Chapter 1

Introduction
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Aging and age-related conditions

Successful aging is probably one of the utmost important goals in the present society. As the number of people aged 65 years and older is likely to increase in the next decades, so is the number of elderly people who are eligible for care or incapable of independent living. The most prevalent age-related discomforting conditions include cognitive deterioration, chronic pain and disturbances of the rest-activity rhythm. The burden is furthermore increased in case of co-occurrence of several of these conditions, such as concurrent chronic pain and cognitive decline. These conditions provide, separately and together, major threats to the ability of independent living.

White matter

Aging is known to induce neurodegenerative processes in various brain regions. For example, age-related neurodegenerative changes are known to include the prefrontal gray and white matter, and the medial temporal lobe (de Leeuw et al., 2001; Raz et al., 1997). With regard to white matter hyperintensities (WMH) in aging, prevalence rates have been reported of up to 95% (de Leeuw et al., 2001), making WMH characteristic for aging. Several mechanisms have been suggested to account for these abnormalities, including ischemia (Pantoni, 1997), with a presumed central role of arteriosclerosis (Pantoni, 2002). Arteriosclerosis is a normal consequence of aging where the arterial walls gradually thicken and arterial fibers decline. As a result, the arteries become stiff. This hardening of the arterial walls can be accompanied by accumulation of lipids inside these walls. These arterial changes, resulting in reduced blood flow and, hence, in a reduction in oxygen supply, may induce WMH. Confirmative of this idea are findings of reduced cerebral blood flow in brain areas with WMH (Kawamura et al., 1993; O’Sullivan et al., 2002). Examples of varying degrees of WMH are presented in Figure 1.

Aging is furthermore related to an increase in the prevalence of cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus (e.g. Jo et al., 2001; Stolk et al., 1997). In addition to aging, these risk factors exaggerate the thickening and hardening of the arterial walls. Indeed, hypertension, a common risk factor with an estimated prevalence varying from around 30% (Wong, Lopez, Tang, & Williams, 2006) to 62% (Brindel, et al., 2006) in the adult population, constitutes a major risk for arteriosclerosis (Ishizaka et al., 2005). Furthermore, the high prevalence of hypercholesterolemia (47%, Wong et al., 2006) and, lower but nonetheless fairly high prevalence of diabetes mellitus (20%; Fillenbaum, Pieper, Cohen, Cornoni-Huntley, & Guralnik, 2000), increase the risk of arteriosclerosis (Campeau et al., 2005; Tatsukawa et al., 2004). As arteriosclerosis might be the major cause of WMH, it is not surprising that these cardiovascular risk factors are associated with increased prevalence of WMH as well (Jagust, Harvey, Mungas, & Haan, 2005; Kidwell & Saver, 1996; Longstreth et al., 2005).
Cognitive functions

It is known that age-related changes in the brain such as loss of gray and white matter mediate the relationship between aging and cognitive decline. Although the extent to which these changes are present and influence cognitive ability varies with each aged individual, diminished memory, speed of processing and executive function (EF) performance are the most pronounced and common cognitive deficits in aging (Bopp & Verhaeghen, 2005; Keys & White, 2000; Rabbit & Lowe, 2000). Deficits in memory are commonly attributed to the hippocampal atrophy that accompanies aging (Persson et al., 2006; Petersen et al., 2000; Rusinek et al., 2003). Executive deficits are presumed to mainly result from age-related prefrontal cortex dysfunctioning (Gunning-Dixon & Raz, 2003; Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002; Rosano et al., 2005) and WMH (Charlton et al., 2006; Deary et al., 2006). Finally, decrements in speed of information processing in aging have been attributed to cortical and subcortical atrophy (Soderlund et al., 2006; Soderlund, Nyberg, & Nilsson, 2004; van Der Werf et al., 2001), including decreased prefrontal cortex volume (Head et al., 2002).

Additional to the aging process, cardiovascular risk factors are associated with neurodegenerative changes and cognitive decline (Gianaros, Greer, Ryan, & Jennings, 2006; Raz, Rodrigue, & Acker, 2003; Verhaeghen, Borchelt, & Smith, 2003). Therefore, a large number of elderly may present with relative mild cognitive decline, more specifically in the context of cardiovascular risk factors.

Figure 2 represents examples of cognitive deficits on the Clock Drawing test in aging. With this test, subjects are instructed to draw the face of a clock, put in all the numbers and set the hands at 10 to 2. The first clock represents a normal clock, with the second, third, and fourth clock indicating disturbed cognitive performance. For example, errors in spatial arrangement of the numbers are present in the second clock, clock 3 displays errors in spatial arrangement and the placement of the hands, whereas in clock 4 missing numbers as well as errors in the placement of the hands are present.
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Figure 2. Four clocks, from left to right: a normal clock, a clock with errors in spatial arrangement, a clock with errors in spatial arrangement and placements of the hands, and a clock with errors in placements of the hands and missing numbers.

Pain

Accumulating evidence suggests that similar brain structures underlying cognitive functioning also subserve the processing of pain. For example, both the hippocampus and the prefrontal cortex are, next to the involvement in memory and EF mentioned above, acknowledged to be involved in pain processing as well (Bingel et al., 2002; Hadjipavlou, Dunckley, Behrens, & Tracey, 2006; Scherder, Sergeant, & Swaab, 2003a). Although the prevalence of chronic pain conditions is known to increase in aging, little attention these days has been dedicated to pain processing in this population. The importance of studying pain processing in aging is highlighted by observations that pain experience may be altered as a result of neurodegenerative changes. Patients with Alzheimer’s disease (AD) constitute one such example in whom altered pain processing has been reported (Benedetti et al., 1999; Scherder, Bouma, Borkent, & Rahman, 1999; Scherder & Bouma, 2000). Compared to elderly people without dementia, these patients present with reduced pain reports (Scherder et al., 1999), increased pain tolerance (Benedetti et al., 1999) and a lower use of analgesics (Semla et al., 1993). On the contrary, evidence suggests that vascular dementia (VaD) might relate to an increase in pain experience (Scherder et al., 2003b). Aging also presents with neurodegenerative changes in the brain, indicating that altered pain processing in this population can be anticipated. Therefore, it is worthwhile to examine possible changes in pain experience and its cause in aging. This information may further be helpful for pain treatment in both demented and nondemented aging.

Rest-activity rhythm

A disturbed circadian rest-activity rhythm constitutes another discomforting condition in aging. The suprachiasmatic nucleus (SCN), a structure commonly acknowledged as the mammalian biological clock (Pace-Schott & Hobson, 2002), is responsible for maintaining a regular rest-activity rhythm. As the SCN undergoes degenerative changes in aging (Hofman & Swaab, 2006), a disrupted rest-activity rhythm is likely to be present in the aged population. Disturbances in this rhythm generally include daytime sleepiness, nocturnal activity and a reduction in amplitude (Bliwise, Ansari, Straight, & Parker, 2005; Haimov &
Lavie, 1997; Huang et al., 2002). However, as the hypothalamus, where the SCN is located, contains many afferent and efferent connections with cortical and subcortical areas (Risold, Thompson, & Swanson, 1997), damage to any of these connections might lead to a disrupted rest-activity rhythm. For example, one study found increased daytime sleepiness in patients with subcortical lesions compared to AD and Parkinson patients (Bliwise, Rye, Dihenia, & Gurecki, 2002). The authors suggested that, as some of the patients had lesions affecting the vasculature, these lesions affected the blood supply to the SCN, causing the altered circadian rhythm.

### Integrating White Matter

#### Executive Function

EF has been defined as the higher-order functions operating in non-routine, i.e. novel, complex, and/or conflicting situations (Godefroy, 2003). As such, they are extremely important for independent living and the maintenance of daily activities (Cooney, Kennedy, Hawkins, & Hurme, 2004; Royall, Palmer, Chiodo, & Polk, 2004). Although described as higher-order functions, EF requires and interacts with more basic functions (Royall et al., 2002). The prefrontal cortex is probably most crucial for intact EF (Royall et al., 2002). The prefrontal cortex is an extensive and heterogeneous structure with connections to both cortical and subcortical areas (Pandya & Yeterian, 1996). As such, it is highly suited for the integration of multiple functions. Indeed, frontal lobe damage has profound effects on EF (Baldo, Delis, Wilkins, & Shimamura, 2004; Leskelä et al., 1999; Stuss, Floden, Alexander, Levine, & Katz, 2001a), although damage to other non-frontal brain structures might result in EF deficits as well (Leskelä et al., 1999; Stuss et al., 1998). An explanation for this observation is that EF requires more basic cognitive abilities situated in non-frontal cortical and subcortical regions. As such, a distortion in EF as a result of damage to one of these brain regions can be expected.

The connections of the prefrontal cortex with the cortical and subcortical brain structures are formed by the white matter. It is therefore not surprising that WMH may most profoundly disrupt prefrontal cortex functioning and, as a consequence, EF. Indeed, a unique relationship between WMH and deficits in EF has been suggested (O’Sullivan et al., 2001). Studies examining EF and WMH have generally adopted EF as a general phrase including various functions such as planning, flexibility, inhibition, and working memory. However, these functions include distinctive processes and not all may be equally affected as a result of WMH. For example, results with regard to working memory and flexibility tests are inconsistent (Bartres-Faz et al., 2001; Baum, Schulte, Girke, Reischies, & Felix, 1996; Boone et al., 1992; Sachdev, Wen, Christensen, & Jorm, 2005). Planning ability, highly affected by aging (e.g. Andres & van der Linden, 2000), has never been examined in relation to WMH. Also, there is a lack of detailed data examining the influence of the precise locations of WMH: it could be
argued that the frontal white matter is most important for EF, or that, by examining different WMH locations, one might be able to differentiate between various EFs.

Pain processing

The functional architecture of pain involves two distinct systems, namely the medial and lateral pathways (Vogt & Sikes, 2000). These pathways are involved in the processing of distinct pain aspects and are presumed to act fairly independent of one another (Vogt & Sikes, 2000). The processing of pain requires several distinct components, including a sensory-discriminative, a motivational-affective, a cognitive-evaluative and an autonomic-neuroendocrine component (Treede, Apkarian, Bromm, Greenspan, & Lenz, 2000). The lateral pathway processes the sensory-discriminative aspects, whereas the medial pathway processes the motivational-affective, cognitive-evaluative and autonomic-neuroendocrine components. Most studies these days have focused on the sensory-discriminative and motivational-affective aspects. The former concerns the intensity and location of pain while the affective-motivational aspects include the emotional responses to pain.

The experience of both pain intensity and pain affect may change in aging. However, contrasting findings about the nature of this alteration have been reported with different possible underlying mechanisms. For example, a decrease in pain experience in aging has been observed (Gagliese & Melzack, 2003; Lasch, Castell, & Castell, 1997). Age-related changes in nociceptive pathways, such as decreased density of peripheral nerves, may explain these observations (Gibson & Farrell, 2004). However, pain experience may also increase as a result of neurodegenerative processes in the central nervous system (Edwards, Fillingim, & Ness, 2003; Lautenbacher et al., 2005). An extensive neural network with widespread connections is involved in pain processing, and a disruption somewhere in this network may have profound effects. The frontal cortex, and especially the dorsolateral prefrontal cortex, may play a crucial role in pain inhibition by suppressing medial thalamus-midbrain connections (Casey, Lorenz, & Minoshima, 2003; Lorenz, Minoshima, & Casey, 2003). As WMH are known to reduce dorsolateral prefrontal cortex functioning, through the process of deafferentiation (Farrell, Katz, & Helme, 1996), possible alterations in pain experience due to WMH can be anticipated. More specifically, WMH may decrease pain inhibitory functioning which is exerted by the dorsolateral prefrontal cortex. A possible increase in pain experience is furthermore supported by the observation that, in the context of pain, the aged population reveals a reduction in endogenous analgesic response (Washington, Gibson, & Helme, 2000). As such, various mechanisms may result in possible alterations in pain experience.
Rest-activity rhythm

Actigraphy is a frequently applied method to assess the rest-activity rhythm. Several variables can be deduced from these measurements, including the interdaily stability (IS), the intradaily variability (IV), nocturnal activity (L5) and the amplitude (AMP). The IS represents stability of the rhythm over 24-hour periods, the IV is a measure of rhythm fragmentation, L5 displays activity in the least active 5-hour period, whereas AMP is denoted by subtracting L5 from the most active 10-hour period (M10). Several of these variables do reveal age-related alterations (Huang et al., 2002). Reasons suggested for this observation include degeneration of the SCN, decreased sensitivity to zeitgebers, or a decrement in output variables generated by the SCN (van Someren et al., 1996). For example, decreased sensitivity to light, a very important zeitgeber for rest-activity rhythm functioning, increases in aging (Duffy, Zeitzer, & Czeisler, in press). These factors may disrupt input and/or output of the SCN and, thereby, the rest-activity rhythm.

Also, disruption of efferent or afferent SCN pathways can be postulated as one explanation of the distorted rest-activity rhythm in aging, considering the neurodegenerative processes that accompany the aging process. Previous research does suggest involvement of the white matter in the circadian rhythm (Kanda, Matsui, Ebihara, Arai, & Sasaki, 2003; Meguro et al., 1995), although data concerning specific white matter regions and detailed rest-activity rhythm variables as assessed with actigraphy is lacking.

A mediating role of cardiovascular risk factors

Cardiovascular risk factors are commonly acknowledged to induce both WMH and cognitive decline in aging. As such, they may mediate part of the relationship between WMH and EF. Furthermore, the phenomenon of blood pressure-related hypoalgesia, in which an increase in blood pressure (BP) is associated with a decrease in pain sensitivity, suggests an interaction between the pain and cardiovascular regulatory systems. Increasing our knowledge about the precise contributions of cardiovascular risk factors and BP to WMH-related executive deficits and pain experience is therefore crucial.

Cognition

Accumulating evidence indicates that cardiovascular risk factors may account for part of the age-related cognitive decline, including executive dysfunctioning (Kilander et al., 1998; Pugh, Kiely, Milberg, & Lipsitz, 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Starr, Deary, Fox, & Whalley, in press; Teunissen et al., 2003; Verhaeghen et al., 2003). The far majority of these studies has focused on hypertension or high BP in the elderly, with an increasing interest in other factors including diabetes mellitus and cardiac disease. Negative
associations of BP with cognitive functioning are extensive and have been found for hypertension (Raz et al., 2003), midlife BP (Swan et al., 1998) and current BP (Kuo et al., 2004). Similar results have been reported for both diabetes mellitus and cardiac disease (e.g. Verhaeghen et al., 2003). However, several limitations exist. First of all, these studies examined only a view EF tests instead of trying to cover the entire EF domain. Furthermore, these studies are commonly restricted to relatively young elderly persons, whereas studies examining the association of BP with cognition in the very old are limited and inconclusive. Those studying this age population report varying results such as either low BP relating to cognitive deterioration (Guo, Viitanen, & Winblad, 1997; Kuo et al., 2005), or a negative (Harrington et al., 2000) or positive (Guo, Fratiglioni, Winblad, & Viitanen, 1997) effect of high BP on cognition. The discussion of whether low BP primarily causes (Waldstein, Giggey, Thayer, & Zonderman, 2005) or is secondary to (Burke, Coronado, Schmitt, Gillespie, & Chung, 1994) cognitive deterioration further impedes drawing conclusions from these inconsistent findings.

Blood pressure and pain

Next to effects of aging, BP may be related to pain experience. More specifically, interactions between the cardiovascular and pain regulatory systems have been postulated (Randich & Maixner, 1984). Through yet unknown mechanisms, the height of BP can be associated with pain experience. Both hypertension and elevated ‘normal’ BP have been found to relate to a decrease in reported pain following a pain stimulus (Bruehl, Carlson, & McCubbin, 1992; Campbell, Hughes, Girdler, Maixner, & Sherwood, 2004; Guasti et al., 1996). However, in chronic pain patients, a reversed relationship has been observed for both acute and chronic pain sensitivity (Bruehl, Burns, & McCubbin, 1998; Bruehl, Chung, Ward, Johnson, & McCubbin, 2002), suggesting an altered interaction between the cardiovascular and pain regulatory systems.

How are all these processes interrelated and why are they so important to investigate? First of all, when considering white matter-related conditions, most studies focus on general cognitive deterioration, including EF and a variety of cognitive functions (Deary et al., 2006; Dufouil, Alperovitch, & Tzourio, 2003; Ylikoski et al., 1993). However, not all EFs may be equally affected by WMH. Also, as can be deduced from the existing literature, the white matter may be involved in pain processing as well as the rest-activity rhythm. The question is, whether WMH in general or specific white matter regions are important when considering EF, pain, and the rest-activity rhythm. It can also be argued that examining these three topics induces a differentiation within the white matter, i.e. periventricular and deep white matter hyperintensities may not similarly affect EF, pain processing, and the rest-activity rhythm.

The clinical relevance of this research is highlighted in several ways. Although our knowledge about altered cognitive processes in aging is expanding, little is known about the precise pattern of cognitive deterioration, pain processing and
the rest-activity rhythm in aging with underlying changes in brain structures. The presence of pain, for example, might still go unnoticed either because elderly simply accept it as part of the aging process or do not want to complain about pain in case it negatively affects their care (Ferrell, Ferrell, & Osterweil, 1990). Establishing possible alterations in pain experience following age-related changes in the brain is therefore crucial.

Although the severity of neurodegenerative changes differs remarkably between aging and dementia, similarities between these clinical populations do exist. For example, WMH are observed in both aging and dementia, including VaD and AD (Varma et al., 2002). Research in the demented populations is limited by severe cognitive deterioration and reduced communicative ability. As such, expanding our knowledge about changes in EF, pain experience, and the rest-activity rhythm in a population with relative minor changes in the brain might increase our knowledge with regard to clinical populations with more extensive neuropathological abnormalities. Examples illustrating the high priority of increased knowledge include the risk of undertreatment of pain in dementia, as a result of communicative and cognitive disability (Scherder, 2000; Scherder et al., 2005)

Outline of the present thesis

The present thesis focuses on several aspects in aging, with the examination of possible widespread associations of WMH with EF, pain, and the rest-activity rhythm as the central theme. Furthermore, attenuating effects of cardiovascular risk factors on these topics will be examined. Finally, possible similarities and relationships with the field of dementia will be discussed. To accomplish this, the present thesis describes a variety of topics that together provide more insight in all of the above-mentioned research questions.

In chapter 2 a meta-analysis of existing literature on WMH and neuropsychological test performance is performed. The main goal is to examine different tests separately, with the emphasis on EF, in patients with WMH that are either related or unrelated to the presence of cardiovascular risk factors. A specific issue that is addressed here is whether the several EF tests, despite that they theoretically are all constructs of EF, are equally related to WMH. Next to WMH in general, a differentiation between periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) is made. Also, various EF domains in relation to WMH are examined.

In chapter 3, the question is addressed whether AD and VaD patients can be distinguished based on cognitive performance on a test battery generally applied to assess IQ. It is hypothesized that, although representing groups with severe cognitive deterioration, they may still display distinguishable cognitive profiles as proven with the Wechsler Adult Intelligence Scale test battery, which is frequently applied in clinical settings. More specifically, VaD patients are expected to reveal deficits in EF as opposed to AD patients. AD patients,
however, are hypothesized to reveal exacerbate deficits in memory functioning compared to VaD patients.

Chapter 4 discusses three different working memory tests in relation to WMH. The goal of this chapter is to explore whether these different working memory tests are or are not equally related to WMH. Differences in task properties may reveal distinct WMH effects. Also, decrements in task performance may, due to the varying cognitive abilities a test assesses, be related to diverse WMH regions. In order to examine this postulation, we included total WMH, separate PVH and DWMH, and WMH subscores (e.g. frontal DWMH) in the analyses. Further possible attenuating effects of cardiovascular risk factors are explored.

In chapter 5, several tests known to assess various components of EF are examined. Domain scores for the varying EF components were computed, and associations with the WMH subscores calculated. How aging and cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease, smoking) relate to WMH subscores is investigated. Furthermore, it is determined to what extent aging and the cardiovascular risk factors mediate the associations of the EF domains with the WMH subscores.

Chapter 6 explores possible associations between pain experience and WMH. This question is addressed in order to investigate the possibility of deafferentiation to relate to an increase in pain experience. Therefore, the experience of both pain intensity and pain affect was assessed, and associations with WMH examined. A total WMH score, separate PVH and DWMH scores, and WMH subscores were used for analysis.

In chapter 7 associations between WMH and the rest-activity rhythm are investigated. This study focuses on stability of the rhythm over days (IS), the variability of the rhythm within days (IV), and level of activity (AMP) in relation to WMH. A differentiation between white matter subregions is made.

Chapter 8 focuses on possible associations of current BP with EF in nursing home residents. It is investigated whether associations between BP and EF are still present in the oldest old, and whether BP-related effects extent to all EFs examined. A distinction between systolic (SBP) and diastolic (DBP) BP is made.

Chapter 9 examines possible associations of SBP and DBP with pain experience in nursing home residents, while distinguishing between residents with and without chronic pain. A negative association between BP and pain in subjects without chronic pain has been reported, whereas this association might be reversed in chronic pain patients. Nursing home residents were included in order to investigate whether these associations are still present in the oldest old.

In chapter 10 a summary and discussion of the current work is presented. The major aim is to discuss the implications of the studies and to provide some general conclusions.