Several issues were addressed in the present thesis, with white matter hyperintensities (WMH) and executive function (EF) in aging as central topics. It was examined how WMH relate to various EFs, pain and the rest-activity rhythm. Effects of cardiovascular risk factors, as they are common in normal and neuropathological aging, on WMH, EF, and pain experience were additionally explored. Finally, we compared cognitive functioning between patients with Alzheimer’s disease (AD) and vascular dementia (VaD).

Summary

In chapter 2 a meta-analytic review of studies examining the relationship between WMH and cognitive tests was provided. Studies published between 1990-2003 and examining WMH in relation to cognitive performance in aging were examined. Prerequisites for inclusion of these studies included the following: the study population was either a selection of non-demented aged subjects or representative of the community dwelling elderly, associations between task performance and WMH were corrected for age, and cognitive functioning was reported at an individual task-based level. We differentiated between studies that did and did not establish an association between WMH and cardiovascular risk factors. A total of 22 studies met the selection criteria and were included in the meta-analysis. Thirteen of these examined WMH without a specific association with cardiovascular risk factors, and 10 studies were enrolled into part of the analysis examining WMH related to cardiovascular risk factors (1 study entered both parts of the analysis). A minimum of three studies applying a certain cognitive test was a requisite for this test to be meta-analytically examined. This resulted in the inclusion of the following tests in the group without cardiovascular risk-related WMH: the Mini Mental State Examination (MMSE), Trail Making Test (TMT) part A and B, Stroop Colour (C) and Colour/Word (C/W) cards, Digit Symbol Substitution test (DSS), Letter and Category Fluency, Digit Span forward and backward, Similarities, Information, Block Design, Visual Reproduction immediate and delayed recall, Logical Memory delayed recall, and reaction time tests. WMH significantly correlated with TMT-A, Stroop C and C/W cards, Letter and Category Fluency, DSS, and, marginally, the Block Design test. In the group where cardiovascular risk factors constituted WMH, the following tests were examined: MMSE, TMT part A and B, Stroop C/W, DSS, Digit Span forward and backward, Wisconsin Card Sorting Test (WCST) number of categories achieved, perseverative errors and total errors, complex reaction time test, and the Purdue Pegboard test with preferred, non-preferred, and both hands trials as well as an assembly trial. The MMSE, TMT-A, Stroop C/W, DSS, complex reaction time test, and the Purdue Pegboard assembly trial related to WMH. The main conclusion was that, in patients with WMH either initiated or not by cardiovascular risk factors, EF, but not memory or motor speed performance, is related to WMH. More specifically, mostly timed EF proved sensitive to WMH. EF tests such as the Digit Span backward and WCST, tests without a time component, did not relate to WMH. Also, a composite Working Memory domain, composed of mainly non-timed tests of working memory, was not associated with WMH. One plausible explanation for this
observation states that WMH mainly affect mental speed, a function that deteriorates in aging and is known to mediate a major part of the age-related cognitive decline, including executive dysfunctioning (Salthouse, 2005; Salthouse & Meinz, 1995).

In chapter 3 the possibility was explored whether a frequently applied neuropsychological test battery, the Wechsler Adult Intelligence Scale (WAIS), might be useful in differentiating between patients with AD and VaD. The purpose was to examine whether, despite that severe cognitive deterioration is present, differences in cognitive performance between these populations do exist and can be established by means of the WAIS. We expected that tests with a high load on EF (i.e. Block Design, Digit Span backward, Digit Symbol Substitution, Object Assembly, Picture Arrangement, Picture Completion) would be most strongly impaired in VaD compared to AD patients, whereas tests that mainly require memory processes would be most strongly affected in AD patients (i.e. Information, Vocabulary). We searched for studies examining any of the WAIS subtests in AD and VaD patients. Selection criteria were as follows: a diagnosis of AD and VaD based on standardized diagnostic criteria including imaging techniques, AD and VaD groups matched on age and severity of dementia, and the reporting of cognitive test outcomes useable for the meta-analysis (means ± SD). Eventually, 16 studies were enrolled. The primary analysis revealed that VaD patients performed superior on the Information subtest whereas inferior performance compared to AD patients was noted on the Digit Span backward and Object Assembly tests. VaD is a heterogeneous disorder with varying clinical and pathological presentations, which disables comparing AD with VaD. To overcome this limitation, a further analysis was restricted to studies documenting the inclusion of subcortical VaD (sVaD) patients. In this second analysis, nearly all EF tests, with the exception of the DSS task, revealed diminished performance in the VaD group, whereas AD patients revealed marginal inferior performance on the Information subtest, the only memory test included in this part of the analysis. It was concluded that the WAIS can be used to distinguish between VaD and AD, indicating mainly disproportional executive deficits in VaD patients. However, it should be taken into account that the VaD diagnosis encompasses a variety of heterogeneous disorders.

Chapter 4 focused in more detail on the relationship between working memory and WMH. The association of the Digit Span backward and other working memory tests with WMH in aging was examined. Following both chapter 2 and previous studies in which the Digit Span backward was found not to relate to WMH, this chapter examined possible explanations for this observation. These included the following: Digit Span backward performance may simply not relate to WMH; when establishing an association between the Digit Span backward and WMH, more detailed WMH regions (e.g. frontal periventricular hyperintensities) should be examined; or it can be argued that the presence of cardiovascular risk factors attenuates a possible relationship between WMH and Digit Span backward performance. Since more recent studies do suggest impaired working memory performance as a result of WMH (Deary et al., 2006; Nordahl et al., 2006), an association between WMH and working memory function was expected.
Conform previous observations, performance on the Digit Span backward test did not relate to any white matter variable, and was not significantly contributed to by cardiovascular risk factors. Other working memory variables related to, particularly, frontal deep white matter. Results are discussed in terms of test properties, distinguishing between tasks that do (other working memory tests) or do not (Digit Span backward) require concurrent storage and manipulation of information. These differences directly relate to demands that are placed on cognitive and working memory capacity, which are increased in case of concurrent storage and manipulation. It could be argued that, in order to detect the relative minor cognitive decline that accompanies aging, test selection is crucial in that the more cognitive capacity is required, the more likely it is to find a decrease in cognition or, in this case, working memory. As such, the Digit Span backward might be insensitive in detecting the minor cognitive decline that results from WMH in aging.

Chapter 5 highlights that diverse EF domains may not equally relate to white matter subscores. The EF domains examined in this chapter included Flexibility, Fluency, Inhibition, Planning, Set Shifting, and Working Memory. A general involvement of white matter in EF, as was proposed previously (Tullberg et al., 2004), implies that all white matter subscores, regardless of location, should relate to EF. To test this possibility, correlations between the EF domains and WMH subscores were calculated. The results indicate that for some EF domains, namely Inhibition and Working Memory, significant associations between performance and various WMH subscores emerged, whereas for other EF domains significant correlations were restricted to some WMH subscores. For example, posterior deep white matter hyperintensities (DWMH), including the temporal and occipital regions, related to Fluency, Flexibility and Set Shifting performance, whereas other white matter regions did not. This implies that EF tests are not equally affected by WMH and, therefore, differentiating between these tests is vital. The heterogeneous nature of EF tests may determine the associations with WMH regions in aging. For example, temporal DWMH most strongly predicted Flexibility performance as assessed with TMT-B. This observation could reflect the previous established involvement of the temporal lobe in performing this task (Baillon et al., 2003; Zakzanis, Mraz, & Graham, 2003). Working memory performance, which reveals an increase in frontal activity in aging (Grossman et al., 2002), was most strongly affected by frontal DWMH. Furthermore, age emerged as the major risk factor for WMH, with increases in all WMH subscores relating to increasing age. Also, age was a strong predictor of EF, with a decline in each EF domain accompanying an increase in age. Hypertension additionally negatively affected some WMH subscores, whereas smoking behavior predicted both Inhibition and Working Memory performance.

In chapter 6 it was investigated whether WMH relate to pain experience. The processing of pain is acknowledged to involve two distinct pathways, a lateral and medial pathway. The lateral pathway is involved in transmitting signals about pain intensity and pain location, whereas the medial system processes information about affective and cognitive aspects of pain. These pathways are
presumed to work largely independently from one another. Both pain intensity and pain affect were examined, and possible associations with total WMH and white matter subscores were the focus of interest. Pain intensity was assessed with the Coloured Analogue Scale (CAS), whereas the Number of Words Chosen-Affective (NWC-A) was chosen as a measure of pain affect. Total WMH and, more specifically, PVH positively related to pain affect, but not pain intensity. Results are discussed in terms of deafferentiation as a result of WMH, with the presumed strongest implications for altered functioning of the dorsolateral prefrontal cortex (DLPFC), an area known to be involved in pain inhibition. The involvement of the PFC in processing of emotional information probably explains the relationship of WMH with pain affect, but not intensity.

Chapter 7 focused on another issue in aging, namely distortions in the circadian rest-activity rhythm. Despite that age-related neurodegenerative changes of the suprachiasmatic nucleus (SCN) have generally been optioned to underlie the disturbed rest-activity rhythm in aging, some studies suggest a role for WMH as well. The rest-activity rhythm was assessed by means of an objective registration method, actigraphy. Three variables were deduced from this registration, namely interdaily stability (IS), intradaily variability (IV), and amplitude (AMP). IS quantifies the strength of coupling of the rest-activity rhythm with zeitgebers (e.g., light). IV indicates the fragmentation of the rhythm, i.e. the frequency and extent of transitions between rest and activity within a 24-hour period. Finally, AMP was calculated by subtracting the least active 5-hour period (L5) from the most active 10-hour period (M10), representing level of activity. Results revealed that frontal DWMH was the strongest predictor of both IS and AMP, whereas not a single white matter subscore was significantly related to IV. Possible explanations focus on the functional implications of frontal DWMH, including a reduction in self-initiated movements and possible diminished SCN input through reduced light transmission.

Chapter 8 examined whether blood pressure (BP) relates to a variety of EFs. Previous studies are inconclusive in whether all EF relate to BP and if this effect maintains into very old age. This is specifically important when considering previous studies reporting a favorable effect of high BP on cognition or a detrimental association of low BP with cognitive ability in the oldest old. Results revealed that normal systolic BP (SBP), that is SBP < 120 mmHg, related to better Flexibility and Fluency performance. No additional associations of SBP or diastolic BP (DBP) with EF were noted.

Chapter 9 explored possible associations of SBP and DBP with pain intensity and pain affect in nursing home residents. A differentiation between residents with and without chronic pain was made, considering the implications for a negative association of BP with pain in subjects without chronic pain, whereas a positive relationship between BP and pain has been established in chronic pain patients. However, these findings were limited to middle aged subjects without clinical implications for a relationship between BP and pain in the oldest old. Results revealed that in the chronic pain group, but not the group without chronic pain,
DBP was positively associated with pain affect, implying that higher DBP relates to an increase in reported pain affect.

**Implications of the present study**

**White matter and executive functions**

A general conclusion that can be drawn from this thesis is that the precise relationship between EF and WMH requires elucidation. For example, in chapter 2 we argued that, in accordance with additional studies, the mental speed component that is involved in EF tests is sensitive to WMH, which is conform the postulation of a general slowing effect mediating a large part of the executive deficits in aging (Salthouse, 2005; Salthouse & Meinz, 1995). Alternative explanations, however, can be optioned and should be examined. When one considers the relatively mild cognitive decline in aging, it can be imagined that test properties might attenuate cognitive outcomes on these measures. An example of these properties includes the sensitivity of a test to detect minor cognitive deterioration. This notion may directly relate to speed of processing: it can be argued that performance expressed as speed of processing is a more sensitive measure of cognitive functioning compared to measures such as number correct, irrespective of aging. One implication of this suggestion is that the association between WMH and timed EF tests may exist because test properties are more sensitive to the effects of age-related cognitive decline, not because of a specific age effect on processing speed.

This discussion incorporates a weakness of several previous studies, as most of them examined timed EF tests, lacking a critical appraisal of underlying test characteristics. Furthermore, studies mostly focused on a single or a few EF tests as representative of EF, disregarding the different cognitive properties that make up these tests. As such, several research questions arise around the nature of the relationship between WMH and EF. One of them concerns whether a specific processing speed or test sensitivity determines the association between WMH and timed EF tests. Also, are various EF domains equally sensitive to WMH or do differences between these domains exist?

With regard to test selection, previous studies frequently employed the Digit Span backward test as a measure of working memory. The vast majority of these studies failed to show an association between performance and WMH (Sachdev, Wen, Christensen, & Jorm, 2005; Schmidt et al., 1993; Skoog, Berg, Johansson, Palmertz, & Andraessson, 1996; Ylikoski et al., 1993), and commonly concluded that working memory is unrelated to WMH. Test selection, however, appears crucial when assessing working memory performance (chapter 4). Digit Span backward performance appeared to be unrelated to WMH, but a decrease in working memory performance as a result of WMH was supported. More recent studies examining other working memory tests, such as the Letter-Number sequencing test, do support decreased performance to relate to increasing levels
of WMH (Deary et al., 2006; Nordahl et al., 2006). This indicates that a critical examination of neuropsychological tests of working memory is warranted. With regard to the question whether speed of processing mediates the EF-WMH relationship, neuropsychological testing in the present thesis included both EF tests with and without a time component (Chapter 4 and 5). A reduction in performance on both types of EF tests as a result of WMH was confirmed. In agreement with aging research, where the association between age and EF has been shown to extend beyond a mediating effect of processing speed (Keys & White, 2000), WMH induce deficits in EF, regardless whether timed or untimed.

It further seems promising to distinguish between different EF domains. The involvement of diverse WMH regions in these domains implicates a differentiation between various EF domains is essential. This suggestion is furthermore supported by the observation that not every white matter subscore correlated with each EF domain. It is possible that the diverse cognitive functions required for a particular EF domain determine the associations between performance and subregions of the white matter.

How pain experience relates to brain regions and cognition

Based on previous research suggesting an alteration in pain experience as a result of deafferentiation, it was examined whether WMH, by inducing cortical disconnection and, thus, deafferentiation, would already reveal a positive relationship with pain experience in nondemented elderly people. The present study confirms such an association, resulting in a number of questions to be asked. First of all, as WMH apparently relate to both pain experience and EF, it can be questioned whether a common process underlies both deficits. This implies that an alteration in pain experience as a result of WMH could concomitantly present with executive deficits. If this is the case, a direct relationship between pain and EF is to be expected, suggesting that executive dysfunctioning should be indicative of an increase in pain experience. However, both pain (Eccleston & Crombez, 1999) and cognitive processes demand attention. It can therefore be postulated that the co-occurrence of these two elements induces a competition between attentional processes. This implies that the presence of one of these factors reduces the availability of attentional resources with regard to the other factor. In detail, performing a cognitive task limits attention to be dedicated to pain, whereas the continuous presence of pain (i.e. chronic pain) should reduce attentional processes available for cognitive task performance. Indeed, it has been reported that, compared to the sole application of a pain stimulus, this application is perceived as less intense when subjects are engaged in a demanding cognitive task (Bantick et al., 2002; Valet et al., 2004). Also, decreased cognitive performance in chronic pain patients (Harman et al., 2005) and an improvement in cognitive functions following pain relief (Tassain et al., 2003) have been reported. Final evidence for increased pain experience to co-occur with decreased cognitive functioning was provided by Pickering and coworkers (Pickering, Jourdian, Eschalier, & Dubray, 2002). In an interesting
study, these authors showed that a positive relationship between cognition and pain tolerance exists, in that better cognitive functioning relates to increasing levels of pain tolerance. Alternatively, in aging, pain anticipation and reactivity may positively relate to cognitive ability (Benedetti et al., 2004). As such, based on existing literature, several explanations regarding a relationship between pain and cognition can be proposed, implicating that further research regarding this association is necessary.

Secondly, as a presumed similar process underlies pain experience in both VaD and aging, do such similarities also exist with regard to other neurodegenerative disorders? For example, the hippocampus, a structure that is involved in both memory (Burgess, Maguire, & O’Keefe, 2002; Tulving & Markowitsch, 1998) and pain processing (Bingel et al., 2002; Kwan et al., 2005), undergoes relative mild degenerative changes in aging and more severe in AD (Jack et al., 1998). It has been well documented that AD patients report less pain intensity and pain affect (Scherder, Bouma, Borkent, & Rahman, 1999; Scherder et al., 2001) and may present with increased pain tolerance (Benedetti et al., 1999). One possibility is that hippocampal damage, diminishing functionality of the medial pain system, underlies the observation of reduced pain experience in AD patients. A following conclusion might be that the relative minor neurodegenerative changes of the hippocampus observed in aging do relate to reported pain experience, which may be lower in case of more damage. As the hippocampus plays an important role, next to pain experience, in memory ability, it can be argued that memory dysfunctioning is an important mediator of the changes in pain perception and experience in both AD and non-demented aged population.

Rest-activity rhythm

Frontal DWMH was the strongest predictor of both IS and AMP, and might be attributed to either reduced physical activity or reduced light input. With regard to physical activity, frontal DWMH impairs frontal lobe functioning (Nordahl et al., 2006), an area known to be involved in self-initiated movements. Several retinofugal pathways exist, including a path from the retina to the SCN called the retinohypothalamic tract (Moore, Speh, & Card, 1995), which may be affected as a consequence of frontal DWMH. Next to frontal DWMH, occipital PVH revealed negative associations with both IS and AMP, in that an increment in hyperintensities in this white matter region related to a decrement in IS and AMP. The observation that no additional WMH subregions correlated with the rest-activity rhythm variables implies a specific involvement of frontal DWMH and occipital PVH, and not a general disconnection effect as a result of WMH (Meguro et al., 1995). An involvement of occipital PVH with regard to the processing of light can be incorporated as well. Retinofugal pathways include, next to the SCN, projections to the lateral geniculate nucleus (LGN), and the midbrain (superior-colliculus (SC) and pretectum (PT)). The LGN projects immediately to the primary visual cortex (V1), which is situated in the occipital lobe. There are two processes through which the visual cortex (VC) might be related to altered processing of visual input. First of all, lesioning of the VC in
rats was found to result in larger differences in waking amounts between light and dark periods, and postulated to occur by inducing increased excitation of the SC and PT (Miller, Obermeyer, Behan, & Benca, 1998). Secondly, V1, through layer 6, projects back to the LGN (Sillito & Jones, 2002). The observation that deactivation of the VC results in SC and, to a lesser extent, dorsal LGN deactivation (Rushmore, Payne, & Lomber, 2005), confirms the functional connectivity between the VC and these brain structures. As such, WMH may directly reduce input to the SCN by affecting the retinofugal tracts or indirectly by reducing the functional connectivity between VC and SC or LGN.

White matter regions

One of the main questions of this thesis was whether differentiating between the various white matter subregions is of value. The present study does support that with respect to all examined research topics, which included different EF domains, pain, and the rest-activity rhythm, distinguishing between these regions is essential. For example, lateral PVH was the strongest predictor of Inhibition performance on cognitive tests, as well as of reported pain affect. Frontal DWMH was the strongest contributor to both working memory and the rest-activity variables IS and AMP. Finally, temporal and occipital DWMH constituted the most important predictors of Flexibility and Set Shifting performance.

These results might point to an overlap between diverse functions. For example, a concurrent involvement of lateral PVH in both cognitive inhibition and pain processing was noted. More specifically, an increase in pain affect related to increasing levels of lateral PVH, and was hypothesized to be attributable to a decrease in prefrontal inhibitory processes. As such, a similar neural and functional basis may account for both observations. Perhaps, lateral PVH, through connections with the PFC and other cortical and subcortical regions, is involved in a general inhibitory function, evident in both cognitive and pain processing. Equally, a similar neural and functional basis for working memory, IS, and AMP is suggested by the involvement of frontal DWMH in both processes. Although an apparent contradictory suggestion, the previous optioned explanation of physical activity to possibly underlie the relationship between IS, AMP and frontal DWMH provides support for this similar basis. Studies report physical activity to relate to the rest-activity rhythm (van Someren, Lijzenga, Mirmiran, & Swaab, 1997b), in which the frontal lobe may be a key structure in this activity through self-initiated movements (Jahanshahi et al., 1995; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). As such, frontal DWMH may reduce frontal lobe functioning, resulting in a reduction in self-initiated movements, thereby affecting IS and AMP. How to integrate working memory? A previous study has suggested a specific role of working memory processes in self-initiated movements (Wiese, Stude, Nebel, Forsting, & de Greiff, 2005). These working memory processes were presumed to be involved in the monitoring of task performance, and related specifically to PFC activation (Wiese et al.). A deficit in working memory functioning may therefore mediate deficits in both
cognitive task performance and physical activity, the latter relating to IS and AMP.

Effects of blood pressure

The observation of a concurrent involvement of BP in EF and in pain experience indicates the possibility of a similar mechanism underlying these associations. Take for example a patient with chronic pain and high BP. In this patient, an increase in pain report together with a decrease in EF would be expected. Furthermore, in a subject without chronic pain and with high BP, a decrease in pain report together with a decrease in EF might be noted. If a similar mechanism is involved, one would expect to find direct associations between EF and pain experience in both groups.

As the effect between BP and EF was previously suggested to be mediated through frontal and temporal lobe involvement (chapter 8), the question arises whether one (or both) of these cortical regions underlies the association between BP and pain experience. Previous reports suggest involvement of the PFC in pain inhibitory processes (Casey, Lorenz, & Minoshima, 2003; Lorenz, Minoshima, & Casey, 2003), and as such the PFC may be our target area. In order to understand the involvement of the PFC in both pain experience in chronic pain patients and in EF, the precise interaction between the cardiovascular and pain regulatory systems needs to be considered. In general, the presence of pain induces an increment in sympathetic arousal that leads to increased BP. The increase in BP subsequently triggers activation of the descending pain inhibitory pathways, reducing arousal and, as a consequence, BP. In chronic pain patients, a prolonged activation of the descending pain inhibitory pathways may lead, through desensitization or exhaustion, to dysfunctioning of these pathways and, hence, pain and BP levels remain high (Bruehl & Chung, 2004). Further support for dysfunctioning of pain inhibitory pathways in chronic pain patients comes from studies showing an increase in acute pain sensitivity in these patients compared to normal controls (Lautenbacher & Rollman, 1997; Lautenbacher, Rollman, & McCain, 1994). This indicates that, in chronic pain patients, a similar dysfunctional mechanism might be involved in both BP and pain. So how can the frontal lobes be comprised? Some studies do suggest involvement of the PFC in cardiovascular reactivity regulation in response to stressors (Resstel, Fernandes, & Correa, 2004; Sevoz-Couche, Comet, Bernard, Hamon, & Laguzzi, 2006; Tavares & Correa, in press), and, considering the involvement of the PFC in pain inhibition, it can be suggested that the PFC may be a key structure in the pain and cardiovascular regulatory systems. As such, it may be an important mediating structure of the dysfunctional regulation of BP and pain in chronic pain patients. If this is the case, dysfunctioning of the inhibitory pain systems and, hence, the PFC, that occurs through continuous stimulation as a result of chronic pain, might relate to maintenance of high BP and precedes BP dysregulation in chronic pain patients. Evidence exists supporting selective impaired PFC metabolism and decreased PFC grey matter volumes in chronic pain patients compared to normal controls (Apkarian et al., 2004b; Grachev,
Fredrickson, & Apkarian, 2000). A unique contribution of PFC dysfunctioning to the modulation of BP in chronic pain patients can therefore be postulated.

One question remains unanswered though. One would expect that high BP in normal controls, by causing damage to the PFC, reduces PFC integrity (Raz et al., 1997) and, hence, diminishes pain inhibitory processes. So why would the PFC be dysfunctional in chronic pain patients only? One answer is that, in our study population, this is not the case. Previous studies on BP and pain experience have focused on young and middle aged adults. As such, the detrimental effects of BP on PFC integrity might not be noticeable yet, resulting in the observed negative relationship between BP and pain experience. However, in an old population, such as examined in chapter 9, the effect of BP on PFC integrity is likely to be established, explaining why no expected negative association between BP and pain in nursing home residents without chronic pain was observed in that study.

Future directions

Functional imaging

To further elucidate the relationship between EF and white matter regions, insight into how WMH alter cognitive processes is required. For example, studies do reveal that WMH are directly related to reduced frontal lobe metabolism (Reed et al., 2004; Tullberg et al., 2004) and activity (Nordahl et al., 2006). Although evidence supports a dominant role of frontal WMH in this relationship (Nordahl et al., 2006), overall WMH burden is important as well (Nordahl et al.; Tullberg et al., 2004). The present observation of a differential effect of WMH subscores with regard to various EF domains (chapter 5), suggests that, when examining the effect of WMH on brain activation, a differentiation between the various white matter regions is of interest. For example, do the diverse white matter regions relate to frontal lobe activity or metabolism to the same extent in all EF domains or do differences between these regions exist? Latter option seems more likely, considering observations such as temporal DWMH to be the strongest predictor of Flexibility performance whereas it was unrelated to Working Memory performance. Again, the cognitive processes that are involved in certain EF tests are likely to determine how diverse WMH subscores influence frontal functioning.

Equal suggestions can be made regarding the examination of pain experience. How do WMH alter functioning of brain regions, with the emphasis on frontal lobe function, when someone experiences pain? One would expect to see that WMH do affect DLPFC functioning, in that imaging techniques such as functional Magnetic Resonance Imaging (fMRI) would reveal diminished functioning of the DLPFC reflecting reduced pain inhibitory control function. Also, do structural and functional images of other brain structures that are known to be involved in pain processing and undergo degenerative changes in
aging, such as the hippocampus, reveal direct evidence for possible alterations in pain experience? In more detail, does a structure such as the hippocampus, when mild neurodegeneration is present, reveals altered activity that corresponds to changes in pain experience? Do functional imaging techniques, in case of high BP and chronic pain, support a decrease in PFC functioning that corresponds to reduced pain inhibitory processes? Applying fMRI or other imaging techniques that indicate functioning of the brain (e.g. single photon emission computed tomography) in order to visualize pain and cognitive processing allows a direct connection to be made between these processes in terms of similar underlying brain structures and functions.

Chronic pain and dementia

Further insight into neuropathological changes in the brain in aging and how they relate to cognitive and pain processes may increase knowledge about possible alterations in these functions in dementia subtypes. We already showed that executive dysfunctioning is characteristic for VaD (chapter 3). Although they represent two different clinical populations and are characterised by a different neuropathological spectrum, support for similarities between nondemented aging and VaD exists in both the field of cognitive and pain research. Increasing our knowledge about pain processing is incredibly important with regard to effective pain treatment. For example, as VaD patients may present with an increase in pain experience (Scherder et al., 2003b), pain treatment possibly should be adjusted to meet the demands in this population. Alternatively, several studies suggest that AD patients receive less analgesic medication (Pickering, Jourdan, & Dubray, 2006; Scherder & Bouma, 1997; Semla et al., 1993). Balfour and O’Rourke (2003) observed that less than half of AD patients with a chronic painful condition (i.e. arthritis or rheumatism) were treated for pain. Despite that these patients report significantly less pain, the underlying mechanisms for this observation are unclear, and may include factors such as reduced communicative capability or a lower prevalence of chronic painful conditions in AD patients (Scherder, 2000). This implies that these patients are at risk of undertreatment of pain (Cole et al., in press; Nygaard & Jarland, 2005).

Additionally, support for structural brain changes in chronic pain patients exists. Next to the previously mentioned decrease in PFC density (Apkarian et al., 2004b) and PFC metabolism (Grachev et al., 2000; Shiraishi et al., 2006), further support for altered metabolism in other structures is emerging (Shiraishi et al.; Siddall et al., 2006). It is unknown whether these alterations result from or precede the development of chronic pain. However, these observations suggest that alterations in brain functionality relate to pain experience, and that severe neurodegenerative changes as observed in degenerative diseases such as AD might relate to pain processing.
Conclusions and clinical implications

The present study shows that WMH may be involved in a variety of EF, but also in pain processing and the circadian rest-activity rhythm. Next to a decrease in EF, WMH related to an increase in pain experience, and decreased stability and amplitude of the rest-activity rhythm. More specifically, frontal DWMH was the strongest predictor of working memory and both rest-activity rhythm variables, lateral PVH predicted cognitive inhibition and pain experience, whereas more posterior DWMH regions related to flexibility and set shifting performance. One conclusion might be that white matter is involved in a general control function, such as lateral PVH affecting inhibition functioning which is evident in both cognitive functions and pain experience.

With regard to the question whether AD and VaD patients present with distinguishable cognitive profiles as assessed with the WAIS subtests, this thesis provides a confirmative answer. VaD patients revealed inferior performance on tests tapping EF, whereas AD patients performed worse on a test that requires memory functioning.

Furthermore, effects of SBP on EF were noted for fluency and flexibility performance. A concurrent involvement in these EF domains of frontal and temporal lobe functions, two regions known to be affected by high BP, is likely to explain these specific BP-EF associations. High DBP also related to increasing levels of reported pain affect in chronic pain patients, a finding most likely to involve altered PFC functioning.

One of the most important implications of these findings is the possibility for changes in cognition, pain perception and/or the rest-activity rhythm to co-occur. As such, complaints that accompany aging can be multi-faceted. It might be necessary for clinicians, when cognitive decline is present, whether it includes a decrement in EF or memory functions, to consider alterations in pain processing.

Another possible interesting point is to examine structural brain damage such as WMH in more detail when considering cognition and specifically EF. For example, a test of working memory in case of posterior DWMH might not be an appropriate choice when one wishes to explore possible executive deficits. A test of working memory is, on the other hand, probably highly suitable to detect executive deficits in the context of frontal DWMH.

Equally, high BP in the oldest old should be acknowledged as a possible indicator of executive deficits as well as an increase in pain experience in case of chronic pain. This is probably a highly accessible goal, as BP readings are quite common in daily practice.