and 66% ($p < 0.001$) for the MST% task. However, the regions of interest no longer significantly added to the explained variance after age was entered. Only in one case (i.e., total brain volume and MST3) did the model significantly improve after entering the region of interest ($p < 0.05$).

Table 4.3. Results of hierarchical regression analysis. Sex and education were entered in the first step, age (and age²) in the second step, and finally the brain volumes. Displayed is the proportion of explained variance (R^2) and the significance of the R^2 change after each step.

	step 1	step 2	step 3				
	gender + education	age + age²	hippo-campus	parahip-pocampal gyrus	mamillary bodies	third ventricle	total brain matter
MST %	0.08	0.74‡	0.74	0.74	0.74	0.74	0.74
MST 3	0.12*	0.40‡	0.41	0.42	0.41	0.40	0.45*
Stroop 1	0.09	0.26†	0.30	0.29	0.28	0.28	0.28
Stroop 3	0.09	0.43†	0.44	0.45	0.46	0.45	0.44
WLT total	0.18*	0.29†	0.31	0.30	0.29	0.31	0.33
WLT recall	0.06	0.14*	0.17	0.15	0.14	0.16	0.17

Note. MST = Memory Scanning Task, WLT = Word Learning Test.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Table 4.4. Two examples of regression analyses of the partial model (gender, education and brain volume) and the full model (gender, education, brain volume and age). Shown are the regression coefficients (beta) and the associated p values. Dependent variables are the neuropsychological tests.

		partial model	full model
MST %	gender	0.19*	-0.02
	education	-0.14	-0.04
	total brain matter	-0.71‡	-0.09
	age		0.75‡
	age²		0.19*
WLT total	gender	0.36†	0.43‡
	education	0.13	0.02
	parahippocampal gyrus	0.25*	0.11
	age		-0.31*

Note. MST = Memory Scanning Task, WLT = Word Learning Test.
* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

DISCUSSION

The main hypothesis of the present study was that smaller brain volumes and larger ventricular volumes are related to reductions in neuropsychological test performance. Indeed, a relation was found between most regions of interest and various processing speed and memory tests. However, it was expected that this effect would still hold when controlling the effects of age, but this was not the case. Although higher age is clearly associated with larger ventricular volumes and smaller total brain regions and volumes of brain structures involved in memory processes, these changes do not seem predictive for neuropsychological test performance independent of age.

Normal brain aging

The present cross-sectional study demonstrates that normal aging is associated not only with losses in total brain volume, but also with local atrophy of brain regions important for memory. The total brain volume showed a quadratic relation with age, which is consistent with previous reports (e.g., Murphy et al., 1992; Blatter et al., 1995; Coffey et al., 1998). However, there is still debate as to whether normal aging is necessarily accompanied by atrophy of limbic memory structures. Volumes of hippocampus and parahippocampal gyrus were found to decline significantly with age. Several authors have reported similar age-related volume decreases in these regions (Coffey et al., 1992; Golomb et al., 1993; De Leon et al., 1997; Jack et al., 1997; Raz et al., 1997; Mu et al., 1999). However, other authors have failed to find such a decline in medial temporal lobe volumes (Lim et al., 1990; Sullivan et al., 1995; Raz et al., 1997). Linear increases with advancing age were found for the volume of the third ventricle (taken as an index for atrophy of the dorsomedial thalamus, Jacobson and Lishman, 1990). This is consistent with previous reports (e.g., Murphy et al., 1992; Blatter et al., 1995; Coffey et al., 1998). In line with earlier findings (Charness and DeLaPaz, 1987) volumes of the mamillary bodies were not significantly correlated with age. No sex or educational differences were found for any of the brain volumes, which is in line with other findings (Coffey et al., 1998; Coffey et al., 1999).

Because of the marked age-related reduction in total brain volume, it was examined whether the regional volume decreases were disproportional compared to the global reductions. Other studies have reported that frontal and temporal association areas are particularly affected by advancing age (Jernigan et al., 1991; Coffey et al., 1992; Raz et al., 1997). In this study, none of the regional volume reductions were greater than expected given the decrease in total brain volume. This may indicate that volume decreases in limbic regions are not specific for the aging process and are simply part of more global age-related volume losses.

Relation between brain volumes and cognitive performance

In the present study the hypothesis was tested that age-related declines in cognitive functioning are associated with changes in brain morphology. Based upon what is known from patient studies (e.g., Seab et al., 1988; Victor et al., 1989; Jack et al., 1992; Visser et al., 1999a), it was expected that reductions in total brain volume would be related to a decline in performance on global cognitive tests measuring speed of mental processing, while atrophy of limbic structures (hippocampus, parahippocampal gyrus and mamillary bodies; and third ventricle as an index for the dorsomedial thalamus, Jacobson and Lishman, 1990) would be specifically associated with a deterioration on memory tests. We found a somewhat different pattern. All volumes except that of the mamillary bodies showed a relation with tests measuring speed of processing. In addition, volumes of the parahippocampal gyrus and third ventricle were associated with learning ability. Total brain volume was related to both learning ability and delayed recall. All these relations were in the expected direction.

Not surprisingly (see for instance La Rue, 1992; Birren and Schroots, 1996), increasing age was found to be strongly associated with poorer performance on all speed and memory variables. Therefore we separately investigated the relation between brain volumes and cognitive performance after partialling out the influence of age. After correcting for age the volumes no longer significantly added to the explained variance. In other words, when age-related variance in test performance was taken into account, total and limbic brain volumes were not predictive for cognitive performance.

How can these findings be interpreted? First, a general remark is that inferences that can be drawn from cross-sectional studies such as the present one are rather limited. For instance, age-related brain atrophy may slightly precede cognitive deterioration in time and therefore seem unrelated to it. Indeed, two recent studies showed that medial temporal lobe volume at baseline significantly predicted longitudinal change on memory tests (Golomb et al., 1996; Visser et al., 1999b). Only longitudinal research can clarify the issue of whether age-related losses in brain volumes necessarily lead to cognitive decline.

Second, the lack of volumetry-performance associations after accounting for age may be due to the broad age-range of the present sample. In two other studies with subjects aged 18 to 80 years no relation could be established between brain volumes and neuropsychological test results after controlling for the effects of age (Kaye et al., 1992; Raz et al., 1998). However, in studies where only 55+ subjects were included a significant relation was found between limbic structures and memory test performance (Golomb et al., 1994; Golomb et al., 1996; Raz et al., 1998). Perhaps in older subjects, in whom both cognitive decline and brain atrophy are more obvious, the relation between the two is also stronger. Therefore, in the present study post-hoc analyses were performed to examine whether volumetry-performance associations could be established in subjects

over 55 years (n = 35). Again, no significant relations were found when accounting for the effects of age.

A third explanation, related to the previous one, might be that cognitive functions are affected only by substantial volume losses, and that a threshold must be passed before atrophy leads to performance decline. For instance, in two studies by Golomb and coworkers (Golomb et al., 1993; De Leon et al., 1997) healthy elderly subjects with visually rated hippocampal atrophy were found to perform significantly worse on memory tests than subjects without atrophy and this relation was unrelated to age. The subjects in the present study were included only when they were free of cognitive deficits and may therefore not be representative for the population as a whole. Perhaps the subjects of Golomb et al. performed less 'successfully' (but within normal range) and had more prominent brain atrophy than the ones in the present study.

Finally, a completely different explanation for our findings is that the age-related decreases in test performance are not related to volume decreases in limbic structures or the brain as a whole, but to atrophy of other areas not measured in this study, or a combination of several of these regions. For instance, a region that is frequently reported to show disproportional volume losses during the nonpathological aging process is the prefrontal cortex (Jernigan et al., 1991; Coffey et al., 1992; Raz et al., 1997). Several authors have even suggested that age-related cognitive deterioration is principally the consequence of alterations in prefrontal structure and function (e.g., Moscovitch and Winocur, 1995; West, 1996). Therefore, future research should try to explore also other than limbic brain areas involved in cognition, such as prefrontal regions, and when possible MR scanning should be repeated in the same individuals. Only then can firm conclusions be drawn about regional brain volume losses and their contribution to cognitive aging.

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5

A VOXEL-BASED MORPHOMETRIC STUDY TO DETERMINE INDIVIDUAL DIFFERENCES IN GRAY MATTER DENSITY ASSOCIATED WITH AGE AND COGNITIVE CHANGE OVER TIME

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ABSTRACT

Voxel-based morphometry (VBM) was used to examine the relation between age and gray matter density cross-sectionally, and to study the association between gray matter density and longitudinal decline in performance on cognitive tests in healthy, non-demented elderly individuals. Participants were neuropsychologically tested at baseline and again after three years. Thirty-seven subjects (mean age 72.5 years) who showed a decline in cognitive test performance at follow-up were compared with 38 individually matched control subjects (mean age 71.8 years) whose performance did not change over time. Magnetic resonance imaging (MRI) scans were acquired and individual differences in regional gray matter density were examined with VBM. The largest age effects were found in various regions in the prefrontal cortex, the (medial) temporal lobes and the striate cortex. Longitudinal cognitive decline was associated with decreased gray matter density in prefrontal areas, the (medial) temporal lobes and the posterior parietal cortex. These findings suggest that prefrontal and temporal cortical regions are of particular relevance both in aging and age-related cognitive decline in healthy elderly individuals.

INTRODUCTION

A large number of in vivo imaging studies (using Computed Tomography [CT] or Magnetic Resonance Imaging [MRI]) have considered age-related changes in the whole brain (e.g., Jernigan et al., 1991, 2001; Coffey et al., 1992, 1998; Courchesne et al., 2000; Resnick et al., 2000; Tisserand et al., 2000a) as well as gray and white matter separately (e.g., Jernigan et al., 1991, 2001; Raz et al., 1997; Guttmann et al., 1998; Courchesne et al., 2000; Resnick et al., 2000; Good et al., 2001) . Furthermore, effects of age on specific regions of interest have been reported, such as the hippocampus (Raz et al., 1997; Jack et al., 1998; Tisserand et al., 2000b; Ylikoski et al., 2000; Pruessner et al., 2001), prefrontal lobes (Raz et al., 1997; Salat et al., 1999, 2001; Tisserand et al., 2001, 2002), striatum (Gunning-Dixon et al., 1998) and thalamus (Van der Werf et al., 2001). It has been suggested that volume decreases in the prefrontal cortex (PFC) are a characteristic of the normal aging process, whereas atrophy of medial temporal lobe (MTL) regions is specifically related to pathological aging (Raz, 2000). However, the extent to which regional decreases in brain volume occur in normal aging, and whether the rate of decline differs per region are still a matter of debate.

The majority of imaging studies on aging have used volumetric approaches to determine individual regional differences. The strength of volumetry is that the regions of interest can be precisely outlined, even if there is large intersubject anatomical

variation. A disadvantage is the labor intensiveness of such approaches, which makes them unattractive for the analysis of large datasets (e.g., Tisserand et al., 2002). Also, as a consequence, generally only a limited number of regions is measured in each of these volumetric studies. Finally, regions with ill-defined anatomical boundaries, such as the insular cortex, have been largely ignored. These problems can possibly be overcome by using whole-brain analysis methods such as voxel-based morphometry (VBM). VBM is a relatively recently developed technique to examine regional differences in tissue density throughout the brain (Wright et al., 1995; Ashburner and Friston, 2000). It has been used to characterize morphometric differences between individuals, for instance due to normal aging (Resnick et al., 2000; Good et al., 2001; Goto et al., 2001; Tisserand et al., 2002) and due to pathological conditions, such as Alzheimer's disease (e.g., Rombouts et al., 2000; Thompson et al., 2001). These studies have proven successful in localizing anatomical differences between individuals.

Most imaging studies have been cross-sectional by nature, and therefore one can only speculate about the relation between brain atrophy and age-related cognitive decline. Moreover, it is still not clear whether a direct relation exists between age-related volume losses and cognitive change over time. Some studies have found an association between regional brain volumes and cognitive functioning, for instance, hippocampal volume and memory performance (Golomb et al., 1994), and volume of the prefrontal lobes and mental imagery (Raz et al., 1999). However, most studies have not found evidence for such a relation between brain volume and cognitive performance after adjusting for age effects (Raz et al., 1998; Petersen et al., 2000; Tisserand et al., 2000b; Ylikoski et al., 2000). The purpose of the present study was to evaluate the relation between age-related regional cortical differences and cognitive change over time. VBM was used (1) to consider the association between age and gray matter density cross-sectionally, and (2) to study the relation between gray matter density and longitudinal decline in performance on cognitive tests in healthy, non-demented individuals. It was hypothesized that the largest age effects on gray matter density would be found within the PFC, while cognitive decline would be particularly associated with decreased gray matter density in the MTL.

METHODS

Subjects

Participants were drawn from a larger study on determinants of cognitive aging, the Maastricht Aging Study (MAAS). The aims, population sample and design of this study have been described in detail elsewhere (Jolles et al., 1995; Van Boxtel et al., 1998). In short, 1,877 participants were drawn from a register of family practices in the south of

The Netherlands (Metsemakers et al., 1992). All individuals were aged between 24 to 81 years at baseline and were, according to the practitioner's information, without medical conditions that could interfere with normal cognitive function. People were excluded in the case of (a history of) chronic neurological pathology (e.g., dementia, cerebrovascular disease, epilepsy, parkinsonism and malignancies related to the nervous system), mental retardation or chronic psychotropic drug use. In addition, a score on the Mini-Mental State Examination (MMSE, Folstein et al., 1975) below 24 also resulted in exclusion. The sample was stratified according to age (5-year age groups), sex, and general ability level. All participants underwent a medical and neuropsychological assessment. Of this group, 838 individuals aged 49 years or older at baseline were reexamined after 3 years. For the present study, at this point a selection was made of participants who showed an individual decline on tests of objective cognitive function, using the baseline assessment three years earlier as a reference. The criteria for decline were defined as follows: (1) a score of 24 or lower or a decline of at least 3 points on the MMSE, or (2) a decline of at least 30% on two, or more, of six core tests that were used in MAAS to probe different cognitive domains: verbal memory (immediate and delayed recall, Brand and Jolles, 1985), verbal fluency (animal naming, Luteijn and Van der Ploeg, 1983), basic processing speed (Letter Digit Substitution test, Smith, 1968), and complex information processing (concept shifting digits/letters, Houx et al., 1991, and Stroop interference, Stroop, 1935) (see Jolles et al., 1995, for a full description of these tests). Fourty-four individuals who were thus identified as cognitive 'decliners' were matched for age, sex and educational level as closely as possible to other participants from the MAAS study who showed no decline according to these criteria. None of the participants in this study fulfilled the DSM-IV criteria for dementia (American Psychiatric Association, 1994). All 88 individuals were invited to the Maastricht University Hospital for an additional MRI session within four weeks of the cognitive screening. All MRI scans were inspected by a neuroradiologist for clinically relevant abnormalities. Seven individuals in the case group and six in the control group were excluded from further analysis because of movement artifacts (n = 8) and anatomical abnormalities (n = 5). Thus, 37 cases and 38 controls proceeded to the voxel-based morphometry analysis.

Written informed consent was obtained from all participants, for the MAAS study and this additional scan study separately. The MAAS-protocol and the additional scan protocol were approved by the Medical Ethics Committee of the Maastricht University Hospital.

MRI acquisition and analysis

MRI scans were acquired with a 1.5 T Gyroscan NT MRI scanner (Philips, Best, The Netherlands). T1-weighted images were obtained in the coronal plane (perpendicular to

the anterior commissure – posterior commissure [AC-PC] line). A 3D-gradient fast field echo (FFE) sequence was applied with TR=35 msec and TE=7 msec, and a flip angle of 35°. Slice thickness was 1.5 mm with no interslice gap. The image matrix was 256 × 256 and the field of view 240 mm. Voxel size was 0.94 × 0.94 × 1.5 mm.

To prepare the original images for the VBM analysis, a number of preprocessing steps were applied. First, the image volumes were corrected for MR signal non-uniformities due to magnetic field inhomogeneities in the scanner (Sled et al., 1998). Second, the original images were linearly transformed into stereotaxic space (Talairach and Tournoux, 1988) using an automatic registration program developed at the McConnell Brain Imaging Center of the Montreal Neurological Institute (Collins et al., 1994). This transformation results in an alignment along the AC-PC axis, and accounts for individual differences in global brain size and shape. This resampling resulted in MRI volumes consisting of 181 axial slices, with an isotropic voxel size of 1 mm. Third, images were classified into gray matter, white matter, and cerebrospinal fluid (CSF) partitions, by means of an automatic tissue classifier algorithm (Evans et al., 1996; Collins and Evans, 1999). This procedure included the removal of all extracranial tissue and the cerebellum, and has been validated before (Collins et al., 1994). Finally, a binary map of all gray matter voxels was extracted from each classified image, and this gray matter map was smoothed using a Gaussian kernel of 10 mm full-width at half-maximum. Smoothing converts the binary data into a range of continuous data, which is required for the statistical procedures in VBM, which are based upon Gaussian random field theory. Furthermore, smoothing also reduces the effect of individual variation in the exact location of gyri and sulci (Watkins et al., 2001). These smoothed gray matter density maps were used to localize age-related volume losses. VBM analyses were performed with software developed at the Montreal Neurological Institute, as previously described (Paus et al., 1999; Pruessner et al., 2001; Watkins et al., 2001; Tisserand et al., 2002).

Statistical analysis

Baseline characteristics of the two groups were compared with groupwise *t* tests for continuous variables (age and educational level) and a Chi-square test (sex). MMSE scores at baseline in both groups were compared with a non-parametric test (Mann-Whitney). A general linear model was fitted for all six cognitive variables combined measured at baseline, to test an overall effect of 'caseness' on cognitive functioning. Analyses were performed using a p level of 0.05.

The effect of age on total volume of the gray matter, white matter, and CSF was examined in the healthy, 'non-decliner' group, with linear regression models. Differences in these volumes between the two groups were assessed with groupwise *t* tests. To

examine whether the spatial transformation had an influence on the findings, analyses were repeated with the native image volumes. This was done by transforming the normalized images back into native space using the formula: native_image = normalized_image/(*sx* × *sy* × *sz*), where *sx*, *sy*, and *sz* are the scaling factors of the linear transformation (Pruessner et al., 2001).

To localize the age-related changes in gray matter density with the VBM approach, a linear regression model was applied to the normalized and smoothed gray matter maps of all subjects (Wright et al., 1995; Paus et al., 1999; Ashburner and Friston, 2000). This method, based upon Gaussian random field theory, corrects for multiple comparisons in a given search volume, in this case the gray matter maps of all subjects (Friston et al., 1996; Worsley et al., 1996). The statistical significance of the relation between age and gray matter density was assessed for each voxel, after removal of the effect of sex. Differences between the groups were examined in a similar fashion, while adjusting for the effects of sex and age.

Because our hypotheses were specifically directed at the PFC and MTL, we focused on these predefined regions of interest. Based upon our previous work (Pruessner et al., 2000, 2001; Tisserand et al., 2000b, 2002) the search region was reduced to 25 cm^3, which roughly corresponds to the volume of the hippocampus and PFC in young adults (transformed into Talairach space). As a result, to reach a significance level of $p < 0.05$ corrected for multiple comparisons, t values were thresholded at 3.73 (Worsley et al., 1996).

RESULTS

The two groups did not differ with respect to age, sex or educational level (Table 5.1). MMSE score at baseline was not different between 'decliners' and 'non-decliners' (Mann-Whitney U = 648.0, n.s.), and neither was the general linear model fitted for caseness to test group differences on all six cognitive tests scores at baseline combined (Hotelling's T = 0.134, $F(6, 66) = 1.471$, n.s). Hence, at baseline, the groups did not significantly differ with respect to the performance on any of the cognitive measures. In the group of decliners, 20 individuals were included based on the MMSE-criterion only, 14 based on the cognitive test criterion only, and 3 individuals met both criteria.

Table 5.1. Demographical characteristics (mean ± SD) at follow-up of the study sample.

	Decliners (n = 37)	Non-decliners (n = 38)
Age in years	72.5 (7.9)	71.8 (7.7)
Age range in years	53 - 84	52 - 82
Sex (M/F ratio)	19/18	18/20
Educational level	2.4 (1.4)	2.5 (1.7)

Note. Educational level range: 1-8 (elementary education - scientific education). Scores between 2 and 3 are equivalent to lower vocational education / intermediate secondary education (De Bie, 1987).

An age effect on global tissue volumes (Table 5.2) was found for the gray matter (R^2 = 0.21, $p < 0.001$) and CSF (R^2 = 0.31, $p < 0.001$), but not for the white matter (R^2 = 0.01, n.s.). Likewise, global differences between the 'decliners' and 'non-decliners' were found in the gray matter (541 vs. 604 cm^3, respectively, $p < 0.05$) and CSF (195 vs. 161 cm^3, $p < 0.05$), but not in the white matter (713 vs. 703 cm^3, n.s.). Performing the analyses with the native instead of normalized data did not change the results (data not shown). This was not surprising, given the fact that the scaling factor (used for the spatial transformation) was not different between the groups and was not significantly related to age.

Table 5.2. Global tissue characteristics (volumes in cm^3, mean ± SD) of the study sample, and variance explained by age (R^2) after adjusting for the influence of sex in the non-decliner group.

Brain volume	Decliners (n = 37)	Non-decliners (n = 38)	R^2 age
Gray matter	541.07 (150.7)	603.73 (103.4)*	0.21†
White matter	712.92 (127.9)	703.2 (64.0)	0.01
Cerebrospinal fluid	195.17 (70.2)	160.82 (40.8)*	0.31†
Scaling factor	1.10 (0.4)	1.10 (0.7)	0.00

Note. The scaling factor represents the linear transformation vector which was computed to spatially normalize the images.

*$p < 0.05$; †$p < 0.001$.

Table 5.3. Negative associations ($t < -4.75$; $p < 0.001$) between gray matter density and age.

cortical region	BA	X	Y	Z	*t* value
frontal pole	L10	-25	62	-10	-5.18
	R10	24	63	5	-5.76
	M10/11	-3	61	-13	-5.05
insula	L	-45	25	-2	-5.44
	R	41	26	-1	-5.31
anterior cingulate	M24/32	-2	23	39	-5.27
dorsolateral PFC	R9/44	51	18	25	-5.13
	L6	-53	5	26	-5.80
middle temporal gyrus	L21	-56	-12	-6	-6.70
hippocampus	L	-23	-20	-16	-5.99
hippocampus	R	21	-22	-15	-5.05
superior temporal gyrus	R22	67	-38	18	-5.36
medial occipital lobe	M19	-10	-74	28	-6.07

Note. X, Y, Z are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t* value). BA: approximate Brodmann areas, L: left, R: right, M: midline.

Table 5.4. Areas where gray matter density was lower in 'decliners' than in 'non-decliners' ($t > 3.73$; $p < 0.05$).

cortical region	BA	X	Y	Z	*t* value
frontal pole	L10	-36	52	2	3.99
	L10	-21	53	-10	4.27
inferior frontal	R45	59	26	16	4.29
	R44	62	8	15	4.05
dorsolateral PFC	R6	33	-1	46	4.48
hippocampus	R	25	-16	-19	3.99
inferior temporal gyrus	R37	64	-45	-12	3.90
posterior parietal cortex	R19/39	34	-70	31	4.14

Note. X, Y, Z are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t* value). BA: approximate Brodmann areas, L: left, R: right.

Increasing age was associated with decreases in gray matter density throughout the brain, but the magnitude of the effect greatly differed across regions. The largest age-related decreases ($p < 0.001$; Table 5.3, Fig. 5.1) in gray matter density were found in various frontal regions (right frontal pole, left dorsolateral PFC, anterior cingulate, and the

anterior part of the insula bilaterally), in the temporal lobes (left hippocampus, and middle and superior temporal gyrus), and in the striate cortex. Differences in gray matter density between the cognitive decliners and non-decliners were most prominent ($p < 0.05$; Table 5.4, Fig. 5.2) in the PFC (left frontal pole, right inferior frontal gyrus, and right dorsolateral PFC), in the right temporal lobe (hippocampus and posterior temporal), and in the right posterior parietal cortex. The difference between the groups for the left hippocampus approached significance ($t = 3.5$, $p = 0.10$).

DISCUSSION

In a group of individuals over 50 years of age, a global decrease in gray but not white matter was found. The greatest decreases in gray matter density were located in the PFC and the (medial) temporal lobes, as well as in the striate cortex. Age-related volume decreases in the region of the MTL have been reported in a number of studies (Raz et al., 1997; Jack et al., 1998; Tisserand et al., 2000b; Ylikoski et al., 2000; Pruessner et al., 2001), especially in samples including older adults (e.g., Mueller et al., 1998; Mu et al., 1999). The gray matter density decrease in specific parts of the PFC is in line with previous volumetric studies which have found a disproportionate effect of age on this region (Raz et al., 1997; Tisserand et al., 2001, 2002). VBM has been used in several other studies to study age effects (Resnick et al., 2000; Good et al., 2001; Goto et al., 2001; Tisserand et al., 2002). For instance, in a sample including 465 subjects (Good et al., 2001), the greatest decreases in gray matter density were found in the frontal and temporal cortex, which supports the results of the present study. However, contrary to our findings, these authors reported a relative preservation of the MTL region. An explanation for this discrepancy is the fact that the study by Good et al. (Good et al., 2001) involved subjects aged 20 to 80 years, while in the present study they were all 50 years and over. As mentioned before, age-related volume losses in the MTL region seem to accelerate in older adults (Mueller et al., 1998; Mu et al., 1999), and therefore may appear to be only mild or even go unnoticed in studies with subjects across the complete adult age range.

Cognitive change over time was associated with global reductions in gray but not white matter volume. The areas of greatest difference in gray matter density between cognitive 'decliners' and 'non-decliners' were located in the PFC, the (medial) temporal lobe, and posterior parietal cortex. Several studies have considered differences between healthy elderly and subjects with mild cognitive impairments in regional brain volumes. A significant reduction in the volume of the hippocampus (Parnetti et al., 1996) and parahippocampal gyrus (Visser et al., 1999) was observed in subjects with mild cognitive

impairments compared with healthy age-matched controls. However, other studies did not find evidence for such volume differences between cognitively healthy and mildly impaired individuals in the medial temporal lobes (Soininen et al., 1994), nor in the frontal cortex (Hänninen et al., 1997).

To our knowledge, this is the first study to examine the relation between longitudinal decline in cognitive functioning and differences in gray matter density throughout the brain. In the only imaging study with a longitudinal design similar to ours, it was found that a reduction in the volume of the hippocampus was not significantly related to cognitive decline in healthy elderly individuals (Ylikoski et al., 2000). In that study, no other brain regions were measured. The fact that the strongest effects both of age and cognitive decline were found in the prefrontal cortex and (medial) temporal lobes confirmed our hypothesis that these regions are of particular relevance in aging and age-related cognitive decline. However, we expected that the PFC would be especially implicated in aging, and the MTL in cognitive decline, but this prediction was not supported by the data. Advancing age and cognitive decline had a similar effect on gray matter density in MTL and PFC regions. It may be hypothesized that volume decreases in the PFC characterize normal aging processes during the adult life (Raz, 2000), and that MTL atrophy only becomes apparent in older individuals. In particular the combined effect of these regional volume losses may lead to functional decline.

Methodological issues

The obvious advantage of VBM is that it is fast and automated, and therefore applicable to large samples, including hundreds of subjects (e.g., Good et al., 2001; Goto et al., 2001). Furthermore, there is no need for a priori hypotheses about regions of interest because differences are assessed throughout the cortex. However, a limitation is that, in contrast to what its name suggests, VBM does not offer the possibility to quantify brain volumes. In addition, large anatomical variability in the location even of primary sulci and gyri (Ono et al., 1990; Rajkowska and Goldman-Rakic, 1995; Roland et al., 1997) hampers the interpretation of VBM studies. Consequently, coregistration accuracy is a point of continuing concern and discussion (e.g., Ashburner and Friston, 2001; Bookstein, 2001).

To illustrate this, a probabilistic map was created on the basis of the gray matter maps of the non-decliner group (Fig. 5.3). This map displays the probability for each voxel of being classified as gray matter. Regions with high probabilities ($p > 0.7$) were observed along the longitudinal fissure, in the temporal lobes (especially the MTL), and in the ventral parts of the frontal and parietal cortices. Low probabilities ($p < 0.4$) were found in the dorsal part of the frontal and parietal lobes and in the occipital lobes. The fact that the probabilistic map shows low values particularly in the dorsal part of the

brain can be explained by two factors: (1) sulcal variability in the middle and superior frontal gyri is larger than in other parts of the cortex, or (2) tissue classification has not been completely successful due to field inhomogeneity in the dorsal direction. The first factor points to 'anatomical noise', while the second factor can be designated 'artifactual noise'. To examine whether the results could be explained on the basis of artifactual noise, the gray matter maps were compared with the original, non-classified images to determine whether striking misclassifications could be observed. Such errors, which should have occurred repeatedly to explain the findings of the probabilistic map, were not apparent. Moreover, during the preprocessing, images were corrected for field nonuniformity using a well-validated method (Sled et al., 1998). Therefore, it seems unlikely that the low values in the probabilistic map are due to classification errors. Evidence in favor of a anatomical explanation for lower probability values in the dorsal part of the cortex comes from a study by Thompson et al. (2001), in which normal variability in cortical patterns was examined using 3D displacement maps. Variability was found to be highly region-dependent, with only slight variance in the primary motor and sensory areas and orbitofrontal cortex, and the largest variability in the superior and middle frontal gyri and posterior parietal region. Hence, the present findings are in line with those of Thompson et al. (2001).

To conclude, anatomical variability leads to regionally fluctuating statistical power to detect individual differences with age or between groups with VBM. As a consequence, in areas with large anatomical variability (such as the superior frontal lobes), differences in gray matter density may have been overlooked (Type I error). Nonetheless, in the regions that do show differences the effect must be robust.

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6

REGIONAL FRONTAL CORTICAL VOLUMES DECREASE DIFFERENTIALLY IN AGING: AN MRI STUDY TO COMPARE VOLUMETRIC APPROACHES AND VOXEL-BASED MORPHOMETRY

TISSERAND DJ, PRUESSNER JC, SANZ ARIGITA EJ, VAN BOXTEL MPJ, EVANS AC, JOLLES J, and UYLINGS HBM (2002). *NeuroImage*, 17: 657-669.

ABSTRACT

Recent neuroimaging studies suggest that the frontal lobes are the part of the brain most profoundly affected by the aging process. The present study investigated whether subregions within the frontal cortex show different patterns of brain aging. Magnetic resonance images (MRI) of 57 healthy participants between 21 and 81 years old were used to measure regional frontal gray matter volumes in three ways: with a manual tracing and a semi-automatic 'Talairach boxes' volumetric method, and with voxel-based morphometry. Seven regions within each hemisphere were manually traced: precentral gyrus, inferior frontal gyrus, dorsolateral frontal cortex, ventral medial region, lateral orbital region, anterior cingulate, and frontal pole. With the semi-automatic approach, four regions were measured: lateral, orbital, and medial frontal regions, and frontal pole. Advancing age was strongly associated with decreases in the volume of the whole frontal cortex. Differential age effects on the volumes of frontal subregions were dependent on the method applied. According to the manual approach, age-related volume decreases were strongest in the lateral and orbital frontal gray matter. The semi-automatic and voxel-based analyses found that age effects were most prominent within the lateral frontal and cingulate regions. Overall, it was concluded that although semi-automated and voxel-based methods can provide a reasonable estimate of regional brain volume, they cannot serve as a substitute for manual volumetry.

INTRODUCTION

As people age, a general reduction in brain volume can be observed. Recent magnetic resonance imaging (MRI) studies have shown that such age-related decreases in brain volume are not homogeneous across all brain regions. Atrophy seems to be especially prominent in the frontal lobes (Coffey, 1993; Cowell et al., 1994; Raz et al., 1997; Salat et al., 1999; Tisserand et al., 2001) and the regions with which they have dense reciprocal projections, such as the thalamus (Van der Werf et al., 2001) and striatum (Rubin, 1999; Raz, 2000). Whether this atrophy is due to white or gray matter loss is still an open question. For instance, in a study with participants across the adult age range, a negative association between frontal white matter volume and age was found, but it was small compared to gray matter reductions within the frontal lobes (Raz et al., 1997). In some other studies, the opposite was found, i.e., age-related changes were most obvious in white matter, but only in subjects over 70 years of age (Salat et al., 1999, 2001; Courchesne et al., 2000; Jernigan et al., 2001). Hence, it is possible that a decrease in

white matter does not start until late in life, while the gray matter atrophy takes place gradually during the adult years.

The disproportionate tissue loss in the frontal cortex strongly supports the frontal theory of cognitive aging (Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999). This theory suggests that changes in frontal structure and/or function are responsible for cognitive problems often seen in older people, such as attentional difficulties, forgetfulness, and lack of cognitive flexibility. Evidence for frontal lobe involvement in these functions comes from studies with patients with frontal dysfunctions and from functional imaging data (Cummings, 1993; Knight et al., 1999; Cabeza, 2000). Nevertheless, the large frontal cortex is both structurally and functionally heterogeneous and a distinction should be made between several subregions.

Only few studies have considered the effect of age on the volume of different substructures within the prefrontal cortex (PFC). Raz et al. (1997) distinguished between three 'classical' regions: orbitofrontal, dorsolateral prefrontal, and anterior cingulate cortex (Fuster, 1980; Cummings, 1995). In participants ranging from 20 to 80 years of age, they found a strong negative association between age and volume of the dorsolateral and orbitofrontal cortex, but not between age and the anterior cingulate. By contrast, using a similar subdivision and a similar age range, we found the strongest age-associated decrease within the anterior cingulate and dorsolateral region and a smaller reduction in orbitofrontal volume (Tisserand et al., 2001). Equally, Salat et al. (2001), comparing young-old and old-old subjects, found a relative preservation of the orbitofrontal cortex. An explanation for this discrepancy could be the method that was applied for measurement. Raz et al. (1997) and Salat et al. (2001) manually demarcated the frontal regions on a limited number of slices in only one (i.e. coronal) plane. In our study (Tisserand et al., 2001) a semi-automatic volumetric procedure was used to divide the complete PFC in boxes (Subramaniam et al., 1997), based on the Talairach atlas (Talairach and Tournoux, 1988). Advantages of such a semi-automatic approach are that it has a perfect reproducibility, and the volume of the complete frontal cortex (or any other brain region) can be measured relatively fast. On the other hand, this method may be too crude to apply to smaller brain structures such as subregions within the PFC (Goldszal et al., 1998; Resnick et al., 2000).

A general property of volumetric approaches is the need for a priori definition of regions of interest. This can be avoided by the application of recently developed whole-brain analysis methods, such as voxel-based morphometry (VBM). This approach uses spatially normalized and smoothed gray (or white) matter maps to study individual differences in gray/white matter density on a voxel-by-voxel basis (Wright et al., 1995; Paus et al., 1999; Ashburner and Friston, 2000). Several studies have used VBM to investigate age-related changes in gray matter density (Good et al., 2001; Goto et al.,

2001). Within the frontal lobes, the strongest effects of age were found in lateral and cingulate regions.

In summary, age-related volume loss in the frontal cortex seems to be disproportionate, but there is controversy about which subregions are particularly affected, possibly due to differences in methodologies. The purpose of the present study was to compare the results of a manual tracing approach based upon an anatomical definition of frontal subregions to both a semi-automatic volumetric method and VBM. As an application of all three methods, the association between age and regional frontal lobe gray matter volume was examined. The manual measurements were treated as the 'anatomical standard' with which we compared the results from the other approaches. The study was performed on healthy subjects who had been screened for the presence of health-related problems. In this way, the variation in brain volumes could only be attributed to normal aging and not to age-extrinsic, disease-related factors (Van Boxtel et al., 1998).

MATERIALS AND METHODS

Subjects

The study sample comprised 57 healthy and cognitively normal persons, between 21 and 81 years (mean ± SD = 55.7 ± 16.2). The group consisted of 34 men (mean age ± SD = 54.0 ± 16.2) and 23 women (mean age ± SD = 58.1 ± 16.4). All participants were rigorously screened for presence of health-related problems with a health questionnaire and a medical interview (Van Boxtel et al., 1998). Individuals were excluded if there was a history of hypertension, cerebrovascular or chronic neurological disease, systemic disorders, or major psychiatric illnesses (Tisserand et al., 2000). Cognitive status of subjects older than 35 years (n = 38) was assessed with the Mini-Mental State Examination (MMSE, Folstein et al., 1975), and a cut-off score of > 24 was used for inclusion (mean ± SD = 28.5 ± 1.8). Written informed consent was obtained from all participants. The research protocol was approved by the Medical Ethical Committee of the Academic Hospital Maastricht.

MRI acquisition and analysis

MRI scans were acquired with a 1.5 T Gyroscan ACS-II MRI scanner (Philips, Best, The Netherlands). T1-weighted images were obtained in the coronal plane (perpendicular to the anterior commissure – posterior commissure [AC-PC] line). A 3D-gradient fast field echo (FFE) sequence was applied with TR=23 msec and TE=7 msec, and a flip angle of

30°. Slice thickness was 1.5 mm with no interslice gap. The image matrix was 256 × 256 and the field of view 230 mm.

The same preprocessing steps were applied for all three methods. This procedure consisted of three steps. First, the image files were corrected for MR signal non-uniformities due to magnetic field inhomogeneities in the scanner (Sled et al., 1998). Second, the original images were linearly transformed into stereotaxic space (Talairach and Tournoux, 1988) using an automatic registration program developed at the McConnell Brain Imaging Center of the Montreal Neurological Institute (Collins et al., 1994). This transformation results in an alignment along the AC-PC axis, and accounts for individual differences in global brain size and shape. After this resampling the MRI volume consisted of 181 axial slices, and the voxel size was 1 × 1 × 1 mm. Finally, images were classified into different maps of gray matter, white matter, and cerebrospinal fluid (Evans et al., 1996; Collins and Evans, 1999). This procedure included the removal of all extracranial tissue and the cerebellum, and has been validated before (Collins et al., 1994). The gray matter map was used to determine regional cortical volumes in both the manual and semi-automatic approach, and to determine gray matter density in the voxel-based analysis.

Manual volumetric tracing method

The manual tracing analysis was performed with the software package DISPLAY developed at the Montreal Neurological Institute (e.g., Pruessner et al., 2000, 2001). This program allows simultaneous viewing in coronal, sagittal and horizontal sections, as well as a three-dimensional surface rendering. Editing of the images can be performed on the triplanar (two-dimensional) sections but also on the rendered surface (Fig. 6.1 and 6.2). This is important because tracing sulci, in particular those on the lateral side of the brain, is rather complicated using only two-dimensional sections. Seven frontal regions were outlined within each hemisphere and were all measured by the same rater (DT). The total time needed to measure the volumes of the frontal subregions of one individual was approximately 10 hours. This parcellation method slightly differs from the ones described before (Rademacher et al., 1992; Crespo-Facorro et al., 1999). Based upon knowledge about the connectivity and cytoarchitecture within the frontal lobes (Groenewegen and Uylings, 2000; Uylings et al., 2000a), and guided by several anatomical brain atlases (Nieuwenhuys et al., 1981; Ono et al., 1990; Duvernoy, 1991), the following rules were applied for delineation of the regions of interest:

Precentral gyrus. Brodmann area 4 and ventral part of area 6. The posterior border, i.e. the bottom of the central sulcus, was traced on the surface rendered image. This sulcus is generally continuous, starting at the medial surface and ending near the Sylvian fissure (Ono et al., 1990). The anterior border, the bottom of the precentral

sulcus, was traced in a similar fashion. Frequently, this sulcus is interrupted (Ono et al., 1990). The shortest possible line was drawn to connect the various segments. In case of two parallel sulci, the most posterior sulcus was traced, to ensure that the precentral region consisted of only one gyrus. The ventral border was the Sylvian fissure.

Anterior cingulate. Brodmann areas 24 and 32. The anterior cingulate cortex was traced using the sagittal and coronal views. The dorsal border consisted of the bottom of the paracingulate sulcus. When this sulcus was interrupted (which is frequently the case, e.g., Paus et al., 1996), the shortest possible line was drawn between sulci. In no case was the cingulate sulcus taken as the dorsal border. The posterior border was located three slices posterior to the slice where the anterior commissure is most clearly visible (Fig. 6.1, plane A). The anterior border was the first deep sulcus measured from the genu of the corpus callosum, usually the cingulate sulcus. This sulcus was also taken as the ventral border. The ventral-posterior border consisted of the most caudal slice on which the inner curvature of the corpus callosum was visible (Fig. 6.1, plane C). This border was chosen to ensure that area 25 was not included in this region.

Frontal pole. Brodmann area 10. Because it is difficult to apply anatomical criteria near the anterior tip of the frontal cortex, a pragmatic cut-off point was used. This region was therefore defined as all gray matter anterior to the line y = 44 (Fig. 6.1, plane D), which encompassed approximately 25 coronal slices (2.5 cm). Such a cut-off line could be used because the images were spatially normalized and therefore the position of this line was approximately similar in each subject. Only in the case of the anterior cingulate this rule was not applied, i.e. that region was measured completely, even if it included tissue rostrally from the line y = 44.

The orbitofrontal cortex can be subdivided in a ventral medial and a lateral orbital part (Elliott et al., 2000; Öngür and Price, 2000). The ventral medial part consists of Brodmann area 11 and 12. All three planes were used to trace the borders of this region. Based upon our cytoarchitectonic experience (ESA and HU), the posterior border was defined as the inner curvature of the corpus callosum (Fig. 6.1, plane C), and the anterior border consisted of the frontal pole region. The lateral border was the crown of the olfactory sulcus, which is the first orbital sulcus when moving laterally from the midline. The complete gyrus was traced on the five most ventral axial slices; dorsal to this point, only the gray matter medially to the white matter band of this gyrus was included. Dorsally, this region was limited by the anterior cingulate region. The lateral orbital region consists of Brodmann area 47. The posterior border consisted of the posterior tip of the corpus callosum (Fig. 6.1, plane B). On coronal sections, this is seen as a bright spot just below the lateral ventricles. The anterior border was formed by the frontal pole region. The medial border was the one with the ventral medial region. The lateral border was the circular sulcus of the insula on the more posterior slices, and the anterior

horizontal ramus of the Sylvian fissure on the more anterior slices. The dorsal border was the AC-PC line.

Inferior frontal gyrus. Brodmann areas 44 and 45. The ventral border consisted of the anterior horizontal ramus of the Sylvian fissure. The dorsal border was the inferior frontal sulcus. In most cases, these sulci were clearly visible and they were traced on the surface rendered image. The posterior border was the precentral sulcus, and the anterior border the frontal pole region.

Dorsolateral frontal. Brodmann areas 8, 9, and 46. This region had as lateral ventral border the inferior frontal sulcus, and as medial border the paracingulate sulcus. The posterior border was defined by the precentral sulcus, and the anterior border by the frontal pole region. The dorsolateral region was traced on the surface rendered image.

Table 6.1. Reliability (intraclass correlation coefficients, *r*) of the manually traced frontal cortical volumes, $n = 5$.

	left	right
anterior cingulate	0.88	0.98
dorsolateral frontal	0.97	0.96
inferior frontal	0.98	0.94
ventral medial	0.99	0.93
lateral orbital	1.0	1.0
frontal pole	1.0	1.0
precentral gyrus	0.89	0.76
total frontal	1.0	1.0

To determine the test-retest reliability of the measurements, all frontal volumes of 5 randomly selected brains were measured twice by the same rater. Intraclass correlation coefficients (ICCs) were determined using a one-way analysis of variance model (Bartko and Carpenter, 1976). ICCs take into account both within-subject and between-subject variance and it is therefore a very sensitive method to assess the reproducibility of measurements. As can be concluded from Table 6.1, the reliability of the manual volumetric approach was high: all ICCs were > 0.88, except for the right precentral gyrus ($r = 0.76$).

Semi-automatic 'Talairach boxes' method

For this approach, the BrainImage software, developed at the National Institute of Health, was used (Subramaniam et al., 1997) in combination with custom software developed at the Maastricht Brain and Behaviour Institute. The Talairach grid system divides the brain into boxes, based upon the location of the AC and PC, and the outer boundaries of the brain (Talairach and Tournoux, 1988). The only nonautomatic step in this procedure consists of marking the two commissures. Subsequently, a grid consisting of 1056 boxes (11 anterior-posterior × 8 left-right × 12 dorsal-ventral) is automatically placed over the brain (Fig. 6.3). Because the image files were spatially transformed prior to this analysis, the volume of each box was constant across all subjects (i.e., approximately 3.2 cm^3). Using these boxes, specific regions of interest can be defined. It was previously shown that volumes of regions defined with the aid of the grid have a high correspondence to manually traced volumes of the same regions (Andreasen et al., 1994). Furthermore, a great number of functional neuroimaging studies have referred to the Talairach coordinate system to localize and compare brain regions between individuals.

In the present study, 'Talairach boxes' representing the frontal lobes were subdivided into four regions based upon anatomical knowledge and with the use of the Talairach atlas (Talairach and Tournoux, 1988):

- lateral prefrontal region
- anterior cingulate region
- orbital prefrontal region
- frontal pole region.

This subdivision is a slightly adapted version of the one described in Tisserand et al. (2001), to ensure the best possible comparison between the manual and semi-automatic method. The complete frontal region was defined as the region starting at the frontal tip and ending posteriorly at a plane orthogonal to the AC-PC line, at one-third of the distance between the AC and PC (see Fig. 6.3 for an example). The definition of the subregions was based upon the landmarks as defined in the former section. The frontal pole consisted of the most rostral quarter of the region between the frontal tip and the AC. The anterior cingulate region included the boxes encompassing the cingulate and paracingulate sulci. The lateral PFC region included all boxes containing the inferior frontal and dorsolateral region as described in Method 1. The orbitofrontal region included all ventral medial and orbital boxes. When a box included two different regions, it was assigned to the region which contributed most of the tissue in the box. A random image file was used to assign the boxes to the various regions, based upon the anatomical characteristics of this image. Subsequently, five image files were inspected to test whether this subdivision fitted the individual brains best, or that boxes needed to be shifted from

one region to the neighbouring one. Then, after agreement had been reached, the gray matter maps of all 57 brains were analysed using this standard protocol. The approximate total time needed to measure the volumes of frontal subregions of one individual was 15 minutes. All ICCs of the semi-automatically determined frontal volumes were 1.0 (data not shown). In Table 6.2, a comparison of the frontal regions as defined by the manual and semi-automatic methods is presented.

Table 6.2. Nomenclature used in the two volumetric methods and corresponding Brodmann locations. The clustering of the manually traced frontal cortical areas as presented in this Table was performed to allow for a comparison between the two volumetric methods (cf. Table 6.5).

Talairach boxes	Manual tracing	Approximate Brodmann area
lateral frontal	inferior frontal gyrus	44, 45
	dorsolateral frontal	8, 9, 46
anterior cingulate	anterior cingulate	24, 32
orbital frontal	ventral medial	11, 12
	lateral orbital	47
frontal pole	frontal pole	10
--	precentral gyrus	4, 6

Voxel-based morphometry (VBM)

The gray matter images, resulting from the normalization and classification as described before, were smoothed using a Gaussian kernel of 10 mm full-width at half-maximum. These gray matter density maps were used to localize age-related volume losses. Because this approach is fully automated, test-retest reliability is perfect. VBM analyses were performed with software developed at the Montreal Neurological Institute (e.g., Paus et al., 1999; Pruessner et al., 2001; Watkins et al., 2001).

Statistical analysis

Pearson product-moment correlations between the semi-automatically and the manually traced regions were calculated to compare these volumetric methods. Furthermore, the effect of age on the frontal subregions, measured with both volumetric methods, was examined by using linear regression analysis. Because the brain images were spatially normalized before measurements were started, no further correction for individual variation in head size was required. To investigate whether the age-related atrophy was disproportionate within the frontal lobe, total brain volume and age were entered

successively into a regression model with the regional frontal gray matter volumes as dependent variables (Tisserand et al., 2000).

To localize age-related decreases in gray matter density with the VBM approach, a linear regression model was applied to the normalized and smoothed gray matter maps of all subjects (Wright et al., 1995; Paus et al., 1999; Ashburner and Friston, 2000). The statistical significance of the relation between age and signal intensity was assessed for each voxel, after removal of the effect of sex. This method, based upon Gaussian random field theory, corrects for multiple comparisons in a given search volume, in this case the gray matter maps of all subjects (Friston et al., 1996; Worsley et al., 1996).

RESULTS

Table 6.3. Volumes (mean ± SD) of the frontal regions (cm^3) for all subjects and men and women separately, and agreement between the two volumetric methods (Pearson product-moment correlations).

	men (n = 34)		women (n = 23)		all (n = 57)		
	manual volume	Talairach volume	manual volume	Talairach volume	manual volume	Talairach volume	corre-lation
anterior cingulate	19.92 (3.6)	32.43 (5.6)	21.13 (4.4)	33.07 (5.6)	20.41 (4.0)	32.69 (5.6)	0.90
lateral frontal	80.96 (15.0)	91.26 (16.5)	91.22 (20.6)*	100.74 (21.5)	85.10 (18.0)	95.09 (19.1)	0.93
orbital frontal	27.99 (5.2)	31.63 (6.0)	28.49 (5.3)	33.34 (6.4)	28.20 (5.2)	32.34 (6.2)	0.85
frontal pole	34.53 (6.2)	21.11 (3.8)	40.05 (7.0)*	24.31 (5.5)*	36.76 (4.8)	22.41 (4.8)	0.89
total frontal	163.40 (28.3)	176.44 (28.9)	180.90 (35.2)*	191.51 (37.1)	170.46 (32.2)	182.53 (33.0)	0.98

Note. *significant sex × region interaction ($p < 0.05$).

Frontal cortical volumes - a methodological comparison

To enable a comparison between the two volumetric methods, several of the manually traced frontal areas were merged to match the four semi-automatically measured regions ('Talairach boxes') as described in Table 6.2. Left and right regional volumes were combined. Pearson product-moment correlations between the volumes as measured with each of the two methods were calculated. A high correspondence was found between the

manual and semi-automatic method for the frontal cortex as a whole (r = 0.98, Table 6.3). Equally, the correlations between both methods within the four large subregions were adequate, ranging from 0.85 (orbital frontal) to 0.93 (lateral frontal).

As can be seen in Fig. 6.4a-d, the semi-automatically measured volumes of all regions were smaller (frontal pole) or larger (other regions) than the manually traced volumes. The fact that the correlations nevertheless were high suggests that the volumes differed in a systematic fashion.

Effects of age on the frontal cortical volumes

The age effects will first be described for the manual tracing method, followed by the results of the semi-automatic ('Talairach boxes') approach. Age accounted for a considerable part of the variation in all of the manually determined frontal cortical volumes (Table 6.4), ranging from 18% (frontal pole) to 44% (inferior frontal). To investigate whether the frontal volume decreases were disproportional, i.e. to adjust for the fact that age-related volume losses also occur in other parts of the brain, analyses were repeated, controlling for the total brain volume. It was found that, after correction, older age was significantly associated (p < 0.01) with smaller dorsolateral and inferior frontal, ventral medial, and lateral orbital frontal volumes, but not with smaller volumes of the anterior cingulate, frontal pole and precentral gyrus. Although there were significant differences between males and females in regional frontal volumes (Table 6.3), no sex × age interactions were found.

Table 6.4. Explained variance (R^2) of age on frontal cortical volumes (manual tracing method), uncorrected and corrected for global decreases in brain volume.

	age, uncorrected for brain volume	age, corrected for brain volume
anterior cingulate	0.30*	0.03
dorsolateral frontal	0.39*	0.09*
inferior frontal	0.44*	0.15*
ventral medial	0.40*	0.13*
lateral orbital	0.41*	0.08*
frontal pole	0.18*	0.00
precentral gyrus	0.20*	0.01

Note. *p < 0.01.

To compare the two volumetric methods, analyses as described for the manually traced frontal volumes were repeated with the semi-automatic method, using the four frontal regions specified in Table 6.2 (Fig. 6.4a-d, Table 6.5). As with the manual tracing method, age was strongly associated with lateral frontal volumes. Differences between the two volumetric methods are clearly noticeable, however. In contrast to the manual tracing approach, the semi-automatic method showed a lack of disproportional age effects on the volume of the orbital frontal cortex, whereas a significant disproportional age effect became apparent on the volume of the anterior cingulate cortex.

Table 6.5. Explained variance (R^2) of age on frontal cortical volumes (comparison of the manual tracing and semi-automatic 'Talairach boxes' method), uncorrected and corrected for global decreases in brain volume.

		age, uncorrected for brain volume	age, corrected for brain volume
anterior cingulate	Talairach	0.49*	0.11*
	Manual	0.30*	0.03
lateral frontal	Talairach	0.40*	0.09*
	Manual	0.45*	0.12*
orbital frontal	Talairach	0.24*	0.01
	Manual	0.47*	0.10*
frontal pole	Talairach	0.22*	0.01
	Manual	0.18*	0.00
total frontal	Talairach	0.42*	0.07*
	Manual	0.42*	0.07*

Note. *$p < 0.01$.

Effects of age on gray matter assessed with voxel-based morphometry

The association between age and regional gray matter volume was also investigated with a voxel-based linear regression analysis, resulting in a 3-D *t*-statistic map. In this paper, we will focus on the results for the frontal lobes. Significant age-related decreases in gray matter density ($t < -5.0$, $p < 0.01$, corrected) were found throughout the frontal cortex. The highest associations with age ($t < -8.0$, Table 6.6) were found within the anterior cingulate, the lateral orbitofrontal area predominantly in the right hemisphere, and within the region of the inferior frontal cortex bilaterally, extending into the insula. The largest clusters were located in the cingulate and lateral frontal regions.

Table 6.6. Results of the voxel-based morphometry analysis: negative associations ($t < -6$; $p < 0.001$) between frontal gray matter density and age.

cortical region	Brodmann area	X	Y	Z	*t* value
frontal pole left	10	21	55	-9	-6.76
	10	30	55	15	-6.37
lateral orbital left	47	31	34	-12	-7.87
lateral orbital right	47	-28	33	-14	-9.00
anterior cingulate	24/32	1	35	19	-8.93
	24/32	-6	31	40	-8.30
	24/32	1	17	-11	-8.08
dorsolateral frontal left	10/46	47	42	-1	-6.37
	9	19	29	44	-6.81
	9	54	18	26	-8.22
inferior frontal left	44/45	52	22	1	-8.44
dorsolateral frontal right	9	-54	-15	25	-6.10
inferior frontal right	44/45	-44	21	-2	-8.01

Note. X, Y, Z are the coordinates in Talairach space; *t* value is the peak value.

DISCUSSION

Comparison of the manual and semi-automatic volumetric method

In this study two volumetric approaches to measure frontal cortical subregions were compared. Guided by knowledge about the cytoarchitecture and connectivity within the frontal lobes (Groenewegen and Uylings, 2000; Uylings et al., 2000a), seven frontal cortical regions were manually outlined in each hemisphere: precentral gyrus, inferior frontal gyrus, dorsolateral prefrontal, anterior cingulate, ventral medial region, orbital region, and frontal pole. This method proved to be highly reliable and reproducible in measuring the volume of these frontal subregions. However, this approach was very labor-intensive (approximately 10 hours per brain). This makes such an approach rather unattractive for the analysis of datasets involving large numbers of subjects. For that purpose, a second, semi-automatic method (Subramaniam et al., 1997), based upon the Talairach coordinate system (Talairach and Tournoux, 1988), was used to determine frontal cortical volumes. Four regions were distinguished using this approach: lateral prefrontal, orbital frontal, anterior cingulate and frontal pole. Application of this method took less than 15 minutes per brain, and the reproducibility was perfect. Correlations between the total and regional frontal cortical volumes as measured with both volumetric methods were high.

The definition and number of functionally distinct macroscopic regions within the brain remain, to a certain extent, uncertain. Therefore, a somewhat crude subdivision may be just as accurate as a more detailed and anatomically correct parcellation in determining a relation with factors such as age. To test this, both volumetric methods were used to examine age-related changes in regions of the frontal lobe gray matter volume.

With the manual method, age was found to explaine almost half (42%) of the individual variation in gray matter volume of the frontal lobes as a whole. This age effect was significantly disproportional relative to volume changes within the whole brain. This is in accordance with studies showing that particularly the frontal lobes are affected by increasing age (Coffey, 1993; Cowell et al., 1994; Raz et al., 1997; Salat et al., 1999; Tisserand et al., 2001). Furthermore, the present study is one of the first to show on a detailed scale that there are regional differences in the amount of age-related frontal atrophy. For example, the least volume losses were found in the precentral and frontal polar regions. The fact that volume decrease was only moderate in the precentral area is not surprising, given the evidence that primary sensory and motor areas are less vulnerable to age influences than association areas (Kemper, 1994). The finding that volume losses were also limited in the region of the frontal pole has not been reported before. Remarkably, several older studies have found the largest decreases in neuronal densities in exactly these two frontal regions (Haug, 1985; Kemper, 1994). However, the correctness of these older cell counting methods has been criticized in recent years: age-related neuronal loss appears to be only mild (Uylings et al., 2000b). Cortical atrophy is now thought to be the result of cell shrinkage rather than a decrease in neuronal number (Kemper, 1994; Uylings et al., 2000b).

When comparing the two approaches with respect to age effects, the results of the semi-automatic 'Talairach boxes' method were highly similar to those of the manual tracing approach for the frontal cortex as a whole. However, for the frontal subregions the results were largely dependent on the method applied. That is, despite equal preprocessing steps, and despite the fact that the data from both methods were highly correlated, there were clear differences in age effects on frontal cortical subregions. These differences were the most striking for the anterior cingulate and orbitofrontal regions. With the manual tracing method the age effects on the volume of the anterior cingulate were relatively small, whereas they were outspoken with the semi-automatic method. Conversely, the orbital region was the most severely affected region according to the manual tracing method, and the least affected according to the semi-automatic approach. A possible explanation is that part of the orbital frontal cortex was included in the anterior cingulate Talairach boxes. All boxes are complementary, hence when a frontal subregion is excluded from one Talairach region, it automatically belongs to the

neighbouring region. The volume of the anterior cingulate region was indeed larger according to the semi-automatic approach than when calculated with the manual method. Furthermore, visual inspection of the images (by overlaying the Talairach boxes on the manually outlined regions) pointed out that the anterior cingulate boxes included tissue from the ventral medial cortex, and to a lesser extent, the medial wall of the superior frontal gyrus, which is part of the dorsolateral region. Due to the size of the boxes it was impossible to be more precise in determining the borders between regions.

Another explanation for the discrepancy between the methods with respect to age effects, could be that more variance was present in the data of one of the two approaches. Indeed, the standard error tended to be larger for the semi-automatically measured frontal volumes than for the manually traced volumes.

The results of the semi-automatic 'Talairach boxes' method are consistent with our previous findings (Tisserand et al., 2001), i.e. age-related volume decreases are strongest in the medial frontal cortex. This is evident, because in that study the same subjects were examined with the same method (with some small adjustments). It also shows that our current attempt to match the 'Talairach regions' as closely as possible to the manually defined anatomical regions did not change the findings with respect to age.

Our manual measurements are in agreement with the study by Raz et al. (1997), pointing to a disproportional volume decrease in the orbitofrontal cortex. By contrast, a recent study (Salat et al., 2001) using a manual volumetric approach found a relative preservation of the orbitofrontal cortex as compared to three other frontal regions. However, the subjects they studied were older than those in the present study and those of Raz et al. (1997). Furthermore, the anterior cingulate region could not be reliably measured in that study and was therefore excluded from the analysis. The results from these studies can therefore not easily be compared.

To conclude, when manual measures are taken as anatomical reference, the semi-automatic 'Talairach boxes' approach does not seem to be accurate enough to quantify brain volumes, unless the regions are as large as complete lobes (as in Andreasen et al., 1994; Goldszal et al., 1998; Resnick et al., 2000).

Comparison of volumetric methods and voxel-based morphometry

To consider manual delineation of cerebral subregions as the 'gold standard' might be debatable. Despite the high ICCs in the present study, manual demarcation of regions often goes at the expense of reproducibility (e.g., Salat et al., 2001), particularly in regions where anatomical borders are ill-defined, such as the highly convoluted frontal cortex. Furthermore, manually outlining cortical regions is a time-consuming operation. Alternatively, the effect of age on gray matter volume can be investigated with voxel-based morphometry. The advantage of such an approach is that it is completely

automated, and it allows determination of changes within highly local regions of the brain. However, VBM can only provide a qualitative, not a quantitative measure of brain volume. In the present study, the strongest associations between frontal gray matter density and age were found within the anterior cingulate and inferior frontal cortex. These findings coincide with the results of two other studies that used VBM to study age effects (Good et al., 2001; Goto et al., 2001).

However, there is clearly a discrepancy between the findings of our VBM and volumetric analyses. One explanation could be that the manually determined frontal cortical regions were still too large to adequately capture focal age-related decreases in local volumes. For instance, the VBM analysis revealed that within the anterior cingulate region the effect of age was larger for the dorsal part than for the ventral part. Another explanation for the differences between the methods is a lower sensitivity of VBM to detect changes in brain areas with large anatomical variability. It has been shown that even major sulci vary considerably in terms of continuity and branching (Ono et al., 1990; Thompson et al., 1996; Thompson et al., 2001). This variability (even after nonlinear warping and smoothing, e.g., Uylings et al., 2000a; Bookstein, 2001; Davatzikos et al., 2001) leads to false-negative results (i.e., a failure to detect true effects) and may have influenced our VBM results. For instance, consistent with other voxel-based studies (Good et al., 2001; Goto et al., 2001) the greatest age-related reductions in gray matter density were found near the inferior frontal and cingulate sulci, which have a relatively fixed position in the brain (Ono et al., 1990; Paus et al., 1996; Thompson et al., 2001). On the other hand, in the dorsolateral prefrontal cortex, where the folding pattern is highly variable across individuals (Ono et al., 1990; Thompson et al., 2001), virtually no age-related decrease in gray matter density was found, similar to the results obtained by Good et al. (2001) and Goto et al. (2001). These results differ from volumetric studies, which have consistently found marked reductions in gray matter volume of the dorsolateral prefrontal cortex in aging (present study; Raz et al., 1997; Tisserand et al., 2001).

To conclude, in this study it was shown that age-related decreases in regional frontal cortical volumes are differential, but the age effects are dependent (at least partially) on the method applied. Over the past few years, a lot of effort has been put in the development of more automatic methods to measure specific brain regions (Collins et al., 1995; Goldszal et al., 1998; Kabani et al., 2001). However, despite the clear advantages of automatic and voxel-based approaches (quick, perfectly reproducible, applicable to large datasets), the current findings suggest that, at present, the most accurate method is still an anatomically based manual tracing one.

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7

AGE-RELATED DIFFERENCES IN BRAIN ACTIVITY AND THE RELATION WITH PERFORMANCE DURING WORD PROCESSING: A FUNCTIONAL MRI STUDY

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ABSTRACT

Aging is accompanied by a reduction in the capacity to process incoming information, especially when the task requirements are high. To investigate the neural basis of this decline, functional magnetic resonance imaging (fMRI) was applied to compare brain activity in 12 young (25 ± 1 years) and 11 old (65 ± 1 years) adults while they were processing words. Four different conditions were used: two conditions involving superficial processing (involving a perceptual or linguistic operation), and two involving strategic processing (involving a semantic operation or intentional learning). Although in both age groups, responses were slower and less accurate during the intentional learning condition than during the three other conditions, the difference in performance between the groups was not significant. However, at a subsequent recognition test the young subjects performed better than the old. With respect to their brain activity, a difference between young and old adults was found during intentional learning. Both groups activated various posterior cortical areas during the learning condition, but only young subjects activated additional regions in the frontal cortex. Moreover, there was an age-related difference in the associations between performance and activity. Whereas in young subjects, increased activity was mainly associated with shorter reaction times, in older subjects the reverse was true. These performance associations were located mainly in posterior brain regions in the young subjects, and both in frontal and posterior cortical areas in the elderly. The positive association between reaction times and frontal activity in the older adults may be explained as a compensatory mechanism to deal with the task demands in spite of reduced attentional resources.

INTRODUCTION

Aging is accompanied by a large number of changes in most cognitive domains (e.g., Jolles, 1986; Verhaeghen et al., 1993; Moscovitch and Winocur, 1995; Parkin and Java, 2000; Zacks et al., 2000). It has been suggested that age-related decrements in attentional resources or working memory capacity contribute substantially to this cognitive decline in older adults (Craik and Byrd, 1982; Verhaeghen et al., 1993; Kirasic et al., 1996; Park et al., 1996; Zacks et al., 2000). This is particularly evident in cognitive operations that put a high demand on the available resources, such as tasks requiring executive control or processing strategies (e.g., Craik, 1983, 1986; Jennings and Jacoby, 1993; Moscovitch and Winocur, 1995; Anderson et al., 2000; Reuter-Lorenz et al., 2001). Older adults have been reported to benefit substantially from contextual support, that is, externally presented cues or task strategies (e.g., Craik, 1986). It has been suggested that attentional

resources are not necessarily reduced, but they may be inadequately utilized by elderly individuals (e.g., Logan et al., 2002). Contextual support can be manipulated by providing specific task instructions. For instance, memory for words is better when people are explicitly instructed to try to remember the items (intentional learning) than when they are engaging in a less elaborate processing strategy, such as making a perceptual judgment (Craik, 1983, 1986).

On the neural level, placing a high demand on working memory capacity and attentional resources of young individuals has been associated with increased activity in the lateral PFC, anterior cingulate, and posterior parietal cortex (Kapur et al., 1994; Rypma et al., 1999; Jansma et al., 2000; D'Esposito, 2001). Older individuals have been reported to show a reduced level of activity in these regions during demanding cognitive tasks (e.g., Madden et al., 1996; Grady et al., 1999; Anderson et al., 2000). However, several studies have found the opposite, i.e., higher activity in older adults in comparison to young during task performance, especially in the PFC (Grady et al., 1994; Madden et al., 1999; Anderson et al., 2000). Age-related decreases in prefrontal activity have been suggested to be the result of a loss in neural efficiency (Cabeza et al., 1997b; Esposito et al., 1999; McIntosh et al., 1999). The finding of increased activity has been attributed to a compensatory mechanism (e.g., Grady et al., 1994; Cabeza et al., 1997a; Grady, 2000; Mencl et al., 2000), for instance, in an attempt to cope with the task demands (Madden et al., 1999; Tisserand and Jolles, 2003). However, interpreting differences in activation patterns between young and old individuals is not always straightforward. For example, in young adults, decreases in (frontal) activation have been linked to processing efficiency. That is, when less attentional control is required for task performance, cortical activity is reduced (Raichle et al., 1994; Garavan et al., 2000; Jansma et al., 2001). Hence, a high level of brain activity does not necessarily imply optimal efficiency. The meaning of age-related differences in activation may be understood better by looking at brain-behavior associations directly, namely by examining the relation between neural activity and performance. Reaction times (RTs) can be used to operationalize performance. It can be argued that an increase in brain activity correlated with a decrease in RTs (when accompanied by high levels of accuracy) indicates that this activation is advantageous for task performance. Conversely, activity associated with longer RTs in combination with high accuracy levels suggests that the task is performed at the cost of processing speed, i.e., more effort (Madden et al., 1999; Tisserand and Jolles, 2003). One study showed that in young participants, increases in activity within lateral frontal as well as occipital and medial temporal regions were associated with better performance, indicated by shorter reaction times, whereas in older adults increased activity in these areas was related to poorer performance, i.e., longer RTs (Grady et al., 1998a). This suggests that these regions are used more efficiently by young individuals. However, in several other studies

(Rypma and D'Esposito, 2000, 2001; Reuter-Lorenz et al., 2001) the reverse effect was found, i.e., a positive association between activity in the lateral PFC and RTs in young adults, and a negative association in old subjects. These authors argued that higher PFC activity was associated with improved performance (i.e., shorter RTs) in old but not young adults because the former recruit executive processes (which are supported by the PFC) at lower levels of task demand. These contradictory results suggest that the relation between brain activity and performance is quite complex and requires more research.

Furthermore, it is not yet clear whether these regional age-related differences in activation reflect a local neural deterioration or whether they are linked to a more global reorganization of the network involved in performing a task. Most studies have focused on regional activation differences between young and older adults during cognitive task performance, without considering functional interactions between those brain regions. There is growing evidence that age-related differences in performance are accompanied by a functional reorganization of the brain areas involved in these cognitive processes (Cabeza et al., 1997b; Della-Maggiore et al., 2000). Therefore, multivariate statistical approaches, in which differences in patterns of brain activity are examined, may be more appropriate for the analysis of functional imaging data than univariate methods which separately consider each individual voxel. An example of such a multivariate method is Partial Least Squares, PLS (McIntosh et al., 1996).

The goal of this study was to examine the effect of age on brain activity during a word processing task. The hypothesis was that providing specific task instructions would reduce differences between young and old during later recognition, but would nevertheless be associated with age-related differences in brain activity patterns during the actual word processing. The nature of the task instructions was varied in two ways: by instructing the subjects to make a certain judgment about the stimuli (perceptual, linguistic or semantic), and by explicitly asking subjects to memorize words. It was hypothesized that an age-related difference in brain activity would be found between strategic processing of words (i.e., semantic judgments) and less elaborate processing strategies (i.e., perceptual or linguistic judgments). Furthermore, it was expected that explicitly asking subjects to memorize words would lead to different patterns of brain activity in young and old adults. Age-related changes in brain activity can encompass a difference (increase or decrease) in the use of task-related regions also utilized by young adults, as well as the recruitment of additional brain areas. Furthermore, the relation between brain activity and performance was considered. Performance was specified on the basis of RTs during the word processing task. It was hypothesized that brain activity would be employed more efficiently by young adults than by older adults. Hence, it was expected that in young subjects, the relation between RTs and brain activity would be negative, whereas in older subjects it would be positive.

METHODS

Subjects

Twenty-three healthy volunteers participated in this study: 12 young (aged 25.1 ± 1.0 years), and 11 older adults (aged 64.6 ± 1.2 years). Care was taken to reduce within-group variance (with respect to age, educational background and health status) as much as possible. All participants were right-handed males with an educational level ranging from medium to high vocational training. They were screened using a questionnaire and an interview. Exclusion criteria were a history of medical, neurological, or psychiatric illnesses; medication which could influence central nervous system functioning; diastolic blood pressure > 95 mmHg; habitual use of recreational drugs or alcohol abuse. Subjects were recruited by advertisements in local newspapers. All of them gave written informed consent before participation. The study was approved by the Medical Ethics Committee of the Academic Hospital Maastricht.

MRI procedures

Imaging was performed on a 1.5 Tesla Philips ACS-NT scanner (Philips Medical Systems, Best, The Netherlands). Minimization of head motion was accomplished by using two foam cushions and a tape across the subject's forehead. The functional scan session consisted of a single shot multiple slice T_2^* sensitive echo planar imaging (EPI) sequence, sensitive to the blood oxygenation-level-dependent (BOLD) contrast. Parameters were TR=3.5 sec, TE=40 msec, flip angle 90°, matrix dimension 64 □ 64, 32 contiguous slices and an isotropic voxel size of 3.5 mm. Before the acquisition of the functional images started, two dummy full brain scans were acquired. For anatomical reference, a 3D T_1 weighted fast-field echo scan was acquired with parameters TR=11 msec, TE=3.5 msec, flip angle 90°, matrix dimensions 256 □ 256, 150 continuous slices and an isotropic voxel size of 1 mm.

Task design

The complete experiment was divided in two sessions. First there was a practice session, which was followed by the actual scan session approximately one week later. During the practice session, participants received thorough instructions and were presented with the word processing task once (see below) on a laptop computer. None of the words that appeared in this practice phase were used in the actual experiment. Furthermore, during this practice session, blood pressure was measured. Two subjects were excluded from further participation in the experiment, one due to hypertension and one based upon his poor performance. They were replaced by two other participants. During the actual scan session subjects again received the task instructions. Stimuli were observed as computer

controlled projections on a semi-transparent screen positioned approximately 100 cm from the bore of the magnet. Subjects viewed the stimuli via a mirror attached to the head coil. Magnet compatible glasses were worn when necessary to correct vision. Two older subjects were excluded from the scan session due to claustrophobia, and one older subject was excluded because he failed to perform the task. New participants were recruited to replace them.

The stimuli used in the experiment were mono- or bi-syllabic words, varying in length between 5 and 7 letters. They all appeared centrally on the screen (Times new Roman, 50 pt) in yellow against a black background. The E-prime software was used for the stimulus presentation (Schneider et al., 2002). Words were printed either in lowercase or uppercase letters. There were four task conditions. In the first condition (CASE), subjects were asked to make a decision about the case of the letters. In the second (LETTER), they had to indicate whether or not the words contained the letter E. In the third condition (CATEGORY), they were asked whether the words referred to a living or non-living item. In the last condition (LEARN), subjects again had to make a living/non-living decision, but were also instructed to memorize the words, because they would be tested on these items (intentional learning). The complete task consisted of two runs. Each run contained 12 blocks, in which all conditions were repeated three times. In each block, 16 stimuli were presented, preceded by the task instruction. This instruction was shown for 5 sec, followed by a 'countdown' screen (5.5 sec) showing a decreasing number of asterisks indicating the time remaining before the start of the task. Subsequently, the stimuli were shown for 1 sec with an inter-stimulus interval of 2 sec. A black screen, presented for 3 sec, completed each block. Hence in total, each block lasted 45.5 sec. All word lists were matched for word frequency, word length, and they all contained an equal number of uppercase, 'E', and living items. The lists were counterbalanced across the four conditions with only the task instructions differing. This was done in order to prevent possible version effects on performance or brain activity. Subjects responded with either their left or right index finger using two response buttons. Right button press always indicated 'yes', left button press 'no'. At the end of each run, subjects were asked to recall as many of the words from the intentional learning condition as they could.

In the same scan session, subjects also performed an old/new recognition task. Old words originated from the CATEGORY (i.e., living/non-living) and LEARN (i.e., living/non-living plus memorizing) conditions. The task consisted of 52 old words (26 from the CATEGORY condition, 26 from the LEARN condition) and 52 new words. The instruction and countdown screens were as described before. Stimuli were shown for 2 sec, with an inter-stimulus interval of 12.25 sec. Subjects responded with a left button press when words were new and with a right button press when words were old. The

fMRI data from this part of the study will not be described in the present paper. Age effects on memory performance (i.e., accuracy) during this recognition task were examined, to explore the influence of task instruction at the time of word processing on later performance.

Image analysis

Prior to statistical analysis, images were preprocessed using the SPM99 software (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab (Mathworks, Natick, MA, USA). All subjects' images were realigned to the mean image (head movement was < 3 mm in all cases) and resliced using a sinc interpolation method. Subsequently, images were spatially transformed, by bilinear interpolation, to a standard EPI template using 12 non-linear basis functions (with resulting voxel sizes of 4 × 4 × 4 mm), and smoothed with an 8 mm full-width half-maximum Gaussian filter. The effect of any global differences in fMRI signal intensity between individual subjects was removed by calculating a ratio between the signal in each particular voxel and the mean signal across all voxels for each subject within each scan.

Statistical analysis

Reaction times and accuracy measures were analyzed with repeated measures ANOVAs, with the 4 encoding conditions as within-subject factors, and age group as the independent factor. When cognitive performance in a block was approaching chance levels (i.e., less than 10 out of 16 correct responses), the block in question was excluded from the analyses. This procedure was required in only 8 out of a total of 552 blocks, i.e., 1.4% of the cases.

The fMRI data were analyzed using Partial Least Squares (PLS). The rationale behind this approach has been described in detail before (McIntosh et al., 1996; Grady et al., 1998a) and therefore only a brief account will be provided here. PLS is a multivariate method that operates on the covariance between the signal within brain voxels and the experimental design to identify a limited number of components (so-called Latent Variables, LVs) that optimally relate the two. A difference with univariate methods is that, instead of considering each voxel separately, PLS focuses on the brain as a whole and is thus able to detect brain-wide systems that covary with the experimental procedure. No statistical correction for multiple comparisons at the voxel level is necessary because the statistical assessment is done at the image level (see below). Each LV represents an experimental effect (e.g., a main effect of the task condition, or an interaction of condition and group, Grady et al., 1998a), and identifies both the pattern of condition differences and the brain voxels showing this pattern. Saliences (i.e., weights) are calculated for each brain voxel and indicate how much that voxel

contributes to a particular LV. A salience can be positive or negative, depending on whether that voxel shows a positive or negative relation with the pattern identified by the LV. Multiplying the salience for each voxel by the signal in that voxel and summing the product across the image gives a score for each subject on a given LV (e.g., Grady et al., 1998a), which indicates the degree to which the pattern of activity identified by the LV is expressed in each subject in each condition. Plotting these scores across conditions shows how patterns of brain activity associated with a particular LV are related to the experimental design. Which brain areas most strongly participate in a certain LV can be displayed by means of singular images.

Two analyses were carried out, both within and across the groups, to investigate (1) the effect of task condition on brain activity patterns, and (2) the relation between activity and cognitive performance. The first PLS analysis specified the relation between task condition and brain activity patterns. Mean images were calculated for each condition. Another PLS analysis was performed to examine the covariance between the behavioral measures and the brain activity patterns (Schreurs et al., 1997; Grady et al., 1998a). To do this, the mean RT per condition was calculated for each subject. RTs were then correlated across subjects within condition for both groups. LVs from this analysis reflect similarities and/or differences in the brain-behavior correlations across conditions and groups. Both young and old subjects performed the task nearly perfectly (i.e., ceiling effect), and due to this restricted range of values, it was not appropriate to use the accuracy measures for this brain-behavior analysis.

For both analyses, the statistical significance of the LVs was assessed using a permutation test, which was repeated 500 times (Edgington, 1980). In this procedure, the scans are randomly reordered to calculate the probability of each LV having occurred by chance. Furthermore, to determine the reliability of the saliences for the brain voxels characterizing each pattern, the saliences were submitted to a bootstrap estimation of the standard errors (100 samples, Efron and Tibshirani, 1986). Voxels with a bootstrap ratio (salience/standard error, roughly equivalent to *Z* scores, Grady et al., 2000) >= 3.0 on a given LV were considered to make a reliable contribution to that LV. Clusters of at least 10 contiguous voxels are reported here.

RESULTS

Performance data

As can be seen in Table 7.1, accuracy (i.e., percentage correct responses) for all conditions was high for both age groups, and there was no group difference on these measures. However, there was a significant main effect of condition on the accuracy measures ($F = 34.35$, $p < 0.0001$).

Table 7.1. Performance on the word processing task of the young ($n = 12$) and old ($n = 11$) subjects.

Condition	% correct		Reaction times (msec)	
	Young	Old	Young	Old
Case	96.2 (4.3)	95.6 (3.7)	552.5 (70.5)	615.0 (115.7)
Letter	96.1 (2.9)	95.8 (2.3)	612.8 (54.3)	680.1 (86.8)
Category	90.0 (3.5)	90.7 (2.9)	685.2 (45.3)	758.4 (81.5)
Learn	88.2 (6.0)	90.6 (4.0)	738.8 (48.4)	781.5 (97.0)
Recogn. Category	72.1 (12.3)	59.1 (12.4)*	-	-
Recogn. Learn	78.5 (17.5)	63.6 (13.8)*	-	-

Note. Values are mean ± SD. Recogn. Category/Learn: accuracy of recognizing stimuli from the CATEGORY/LEARN encoding conditions.

*significant group effect ($p < 0.05$).

With respect to the RTs, there was a main effect of condition ($F = 162.09$, $p < 0.0001$), while the effect of group approached significance ($F = 4.04$, $p = 0.057$). Group × condition interactions were not significant for either the accuracy or the RT data. With respect to subsequent memory performance (Table 7.1), subjects were more accurate at recognizing words coming from the LEARN condition than those coming from the CATEGORY condition ($F = 5.42$, $p < 0.05$). The older individuals' performance was significantly poorer than that of the young on both recognition tasks ($F = 6.55$; $p < 0.05$). The interaction between condition and group was not significant.

Table 7.2. Local maxima across the groups, with differential activity in the intentional learning condition.

Region	BA	X	Y	Z	BR Young	BR Old
		Intentional learning > Other conditions				
Frontal lobe	**L46**	**-32**	**44**	**0**	**4.26**	**-0.83**
	L47	**-48**	**36**	**-8**	**4.32**	**-1.63**
	L4	**-44**	**-4**	**40**	**3.67**	**-1.60**
	M32	**8**	**24**	**36**	**7.56**	**-2.57**
Temporal lobe	L37	-56	-52	-28	4.43	4.32
Parietal lobe	L39/40	-52	-60	40	6.16	4.87
Occipital lobe	M7	-12	-68	44	5.96	4.89
Cerebellum	**R**	**48**	**-60**	**-40**	**7.20**	**-1.31**
	R	12	-88	-40	7.20	4.52
	M	0	-40	-44	2.34	4.30
		Other conditions > Intentional learning				
Frontal lobe	R6/8	24	20	56	-3.65	-5.72
	M9	8	56	28	-5.55	-3.73
	M24	**-8**	**8**	**32**	**-5.99**	**-0.86**
	M24	-16	-8	-32	-3.31	-4.16
Temporal lobe	L22/42	-60	-24	12	-7.72	-3.54
	L22/42	**-68**	**-24**	**12**	**-7.71**	**-0.49**
	R22	**56**	**4**	**0**	**-7.22**	**0.50**
	R22/42	64	-24	8	-7.09	-3.78
Parietal lobe	**M23/31**	**0**	**-48**	**28**	**-4.16**	**0.59**
Occipital lobe	R19	28	-80	32	-6.63	-3.11
	M17	0	-72	8	-6.74	-4.38
Amygdala	**R**	**24**	**-4**	**-16**	**-5.89**	**1.91**

Note. Regions reported here have across-group bootstrap ratios (BR) of > 3 and cluster sizes > 10; BRs reported here are derived from the within-group analysis. Regions with a significant group condition interaction are presented in bold. X, Y, Z are coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance within a given cluster.

BA: approximate Brodmann areas, L: left, R: right, M: midline.

Correlations between fMRI signal and task condition

Two LVs were significant when comparing condition-related activity across groups (Fig. 7.1). Both young and old subjects displayed a pattern of brain activity in which the greatest difference was between the LEARN condition and the other three conditions (Fig. 7.1 LV1, Fig. 7.2, Table 7.2). Regions that were associated with the LEARN condition in both groups were the left inferior temporal gyrus (Brodmann area [BA] 37), left posterior parietal cortex (BA 39/40), precuneus (BA 7), and a region in the cerebellum extending from the midline to the right lobule. Regions where activity was lower in the LEARN condition than in the other conditions were located in the frontal lobes (medial bank of the dorsolateral PFC [BA 9], anterior cingulate [BA 32], and regions in the posterior part of the lateral PFC bilaterally [BA 5 and 6/8]), in the superior temporal gyrus bilaterally (BA 22/42), and medial and right occipital regions (BA 17/18/19).

The other LV showed a condition group interaction, with the strongest effect in the LEARN condition (Fig. 7.1, Table 7.2). The young subjects showed higher activity than the old during the LEARN condition relative to the other conditions in various frontal regions (left dorsolateral [BA 46] and ventrolateral [BA 47] PFC, anterior cingulate [BA 32], and left precentral gyrus [BA 4]), and in the right cerebellum. Young subjects had higher activity than old during the first three conditions relative to LEARN in the anterior (BA 24) and posterior cingulate (BA 23/31), superior temporal gyrus bilaterally (BA 22/42), and right amygdala.

Correlations between fMRI signal and performance

In the behavioral PLS (relating the brain activity patterns to RTs), there were two significant LVs, one associated with the RTs in the young group, and the other with the RTs in the old group (Fig. 7.3). Fig. 7.4a and b show the regions where a significant correlation was found with performance in the young and old groups, respectively. The accompanying Talairach coordinates are listed in Table 3.

Within each task condition, there was a strong positive relation between fMRI signal and RT, both in the young and old groups (ranging between $r = 0.75$ and 0.94, data not shown). However, the areas that showed a correlation with performance were markedly different between the two groups. In young subjects, longer RTs were associated with higher activity in regions in the temporal lobes and left ventrolateral PFC, and with less activity in extensive areas in left and right posterior lobes (occipital and posterior parietal cortex). In old subjects, RTs were positively correlated with activity in a number of frontal regions (orbital and lateral PFC and anterior part of the insula bilaterally, and anterior cingulate), as well as in various posterior cortical regions. The only negative associations between RTs and activation patterns were found in the bilateral temporal poles, left posterior parietal cortex, and cerebellum.

Table 7.3. Regions in which brain activity was significantly correlated with performance.

Region	BA	Young				Old			
		X	Y	Z	BR	X	Y	Z	BR
		Positive correlation with RT							
Frontal lobe	L10					-24	56	24	4.44
	L11/47	-36	16	-20	8.71	-20	48	-16	4.70
	L9					-40	24	36	3.93
	L6					-28	4	40	9.22
	R4					36	-8	40	11.49
	M32					-8	28	24	4.09
Temporal lobe	L22/42	-48	16	20	5.22				
	L37					-56	-44	-4	8.82
	R22	32	4	-4	4.52				
	R20/21	36	4	-28	6.55	44	-8	-36	4.67
	R22/42	60	-28	16	4.08				
	R21					52	-32	-4	7.58
Parietal lobe	L40					-64	-48	24	4.99
	L7					-28	-52	56	12.58
	R7					24	-64	40	5.32
Occipital lobe	L20	-36	-20	-28	6.85				
	R19					48	-80	12	8.48
Insula	L					-40	8	4	6.59
	R					40	16	0	17.09
Amygdala	L					-20	4	-12	17.43
	R					28	-4	-16	17.02
		Negative correlation with RT							
Frontal lobe	L4	-24	-16	56	10.92				
	R6	28	-4	64	4.48				
	R4	20	-28	48	16.08				
Temporal lobe	L38					-32	16	-48	5.70
	L37	-48	-60	4	9.41				
	R38					40	20	-48	4.45
Parietal lobe	L7					-28	-64	64	6.98
	R7/40	52	-56	32	11.27				
Occipital lobe	R37	36	-56	-8	16.39				
	R18	16	-88	12	5.84				
	R18	36	-96	-8	11.12				
Cerebellum	R					16	-40	-40	6.33

Note. Regions reported here have across-group bootstrap ratios (BR) of > 3 and cluster sizes > 10; BRs reported here are derived from the within-group analysis. X, Y, Z are coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance within a given cluster.

BA: approximate Brodmann areas, L: left, R: right, M: midline.

DISCUSSION

The present study investigated whether brain regions associated with processing of words differed as a function of age. The clearest age-related difference was that young but not older adults significantly activated regions in the frontal lobes during intentional word learning relative to the other conditions. Furthermore, the relation between brain activity and task performance (i.e., reaction times, RTs) within the two groups were differentially related to performance. Whereas RTs were positively correlated with frontal activity in the old group, correlations (both positive and negative) were mainly found with posterior cortical regions in the young group.

Task-related brain activity

Two patterns were expected: one showing an effect of strategic (elaborate) versus more superficial stimulus processing, and one distinguishing between intentional learning versus stimulus processing without the intention to memorize the items. However, only the latter pattern was observed. Both groups displayed a similar pattern of brain activity that differentiated between the intentional word learning and the other conditions. Although there were many similarities between the young and older adults' activation patterns, differences were also found between the age groups, most notably in the frontal lobes. In both age groups, word learning was associated with increased activity in the left inferior temporal and posterior parietal cortex, and in the cerebellum. Even though this main effect of condition (learning versus other) was significant both within and across the groups, the accompanying pattern of brain activity was less striking in the older compared with the young group. This finding of a general reduction of task differences in brain activity in older adults is consistent with previous reports (e.g., Grady et al., 1995, 1999; Madden et al., 1996; D'Esposito et al., 1999; Anderson et al., 2000). In addition, activity was observed during word learning in the young but not old subjects in the left dorsolateral and ventrolateral PFC, left precentral gyrus and the anterior cingulate. Activation of these frontal regions during intentional learning has been reported previously in functional imaging studies with young subjects (Kapur et al., 1996; Grady et al., 1998b), as well as an age-related reduction in frontal activity during such tasks (Grady et al., 1995, 1998b; Cabeza et al., 1997a, b; Logan et al., 2002).

With respect to brain regions in which activity was higher in the conditions where intentional word learning was not required, similar areas were found in young and old subjects. These were located in right frontal and occipital areas, bilateral temporal lobes and anterior and posterior cingulate cortex. The activation of temporal lobes and anterior cingulate was significally higher in the young group. In a study by Grady et al. (1999) a similar pattern of higher frontal and cingulate activity during semantic stimulus

processing relative to intentional learning was reported. The present finding of strong posterior cortical activation during the 'non-learning' conditions was not observed in that study. This may have been due to the fact that in our study, a perceptual, linguistic and semantic processing condition were included, while in the study by Grady et al. (1999) the activation was associated with semantic processing only. Therefore, it is not surprising that in the present experiment, 'non-learning' produced greater activity in regions throughout the brain. Contrary to the expectations, no indication was found in the present study for a distinction between elaborate (semantic processing, intentional learning) and superficial stimulus processing (perceptual and linguistic operations). Such a distinction has been reported before in young subjects in a neuroimaging experiment with verbal material (Kapur et al., 1994). However, in another study, the effect was reported to be stimulus-dependent, in that the pattern was only found for pictures and not for words (Grady et al., 1999).

To summarize, an age-related reduction in left frontal activation was found during intentional word learning, while the patterns of brain activation in young and old adults showed a great resemblance during stimulus processing without trying to memorize the items. These results may be interpreted in terms of an age-related reduction in attentional resources or working memory capacity (Craik and Byrd, 1982; Verhaeghen et al., 1993; Kirasic et al., 1996; Park et al., 1996; Zacks et al., 2000). That is, older individuals are just as capable of activating brain regions as young adults, as long as the task does not require complex, self-initiated processing, approaching or exceeding the limits of their processing resources (Anderson et al., 2000; Logan et al., 2002). In this study, participants were instructed to make judgments about particular characteristics of words (i.e., perceptual, linguistic or semantic). Older adults have been reported to benefit substantially from externally presented cues or explicitly formulated task strategies (e.g., Craik, 1986). Possibly because both young and old subjects took advantage of this contextual support, no age differences in activity patterns were found. However, by explicitly asking participants to memorize words (intentional learning) while only a limited time was allowed for elaboration of the stimuli, a high demand was put on the available resources. In the young subjects, this resulted in an increase in activity in frontal regions that have been associated with effortful processing and working memory (e.g., Kapur et al., 1994; Nolde et al., 1998; Rypma and D'Esposito, 1999; Anderson et al., 2000; Cabeza and Nyberg, 2000; Logan et al., 2002). The fact that no such activity was observed in the older participants may imply that the resources, required to perform the task, were no longer available and therefore could not be recruited. Alternatively, it may be that the resources were merely reduced instead of depleted, but were inadequately engaged by the elderly. In order to elucidate this issue, the relation between brain activation patterns and cognitive performance was examined. When a positive association

would be found between performance and frontal activity in the elderly, this would suggest that resources were reduced but could, to a certain extent, still be engaged.

Correlations between brain activity and task performance

In both age groups, reaction times (RTs) were significally longer, and accuracy levels lower, during the intentional learning condition compared with the other three conditions. No interaction was found between performance and age group. Accuracy did not differ between the groups, and old subjects' RTs were only marginally longer than those of the young subjects. These results show that older, cognitively normal individuals are able to perform a word processing task just as good as young subjects. It has been shown before that young and older individuals can equally benefit from contextual support (Park et al., 1990). Indeed, the explicit instruction to memorize the items (intentional learning) resulted in significantly better performance during a subsequent recognition task in both age groups. However, young adults were significantly more accurate at recognizing previously presented words than older adults.

The fact that the older group was just as fast as the young group in their responses during word processing is surprising, given the evidence of age-related slowing (e.g., Salthouse, 1994, 1996; Park et al., 1996). This lack of a group difference may be due to the small sample size. It may also be a consequence of the fact that performance was averaged per condition across blocks. Several other factors may also have contributed to the pattern of results. Selection criteria applied in this experiment were very strict. Subjects were included only when they were optimally healthy (e.g., blood pressure within the normal range, no use of medication influencing the nervous system, no neurological or psychiatric history). This was done because health-related factors have been found to contribute to age-accelerated slowing (Houx et al., 1991; Van Boxtel et al., 1998). As a consequence, the older participants may have been healthier than the subjects in most other aging studies, which possibly explains the lack of age-related differences in performance.

With respect to the brain-behavior associations, a strong correlation was found between RTs and neural activity patterns in all conditions, both in young and old subjects. However, the areas that showed a positive or negative correlation with performance were markedly different between the two groups. In young subjects, longer RTs were positively correlated with activity in regions in the temporal lobes and left ventrolateral PFC, and were negatively correlated with extensive bilateral areas in the occipital and posterior parietal cortex. In old subjects, longer RTs were positively correlated with activity in a number of frontal regions (left orbital and lateral PFC, anterior part of the insula bilaterally, and anterior cingulate), as well as posterior cortical

regions. The only negative associations between RTs and activation patterns were found in the bilateral temporal poles, left posterior parietal cortex, and cerebellum.

In the old subjects, longer RTs were associated with higher activity in the frontal lobes without concurrent task-related activity in these regions. Interestingly, the frontal areas where correlations with RTs were observed in the old subjects, largely coincided with the regions that young subjects recruited during the intentional learning condition. The associations between frontal activity and longer RTs signify that processes relying on activity in these regions take longer to be executed in the old group (e.g., Grady, 2000). The fact that accuracy did not differ between the two groups may imply that these longer RTs reflect a compensatory mechanism (e.g., Grady et al., 1998a; Mencl et al., 2000), that is, extra effort to cope with the task demands at the cost of processing speed (Madden et al., 1999; Tisserand and Jolles, 2003). Furthermore, the observation that widely distributed posterior cortical regions were also positively associated with RTs in the older adults may be interpreted as a reduction in inhibitory control of the frontal lobes (Madden et al., 1999).

An opposite pattern was found for the young and older adults regarding the relation between RTs and posterior parietal activity. In this region, which was activated during intentional learning in both groups, a negative correlation with RTs was found in the young group, whereas the correlation was positive in the old group. This implies that activity in the parietal cortex in the young adults during the intentional learning condition was used more efficiently (i.e., more activity was associated with faster responses) than in the old adults (i.e., more activity was linked to slower responses). Note, however, that these brain-behavior associations only reflect how the activity is related to performance during word processing; they cannot predict later memory performance.

Overall, the correlations between higher brain activation patterns and shorter RTs suggest that this activity is beneficial for the performance of young adults. By contrast, higher levels of brain activity in older individuals was mostly associated with slower performance but nevertheless with high levels of accuracy. The positive brain-behavior association in elderly individuals may be explained as a compensatory mechanism to deal with increasing task demands despite a reduction in their attentional resources.

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8

NEUROIMAGING RESEARCH IN COGNITIVE AGING: WHERE DO WE GO FROM HERE?

Aging is associated with cognitive deficits and losses in both the structure and function of the brain. With respect to cognition, changes occur in global processes, such as mental speed (Salthouse, 1996; Earles et al., 1997) and attentional resources (Craik and Byrd, 1982; Kirasic et al., 1996), as well as in specific cognitive functions such as executive control (Jennings and Jacoby, 1993; Moscovitch and Winocur, 1995) and the inhibition of irrelevant information (Hasher and Zacks, 1988; Burke, 1997). At the same time, the aging brain undergoes a number of changes, such as gray and white matter atrophy, blood flow reductions, and neurochemical alterations (Kemper, 1994; Uylings et al., 2000b). It is plausible that cognitive impairments are a consequence of changes in the brain; patient studies have indeed provided strong indications for such brain-behavior associations. However, how these observations relate to comparable mechanisms in normal, non-pathological aging is not yet known completely. For instance, is atrophy necessarily a hallmark of functional decline? And can cerebral changes be considered across the brain as a whole, or should there rather be a differentiation in regional effects? If so, to what extent can such a subdivision be refined? The aim of this thesis was to address some of these issues. To this end, neuroimaging techniques (MRI, fMRI) were used to examine brain mechanisms that underlie age-related cognitive changes in individuals spanning the adult age range.

This chapter aims to link the findings described in this thesis using the frontal lobe theory of cognitive aging. First, this theoretical framework will be described, followed by suggestions for possible extensions. Emphasis will be on the importance of

an anatomical subdivision within the prefrontal cortex (PFC), as well as the need to consider the neuronal circuits that these regions are part of, including their various cortical and subcortical projection areas and communicating fiber tracts. Finally, the contribution of neuroimaging techniques to the understanding of brain aging will be evaluated.

COGNITIVE AGING AND THE PFC

As outlined in Chapters 1 and 2, an influential neurobiological theory in the field of cognitive aging suggests that age-related cognitive impairments can be attributed to changes in the frontal lobes, and more specifically in the PFC (Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001). The PFC supports the formation, monitoring and execution of complex behavior (Fuster, 1980; Cummings, 1995; Knight et al., 1999) and is therefore crucial in most 'higher' cognitive processes. Functions that are subserved by the PFC, such as executive control processes and inhibition of irrelevant information, are differentially impaired in elderly individuals (Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001). Furthermore, as shown in Chapter 2, the greatest degree of volume loss in the aging brain occurs in the PFC (e.g., Raz et al., 1997; Salat et al., 1999). This observation is supported by the studies described in Chapters 4 and 6, in which a disproportionate decrease was found in the volumes of prefontal regions, which was even more pronounced than volume losses in the medial temporal lobes. In addition, the frontal lobe theory predicts that age-related differences in brain activity are most prominent in fontal regions. This pattern has frequently been observed in functional neuroimaging studies (e.g., Grady et al., 1995; Cabeza et al., 1997a; Madden et al., 1999). Similarly, in the fMRI study described in Chapter 7, the main difference between young and older individuals was found in frontal activation patterns. An increase in frontal activity can be interpreted as extra effort to cope with task demands, whereas a decrease may reflect a reduction in frontal inhibitory mechanisms.

DIFFERENTIAL AGE EFFECTS ON SPECIFIC REGIONS WITHIN THE PFC

The PFC is a large and heterogeneous region and can be subdivided into a number of functionally distinct areas. A broad subdivision into an orbital, lateral and medial part has been proposed (Fuster, 1980; Stuss and Benson, 1986; Cummings, 1995). Recent neuroimaging studies suggest that even smaller distinctions should be made (e.g.,

Petrides, 1995; Owen et al., 1996, 1998; Smith and Jonides, 1999; Elliott et al., 2000; and see Chapter 6). For example, within the lateral PFC a dorsal and ventral part can be distinguished. Each of these prefrontal regions belongs to different neural circuits and has specific projection areas, including striatal and thalamic subregions (Alexander et al., 1990). Furthermore, the lateral PFC has reciprocal connections with the orbitofrontal cortex and the anterior cingulate, as well as with posterior association areas and the MTL. The orbitofrontal cortex and anterior cingulate have afferent and efferent connections, particularly with the amygdala (Alexander et al., 1990; Cummings, 1995; Petrides, 1995). Despite the fact that such a notion of prefrontal differentiation has been adopted for a number of years, studies considering the selective structural or functional effects of age on prefrontal subregions are scarce. Aging may selectively affect particular prefrontal areas while sparing others (Chapter 6; see also Kemper, 1994; Raz et al., 1997; Uylings et al., 2000b; Xu et al., 2000; Salat et al., 2001; Tisserand et al., 2001), and this in turn may have consequences for the specific cognitive functions and networks in which these brain regions are involved. Because of the assumed relevance of the PFC for cognitive aging (see previous section), future imaging studies should discriminate between the different frontal regions and their specific functions in relation to aging.

DIFFERENTIAL AGE EFFECTS ON THE WHITE MATTER

More attention should also be directed towards a differentiation between gray and white matter changes in aging. Although this thesis does not include studies on age-related changes in the white matter, it is important to note the growing interest in this field of research. Age-related decreases in the volume of the white matter are not as prominent as those in the gray matter, but there is a remarkable increase in lesions within the white matter (see Chapter 2). In fact, these lesions have been found to be even more common than gray matter atrophy in elderly individuals. Further support for an age-related decrease in white matter integrity comes from MRI studies using diffusion tensor imaging (DTI). DTI is a recently developed technique that provides an index of microstructural tissue properties by assessing the orientation of diffusion of water molecules within the white matter (Pierpaoli et al., 1996). A reduction in this diffusion tensor, implying a disruption of the white matter tracts, with advancing age has recently been found (Nusbaum et al., 2001; O'Sullivan et al., 2001; Sullivan et al., 2001; Abe et al., 2002), with the strongest effects within the frontal white matter (O'Sullivan et al., 2001; Sullivan et al., 2001; Abe et al., 2002). Fiber tracts in the white matter make up the connections between cortical (e.g., frontal) and subcortical gray matter regions. Therefore, the observations that point to changes in the organization of white matter

pathways in normal aging, together with the increase in white matter lesions, have been interpreted in terms of an increased vulnerability of older individuals for cognitive dysfunction due to cortico-cortical and cortico-subcortical disconnection.

NEURAL CIRCUITS IN RELATION TO COGNITIVE AGING

As mentioned at the beginning of this chapter, age-related changes in cognitive functioning are partly a consequence of reductions in global cognitive mechanisms, such as information processing speed (e.g., Salthouse, 1994, 1996; Earles et al., 1997). Interestingly, a strong association has been found between white matter lesions and slowing on information processing tasks in normal, healthy elderly individuals (Ylikoski et al., 1993; DeCarli et al., 1995; De Groot et al., 2000). These results imply that the frontal lobe theory in a strict interpretation fails to account for all age-related cognitive changes. Rather, they strengthen the notion that the connections between cortical and subcortical regions have to be intact to guarantee the efficiency of the communication between them (e.g., McIntosh, 1999, 2000; Greenwood, 2000; Braver et al., 2001; O'Sullivan et al., 2001). A model that applies this idea of the involvement of multiple brain systems to account for the pattern of cognitive impairments in aging has been proposed by Moscovitch and Winocur (1992, 1995). Their model suggests that age does not affect memory per se, but rather influences the capacity to efficiently process information in general. It distinguishes between two types of explicit memory: associative and strategic. The associative memory component involves the relatively automatic encoding, storage and retrieval of information and is largely dependent on structures located in the medial temporal lobe (MTL). The more conscious and 'intelligent' control over this automatic, associative system, both at input and output, is provided by the PFC (Moscovitch and Winocur, 1992). This strategic information processing system consumes more attentional resources than the associative system, and therefore it is more sensitive to an age-related reduction of these resources (Craik and Byrd, 1982). This theory offers an explanation for the finding that, although both medial temporal and frontal regions are required for explicit memory, age effects are more pronounced on 'strategic' memory tasks (e.g., free recall) than on tasks that rely primarily on the associative system (e.g., recognition). It also predicts that older individuals are slower and make more errors particularly on demanding cognitive tasks, such as those requiring divided attention and executive control. Finally, this view coincides with the evidence (cf. Chapters 4, 6 and 7) that the integrity of the PFC is more sensitive to aging than that of the MTL. Nevertheless, this theory does suggest that structures other than the frontal regions are also required for adequate cognitive functioning. This was confirmed by the study

described in Chapter 5, in which it was found that the PFC and MTL were both implicated in protecting against age-related cognitive decline.

EXPANDING THE NEURAL CIRCUIT VIEW: FUNCTIONAL INTERACTIONS IN COGNITIVE AGING

Even when the same brain regions are involved in task performance across age groups, their functional interactions may be different. Indirect evidence for this conception was provided in the fMRI study described in Chapter 7, which showed that even though task performance was comparable in young and old adults, the patterns of task-related brain activity were different for the two age groups. Altered connectivity in the brains of elderly individuals has been reported in various neuroimaging experiments (Grady et al., 1994, 1995; Horwitz et al., 1995; Cabeza et al., 1997a, b; Grady, 1998; Esposito et al., 1999; McIntosh et al., 1999; Della-Maggiore et al., 2000). For example, an age-related modification of the connections between the PFC and the MTL has been observed (Grady et al., 1995; Esposito et al., 1999; Della-Maggiore et al., 2000). These findings indicate that in order to understand the relation between activity in a given brain region (e.g., PFC) and task performance, it is important to consider the region in the context of other, simultaneously activated and functionally connected brain areas (McIntosh, 1999; Della-Maggiore et al., 2000; Braver et al., 2001; O'Sullivan et al., 2001). The suggestion to adopt a more 'dynamic' and multidimensional view with respect to the relationship between cognitive functioning and regions within the brain has also been stressed in recent literature. Mesulam (1998) described five brain circuits, each with a different function in information processing and cognition. Two of these networks are of particular relevance for this thesis, namely an explicit memory and a working memory-executive function circuit. The three additional networks are involved in spatial awareness, language, and face-object recognition. 'Transmodal nodes' in the brain connect the various circuits, thus offering a possibility to combine their information. It is argued that adequate functioning requires activation of each of these large-scale neural networks. It may be speculated that, in aging, functional reorganization of activity in these circuits serves as a mechanism to prevent cognitive decline. To elucidate this, the dynamics of networks in the brain need to be specified in more detail in the future.

METHODOLOGICAL ISSUES IN NEUROIMAGING RESEARCH

A final topic that merits attention is the contribution of neuroimaging techniques to the study of brain aging. It is obvious that these techniques have proven to be extremely valuable. The undisputed advantage is that the human brain can now be studied in vivo (as opposed to postmortem) and dynamically, and that these technologies can be applied to examine healthy individuals (as opposed to patients with cognitive dysfunction). During the past decade, the number of neuroimaging studies in the field of aging and cognition has increased exponentially, but there are still many inconsistencies between the findings obtained in those experiments. This may partly be due to differences in methodology and analysis approach, which makes it difficult to compare the results.

The question then is: is there a neuroimaging technique and an image analysis method that could be considered the most promising to study brain-behavior relations? It is difficult to provide an unequivocal answer to this issue. In practice, the choice of an imaging device is often dictated by the available facilities near the research site. Financial and medical-ethical matters can also determine the study design (e.g., how many participants are recruited, are there any radioactive substances involved?). Furthermore, the analysis of the large image files, consisting of 3-dimensional (MRI) or 4-dimensional (fMRI) data matrices, is largely dependent on and limited by the storage and processing capacity of the computers used to analyze the images. The average size of a structural MRI dataset is 15 MB, while this often exceeds 1 GB for fMRI data. Only recently has it become possible to do complex mathematical and computational processing on such vast data sets within a reasonable amount of time. How recent these developments are can in fact be inferred from the MRI study described in Chapter 4, in which the image analysis was done only in two dimensions instead of three. In the past few years, there has been an increase in whole-brain methods to consider individual differences in brain morphology and function, such as voxel-based and deformation-based morphometry (Ashburner and Friston, 2000), cortical thickness extraction (Kabani et al., 2001), sulcus-based mapping (Thompson et al., 1996), and cortex inflation and flattening (Kriegeskorte and Goebel, 2001). Nevertheless, these approaches cannot - yet - replace manual approaches in determining the exact location of regions in the brain. Actually, an important conclusion drawn in Chapter 6 was that, even within the same study population, the choice of a certain image analysis approach could be crucial for the outcome of the experiment.

The extremely large interindividual anatomical variability in particular (cf. Chapter 5; and see Rajkowska and Goldman-Rakic, 1995; Roland et al., 1997; Uylings et al., 2000a; Thompson et al., 2001) is a persisting matter of concern when individuals are compared with respect to regional brain structure or function using whole-brain

neuroimaging approaches. For instance, a certain location in the brain (with spatial coordinates *x, y, z*) may be occupied by gyrus A in one person, and by gyrus B in another. What, then, does it imply if a difference in tissue density or neural activity is found at this location across individuals? Despite this notion, neuroimaging studies have greatly contributed to the knowledge about the structure and function of the human brain. And with the extremely rapid developments in the field of neuroimaging, current methodological difficulties probably will be resolved in the near future.

CONCLUDING REMARKS

A close association between aging, cognition and the frontal lobes has been reported by various authors (e.g., Jolles, 1986; Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001), and the research presented in this thesis provides further support for the mediating role of the PFC in cognitive aging. Age-related atrophy is most apparent in this region (e.g., Raz et al., 1997; Tisserand et al., 2002) and its projection areas, i.e., the striatum and thalamus (Gunning-Dixon et al., 1998; Van der Werf et al., 2001). In contrast, only moderate volume reductions have been reported within limbic regions (e.g., Raz et al., 1997; Tisserand et al., 2000). Furthermore, differences between young and older individuals in functional imaging studies, both at rest and during cognitive performance, have been observed most consistently within the frontal lobes (e.g., Loessner et al., 1995; Moeller et al., 1996; Cabeza et al., 1997a; Petit-Taboué et al., 1998; Madden et al., 1999; Reuter-Lorenz et al., 2000). Nonetheless, it is important to note that several researchers have criticized the frontal aging hypothesis (e.g., Rubin, 1999; Greenwood, 2000; Braver et al., 2001; Pugh and Lipsitz, 2002). They have stressed that structural and functional changes also occur in non-frontal regions (Greenwood, 2000; Braver et al., 2001) and that adequate cognitive functioning requires the integrity of all the structures involved in that particular function (Rubin, 1999; Pugh and Lipsitz, 2002). It is of course untenable to suggest that age-related cognitive impairments result exclusively from prefrontal declines. In fact, in this thesis it has been argued that cognitive impairments should no longer be considered to be the result of structural or functional alterations within isolated brain regions. Rather, a broader perspective should be adopted to acknowledge the fact that brain regions are clustered in networks interconnected by white matter pathways (Mesulam, 1998; McIntosh, 2000). Damage to any part of these circuits may lead to a reduction in the flow of information and, consequently, to cognitive decline. Disruptions particularly in prefrontal circuits, with their specific role in executive control and in the modulation

of neural activity throughout the brain, may turn out to be crucial for the understanding of age-related cognitive impairments.

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SUMMARY

Aging is associated with a decrease in cognitive abilities, such as slower mental processing and an impaired capacity to learn and remember new information. Although numerous factors may contribute to this decline, the most direct cause of age-related cognitive impairments is a change in brain structure and/or function. This thesis investigates which brain mechanisms may underlie cognitive impairments in normal, non-pathological aging. Emphasis is put on age-related changes in the volume and function of brain regions involved in higher cognitive processes. Neuroimaging techniques, in particular, magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), were used to study these cerebral changes as a function of age.

Chapter 1 outlines the rationale behind the research described in this thesis and the approach that was followed. It highlights the cognitive processes that are affected in normal, non-pathological aging, and provides a short introduction to the frontal lobe theory of cognitive aging. This view offers a neurobiological explanation for the performance decrements seen in older individuals, by suggesting that this decline results from changes in the structure and/or function of the frontal lobes. Furthermore, attention is paid to methodological issues in neuroimaging research.

Chapter 2 provides an overview of the current neuroimaging literature on structural and functional changes within the aging brain. The findings are discussed within the framework of the frontal aging theory. Higher age is associated with volume reductions in the gray matter, with the largest decreases in the volume of the prefrontal cortex (PFC) and the striatum. Age-related changes in the white matter are manifested particularly as an increase in white matter lesions. These lesions may lead to a disconnection between specific regions in the frontal gray matter and other cortical and subcortical structures. Further evidence for disproportionate age effects on the PFC has been obtained from functional imaging studies, which have shown the most substantial age-related changes in that region. Reductions in baseline metabolism and blood flow are largest in the frontal lobes. Moreover, activation studies have reported age-related differences (both increases and decreases) particularly in frontal regions. It has been suggested that increased activity in older individuals reflects the attempt to cope with the task demands. Decreased activity may be due to a reduction in neural efficiency.

Chapter 3 explores the relation between head size (used as an estimate of total brain volume) and cognitive performance in a large population-based study of elderly individuals. Because this measure is easy to apply and much less expensive to obtain than brain scans, the experiment could be carried out in a large sample. Head size was measured in 818 healthy older adults (aged 50-81 years) as part of the Maastricht Aging Study (MAAS). Head size was found to be related to performance on tests measuring intelligence, global cognitive functioning, and mental processing speed. It was examined whether other factors known to be related to cognitive performance could explain these associations between head size and cognition. In particular, the influence of educational level, socio-economic background, and height was explored. None of these variables substantially contributed to the pattern of findings, that is, the head size - cognition relation does not seem to be confounded by any of these factors.

In the experiments outlined in Chapters 4 to 6, MRI was employed to study the associations between age and regional brain volumes. *Chapter 4* focuses on a group of 61 healthy adults (aged 21 to 81 years) who were tested with respect to memory and other cognitive functions. In this study the volumes of the hippocampus, parahippocampal gyrus, mamillary bodies, third ventricle and total brain matter were measured. It showed an evident age-related increase in ventricular volume and a volume decrease in total brain matter, hippocampus and parahippocampal gyrus, but not in the mamillary bodies. However, no associations could be established between the brain volumes and test performance after controlling for age effects. It is concluded from this chapter that variations in these regional brain volumes are not a strong predictor of cognitive performance independent of age.

Chapter 5 describes a study that employed voxel-based morphometry (VBM) to investigate individual differences in regional gray matter density in healthy, non-demented elderly individuals (aged 50 years and over). A selection of participants from MAAS were subjected to neuropsychological tests at baseline and again after three years. Thirty-seven subjects who showed a decline in cognitive test performance at follow-up were compared with 38 individuals whose performance remained stable over time. The relation between age and gray matter density was examined, as well as the association between gray matter density and longitudinal decline in performance on cognitive tests. The largest age effects were observed in the PFC, (medial) temporal lobes (MTL, including the hippocampus) and striate cortex. Longitudinal cognitive decline was associated with decreased gray matter density in PFC areas, the MTL and the posterior parietal cortex. These findings suggest that the PFC and MTL are of particular relevance

both in aging and age-related cognitive decline in healthy elderly individuals. In addition, age differences in the study sample may account for the fact that in Chapter 4 the volume of MTL structures did not significantly predict cognitive performance while the results of the present chapter show that this brain region does seem to play a major role in cognition. It is hypothesized that volume decreases in the PFC characterize normal aging processes during the adult life, and that MTL atrophy only becomes apparent in older individuals.

As demonstrated in the previous chapter, the frontal lobes are profoundly affected by the aging process. *Chapter 6* investigates whether different patterns of brain aging are evident in subregions within the frontal cortex. MRI scans of 57 healthy adult participants (21 to 81 years old) were used to measure frontal gray matter volumes in three ways: with a manual tracing approach, a semi-automatic volumetric method, and with VBM. Seven regions within each hemisphere were traced manually, and four semi-automatically. Although VBM does not permit volumetry, it can be used to determine the exact location of a decrease in gray matter. As expected, advanced age was strongly associated with reductions in the total volume of the frontal cortex. Differential age effects on the volumes of frontal subregions were dependent on the method applied. According to the manual approach, age-related volume decreases were strongest in the lateral and orbital frontal gray matter. The semi-automatic and voxel-based analyses found that age effects were most prominent within the lateral frontal and cingulate regions. Hence, from this study it becomes evident that even within the same study population, the choice of a certain image analysis approach can be crucial for the outcome of the experiment.

In each of the previous chapters, it was assumed that smaller brain volumes could be associated with decreased functioning of the brain. However, this relation cannot be directly determined by means of structural neuroimaging. Therefore, functional MRI was applied in the experiment described in *Chapter 7* to investigate age effects on brain activity during cognitive test performance. Scans were obtained in 12 young (25 $\pm$ 1 years) and 11 old (65 $\pm$ 1 years) adults while they were engaged in a cognitive task, i.e. word processing. Four different conditions were used: three conditions involving a perceptual, linguistic and semantic operation, and one involving intentional word learning. The brain activity patterns showed a clear distinction between the intentional learning versus the other conditions in both age groups. During intentional learning, both groups activated various posterior cortical areas, but only young subjects activated frontal regions, i.e., the lateral PFC and the anterior cingulate. This could not be attributed to group differences in performance levels. Although in both groups, responses were slower and less accurate for the intentional condition than for the other three conditions, there

was no significant age-related difference in performance. Nevertheless, the associations between performance and activity were different in the two groups. Whereas in young subjects increased activity was mainly associated with shorter reaction times, in older subjects the reverse was seen. Moreover, these associations were located mainly in posterior brain regions in the young subjects, and both in frontal and posterior cortical areas in the elderly. On the basis of these findings, it is suggested that young adults use these brain regions more efficiently than older adults do.

Finally, *Chapter 8* summarizes the results of the experiments described in this thesis and tries to link these findings to the frontal lobe theory of aging. Possible extensions to this theory are suggested, in particular with respect to the importance of a subdivision within the PFC. This large cortical area consists of a number of subregions, which are all part of different neural circuits. Furthermore, apart from gray matter volume losses, a decrease in the integrity of the white matter occurs in aging. Hence, it is concluded from this chapter that in order to study brain-behavior relations in aging, one needs to consider brain circuits rather than isolated regions, including the various cortical and subcortical projection areas and white matter fiber tracts. Damage to any part of these circuits may lead to a reduction in the flow of information and, consequently, to cognitive decline.

SAMENVATTING

Veroudering gaat gepaard met een afname in cognitieve vermogens, zoals het trager worden van mentale processen en een verminderde capaciteit om nieuwe informatie te leren en onthouden. Hoewel er zeer vele factoren zijn die kunnen bijdragen tot deze achteruitgang, is de meest directe oorzaak van leeftijdsgerelateerde cognitieve beperkingen een verandering in de structuur en/of de functie van de hersenen. In dit proefschrift wordt onderzocht welke hersenmechanismen ten grondslag kunnen liggen aan cognitieve achteruitgang tijdens normale, niet-pathologische veroudering. De nadruk ligt hierbij op leeftijdsafhankelijke veranderingen in het volume en functioneren van hersengebieden die betrokken zijn bij hogere cognitieve processen. Neuroimaging technieken, in het bijzonder magnetic resonance imaging (MRI) en functionele magnetic resonance imaging (fMRI), zijn gebruikt om deze cerebrale veranderingen tijdens de veroudering te bestuderen.

Hoofdstuk 1 beschrijft de rationale van het onderzoek dat in dit proefschrift beschreven wordt en de aanpak die daarbij gevolgd is. Cognitieve processen die aangetast worden door veroudering worden belicht en de frontaalkwabtheorie van cognitieve veroudering wordt beknopt uiteengezet. Deze opvatting geeft een neurobiologische verklaring voor de achteruitgang in prestatie die bij ouderen optreedt, door er van uit te gaan dat die het gevolg is van veranderingen in de structuur en/of functie van de frontaalkwab. Tevens wordt in dit hoofdstuk de aandacht gevestigd op een aantal belangrijke methodologische kwesties in onderzoek dat gebruik maakt van hersenimaging technieken.

Hoofdstuk 2 geeft een overzicht van de huidige neuroimaging literatuur over structurele en functionele veranderingen in de verouderende hersenen. De bevindingen worden besproken in het licht van de frontale verouderingstheorie. Ouder worden gaat gepaard met een afname in het volume van de grijze stof, waarbij de sterkste effecten optreden in de prefrontale cortex (PFC) en het striatum. Leeftijdsgerelateerde veranderingen in de witte stof manifesteren zich voornamelijk als een toename in het aantal witte stof lesies. Deze lesies leiden mogelijkerwijs tot een disconnectie tussen frontale grijze stof gebieden en andere corticale en subcorticale hersenstructuren. Aanvullende aanwijzingen voor een disproportioneel leeftijdseffect op de PFC komen van functioneel beeldvormend onderzoek, dat heeft laten zien dat de grootste veranderingen in dat deel van de hersenen

plaatsvinden. De afname in basaal hersenmetabolisme en in de doorbloeding is het sterkst in de frontaalkwab. Voorts hebben activatiestudies aangetoond dat leeftijdsgerelateerde verschillen (zowel toe- als afname) voornamelijk frontaal gelokaliseerd zijn. Men heeft gesuggereerd dat toegenomen activiteit bij ouderen hun poging weergeeft om aan de taakeisen te kunnen blijven voldoen. Een afname in hersenactiviteit zou het gevolg kunnen zijn van een afgenomen efficiëntie in de onderlinge communicatie tussen hersengebieden.

Hoofdstuk 3 onderzoekt de relatie tussen hoofdomtrek (als indirecte maat voor het totale hersenvolume) en cognitief presteren in een populatieonderzoek bij oudere individuen. Omdat deze eenvoudig te bepalen maat gebruikt is in plaats van kostbare hersenscans kon dit experiment in een zeer grote groep worden uitgevoerd. Hoofdomtrek werd gemeten bij 818 gezonde ouderen (50-81 jaar oud), als onderdeel van de Maastricht Aging Study (MAAS). Er werd gevonden dat hoofdomtrek samenhing met de prestatie op tests die intelligentie, globaal cognitief functioneren en snelheid van informatieverwerking meten. Onderzocht werd of andere factoren die met cognitief presteren samenhangen deze associaties tussen hoofdomtrek en cognitie konden verklaren. In het bijzonder werd de invloed van opleidingsniveau, socio-economische achtergrond en lichaamslengte onderzocht. Geen van deze variabelen droeg substantieel bij tot een verklaring van de bevindingen, oftewel de relatie tussen hoofdomtrek en cognitie lijkt niet door deze factoren te worden beïnvloed.

In de experimenten beschreven in Hoofdstukken 4 tot en met 6 is gebruik gemaakt van MRI om de associaties tussen leeftijd en regionaal hersenvolume te onderzoeken. *Hoofdstuk 4* heeft betrekking op een groep van 61 gezonde volwassenen (21-81 jaar oud) die getest werden met betrekking tot hun geheugen en andere cognitieve vermogens. Het volume van de hippocampus, parahippocampale gyrus, corpora mamillaria, derde ventrikel, en het totale hersenvolume werd gemeten. Een leeftijdsgerelateerde toename in het ventriculaire volume was onmiskenbaar, evenals een afname in het totale hersenvolume en dat van de hippocampus en parahippocampale gyrus. Het volume van de corpora mamillaria nam niet significant af met de leeftijd. Deze volumeveranderingen bleken echter niet samen te hangen met taakprestatie wanneer er met leeftijdeffecten rekening werd gehouden. De conclusie die in dit hoofdstuk getrokken wordt is dan ook dat variaties in regionale hersenvolumes geen sterke voorspellende waarde hebben voor cognitief presteren onafhankelijk van leeftijd.

Hoofdstuk 5 beschrijft een studie waarin gebruik gemaakt is van voxel-based morphometry (VBM) om individuele verschillen in dichtheid van de grijze stof te

onderzoeken bij gezonde, niet-demente ouderen (van 50 jaar en ouder). Een aantal deelnemers van MAAS werden neuropsychologisch getest bij aanvang van de studie en nogmaals na drie jaar. Zevenendertig mensen die bij de tweede meting cognitief achteruit waren gegaan werden vergeleken met 38 individuen wier prestatie niet verslechterd was. De relatie tussen leeftijd en dichtheid van de grijze stof werd onderzocht, evenals de samenhang tussen grijze stof dichtheid en longitudinale achteruitgang in prestatie op cognitieve tests. De sterkste leeftijdseffecten werden gevonden in de PFC, de (mediale) temporaalkwab (MTK, waar zich onder meer de hippocampus bevindt) en de visuele schors. Longitudinale cognitieve achteruitgang hing samen met afname in dichtheid van de grijze stof in gebieden in de PFC, MTK en de posterieure parietale schors. Deze resultaten suggereren dat de PFC en MTK een mediërende rol kunnen spelen in leeftijdsgerelateerde cognitieve achteruitgang bij overigens gezonde ouderen. Leeftijdsverschillen binnen de onderzoekspopulaties kunnen wellicht verklaren dat in Hoofdstuk 4 het volume van structuren in de MTK niet voorspellend was voor cognitief functioneren terwijl uit de bevindingen beschreven in het huidige hoofdstuk blijkt dat dit deel van de hersenen wèl een belangrijke rol in cognitie speelt. Er wordt gesuggereerd dat volumevermindering in de PFC als onderdeel van niet-pathologische veroudering een fenomeen is dat gedurende het hele volwassen leven plaatsvindt, terwijl atrofie van de MTK enkel bij ouderen optreedt.

Zoals uit het vorige hoofdstuk bleek, is de frontaalkwab erg gevoelig voor de gevolgen van het ouder worden. In *Hoofdstuk 6* wordt onderzocht of er in subgebieden binnen de frontale cortex verschillende patronen van hersenveroudering optreden. MRI scans van 57 mensen tussen de 21 en 81 jaar oud werden gebruikt om volumes van frontale grijze stof gebieden te bepalen. Dit werd gedaan op drie manieren: met een handmatige meetmethode, met een semi-automatische volumetrische methode, en met VBM. Zeven gebieden in elke hersenhelft werden handmatig opgemeten, en vier semi-automatisch. Hoewel volumetrie niet mogelijk is met VBM, kan deze toepassing gebruikt worden om vast te stellen waar precies in de hersenen een afname in grijze stof optreedt. Zoals verwacht hing toenemende leeftijd sterk samen met een verminderd volume van de complete frontale schors. Differentiële effecten op het volume van frontale subgebieden waren afhankelijk van welke methode gebruikt was voor de meting. Volgens de handmatige methode waren de leeftijdseffecten het grootst in de grijze stof van de laterale en orbitale frontaalkwab. Met behulp van de semi-automatische aanpak en VBM werden de sterkste effecten gevonden in het gebied van de laterale frontale cortex en het anterieure deel van de cingulaire schors. Dus de resultaten van deze studie laten zien dat zelfs binnen dezelfde onderzoekspopulatie de manier van beeldanalyse bepalend kan zijn voor de uitkomsten van het experiment.

In elk van de vorige hoofdstukken was de aanname dat kleinere hersenvolumes gerelateerd kunnen worden aan slechter functioneren van de hersenen. Het is echter niet mogelijk om direct bewijs te vinden voor deze veronderstelling met structurele hersenimaging. Daarom werd een onderzoek met functionele MRI uitgevoerd om het effect van leeftijd op hersenactiviteit tijdens het uitvoeren van een cognitieve taak te bestuderen. Dit onderzoek wordt beschreven in *Hoofdstuk 7*. Er werden hersenscans gemaakt bij 12 jonge (25 ± 1 jaar) en 11 oudere (65 ± 1 jaar) volwassenen terwijl ze bezig waren met het uitvoeren van een cognitieve taak, in dit geval het verwerken van woorden. Men kreeg vier verschillende condities aangeboden: drie condities die een perceptuele, linguïstische en semantische beslissing vereisten, en één die intentioneel leren betrof. De patronen van hersenactiviteit lieten in beide leeftijdsgroepen een duidelijk onderscheid zien tussen intentioneel leren en de andere drie condities. Tijdens intentioneel leren activeerden beide groepen verschillende posterieure corticale gebieden, maar enkel de jonge deelnemers activeerden ook gebieden in de frontale schors. Dit kon niet toegeschreven worden aan een verschil in prestatie. Alhoewel beide groepen trager waren en minder accuraat tijdens de intentioneel leren conditie dan tijdens de andere drie condities, was er geen significant leeftijdsgerelateerd verschil in taakprestatie. Niettemin waren er opmerkelijke verschillen in de associaties tussen prestatie en hersenactiviteit tussen de twee groepen. Bij de jonge deelnemers was een toename in hersenactiviteit voornamelijk gerelateerd aan kortere reactietijden, terwijl dat bij de ouderen andersom was. Voorts werden deze associaties vooral in posterieure hersengebieden gevonden bij de jongeren, en zowel in frontale als posterieure corticale gebieden bij de ouderen. Op basis van deze bevindingen wordt er in dit hoofdstuk gesuggereerd dat jonge volwassenen deze hersengebieden efficiënter gebruiken dan ouderen.

Tot slot wordt in *Hoofdstuk 8* een samenvatting gegeven van de uitkomsten van de experimenten die in dit proefschrift beschreven zijn. Getracht wordt om de bevindingen te relateren aan de frontaalkwabtheorie van veroudering. Er worden suggesties gegeven voor uitbreidingen van deze theorie, waarbij vooral het belang van een onderverdeling binnen de PFC wordt aangeduid. Dit deel van de hersenen is omvangrijk en bestaat uit een aantal subgebieden, die elk deel uitmaken van verschillende neurale circuits. Bovendien gaat veroudering niet alleen gepaard met volumevermindering in de grijze stof, maar ook met een afname in de integriteit van de witte stof. De conclusie die in dit hoofdstuk wordt getrokken is dat men, om de relatie tussen hersenen en gedrag tijdens veroudering te bestuderen, meer naar hersencircuits moet kijken in plaats van naar geïsoleerde gebieden, inclusief de verschillende corticale en subcorticale projectiegebieden en de vezelbanen in de witte stof. Beschadigingen van elk onderdeel

van deze neurale circuits kan leiden tot een minder efficiënte informatiestroom en, daaruit voortvloeiend, tot een achteruitgang in cognitief functioneren.

CURRICULUM VITAE

Danielle Tisserand werd op 30 december 1974 geboren te Rotterdam. Na het behalen van haar VWO diploma aan het Maerlandt College in Brielle in 1993 vertrok ze naar Maastricht om daar Gezondheidswetenschappen te gaan studeren. Hoewel ze aanvankelijk vooral in hulpverlening geïnteresseerd was en daarom voor de afstudeerrichting Geestelijke Gezondheidkunde koos, ontwikkelde ze tijdens haar studie een sterke interesse in het functioneren van de hersenen. Ze volgde enkele vakken binnen de afstudeerrichting Neuro- en Revalidatiepsychologie aan de Katholieke Universiteit Nijmegen en binnen de toen net in Maastricht opgerichte faculteit Psychologie. Verder liep ze stage in het Neurologische Revalidatiecentrum van het Universitair Ziekenhuis Gent (België) waar ze ervaring opdeed met behandeling van en onderzoek bij patiënten met niet-aangeboren hersenletsel. Voor haar afstudeeronderzoek keerde ze terug naar Maastricht. Het onderwerp ervan betrof volumetrie van bepaalde hersengebieden bij patiënten met de ziekte van Alzheimer en Korsakoff en bij gezonde ouderen. Dit onderzoek, waarbij gebruik gemaakt werd van MRI scans, wekte haar interesse in hersenimaging. Na haar afstuderen in 1998 besloot ze dan ook het aanbod te aanvaarden om als assistent in opleiding te gaan werken bij de vakgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht. De afgelopen vier jaar heeft ze aldaar gewerkt aan de studies die in dit proefschrift geresulteerd hebben. Tijdens die periode bracht ze vijf maanden door binnen het Montreal Neurological Institute in Canada. Momenteel is ze als postdoctoral fellow werkzaam binnen het Rotman Research Institute in Toronto, Canada.

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