SUMMARY

The aim of the current thesis was to investigate cerebrovascular aspects of cognitive functioning and neuropsychiatric symptoms. First, we provided an overview of the Heart-Brain study and ExCersion-VCI study. Second, we focused on the relationship between cerebral blood flow (CBF) and cognitive functioning. In addition, we investigated the role of disorders in haemodynamics along the heart-brain axis in cognitive functioning. Finally, we investigated the implication of small vessel disease on depressive symptoms.

In this chapter, I summarize the most important findings of this thesis and place them into the context of existing literature, including methodological considerations that should be taken into account when interpreting the results. I finish with discussing the implications of this thesis and provide suggestions for future directions.

Part 1: Introduction

The first part of this thesis described the designs of the longitudinal multi-center Heart-Brain study (chapter 2) and the randomized controlled trial ExCersion-VCI (chapter 3). The Heart-Brain study focuses on the role of haemodynamic abnormalities along the heart-brain axis in vascular cognitive impairment (VCI). Using a multidisciplinary approach, all patients are extensively phenotyped using an extensive and standardized brain and cardiac MRI protocol and a neuropsychological assessment. In addition, relevant biomarkers (blood, cerebrospinal fluid (CSF)), blood pressure measurements and clinical data are collected. The baseline assessment of the Heart-Brain study was completed in 2017, the follow-up assessment is currently ongoing. The Heart-Brain study will provide more information about the role of haemodynamics in VCI. ExCersion-VCI is a substudy within the larger project that focuses on the effect of aerobic exercise on CBF in patients with VCI. Recruitment for ExCersion-VCI is still ongoing. We hope to finish data collection in July 2019, perform statistical analyses and publish the first results.

Part 2: Haemodynamic changes and cognition

The second part of this thesis focused on haemodynamic changes, as measured with arterial spin labeling (ASL), in relation to cognitive functioning. In chapter 4 we investigated the cross-sectional relationship between CBF and cognitive functioning in patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI) and Alzheimer’s disease (AD) dementia from the memory-clinic based Amsterdam Dementia Cohort (ADC). We found that reduced CBF was associated with poor functioning in all cognitive domains, particularly in patients with AD dementia. These results suggest that CBF has particular value in more advanced stages of AD.
dementia and that CBF could be used as a marker of disease severity. In chapter 5 we investigated the potential of CBF as a measure of disease progression. We tested whether reduced CBF at the time of diagnosis was associated with faster cognitive decline in patients with AD dementia from the ADC. We found that reduced CBF in the posterior regions of the brain was associated with a steeper rate of cognitive decline, measured with the Mini-Mental State Examination (MMSE). Results from this study suggest that CBF may have prognostic value in patients with AD dementia. In chapter 6 we examined the association between CBF and cognitive functioning in a multi-ethnic community-based cohort with a high prevalence of vascular risk factors. All European, African-Caribbean and South-Asian participants underwent ASL and a neuropsychological assessment. We found modest associations between CBF and cognitive functioning, which were mainly attributable to the European group. These results support our earlier results that CBF is less sensitive for cognitive changes in the early stages of cognitive impairment and dementia.

In chapter 7 we investigated the occurrence and profile of cognitive impairment in participants from the Heart-Brain study (design of this study described in chapter 2). This study included patients with disorders along the heart-brain axis: heart failure (HF), carotid occlusive disease (COD) and VCI. We found that a substantial part of patients with HF and COD have minor and major cognitive impairment. The cognitive profile of cognitive impairment in HF and COD was similar to the profile in VCI. In all patient groups, memory and attention-psychomotor speed were the cognitive domains most often affected, suggesting shared underlying mechanisms. In chapter 8 we investigated the association between CBF and cognitive functioning in patients with HF, COD and VCI from the Heart-Brain study. We found hardly any association between whole-brain or regional CBF and cognitive functioning, in any group. Our results suggest that the predisposition of cognitive impairment in patients with diseases along the heart-brain axis is driven by (haemodynamic) mechanisms other than CBF.

Part 3: Small vessel disease and depressive symptoms

In the third part of this thesis we examined the relationship between cerebral small vessel disease and depressive symptoms, also described as the vascular depression hypothesis, in memory clinic patients. In chapter 9 we investigated whether visual rating scores of MRI-markers of small vessel disease were associated with depressive symptoms in patients with SCD, MCI and AD from our memory clinic cohort. We found that microbleeds were associated with depressive symptoms in AD, but not in non-demented patients. We found no association between lacunes and white matter hyperintensities (WMH) and depressive symptoms. By contrast, we observed a higher prevalence of depressive symptoms in patients with SCD and WMH, but this effect was borderline significant. To investigate whether specific WMH locations predispose for
the occurrence of depressive symptoms, we investigated in chapter 10 the association between WMH location and depressive symptoms in patients with SCD, MCI and dementia with vascular brain injury, using an innovative method on lesion-symptom mapping. We identified the left corticospinal tract and the forceps minor as strategic white matter tracts in which WMH are associated with depressive symptoms. Our results showed that the impact of WMH location on depressive symptoms was modest, and dependent on WMH location and disease severity.

GENERAL DISCUSSION

In the following paragraph I will place the results of this thesis into the context of existing literature.

The role of CBF in the pathophysiology of Alzheimer’s disease

The current leading paradigm in AD research is the amyloid cascade hypothesis, in which the aggregation of amyloid-β in the brain is thought to be one of the earliest changes in the disease. Amyloid aggregation in the brain can be measured in vivo by demonstrating a low amyloid-β 1-42 protein concentration in the cerebrospinal fluid or an increased retention of amyloid-β tracer visualized with positron emission tomography (PET). The aggregation of amyloid-β is suggested to trigger downstream consequences such as vascular pathology, neurodegeneration, cell death and cognitive decline. Besides the role of amyloid-β, there is growing evidence that a complex interaction of additional pathophysiological mechanisms contributes to the syndrome of AD dementia. However, the temporal ordering of these pathological events related to AD remains largely unknown. A better understanding of the early changes in the pathophysiology of AD could improve the diagnosis of AD before onset of dementia. This is necessary to develop and implement secondary prevention strategies and identify patients at risk for AD dementia. The contribution of vascular pathology to the pathophysiology of AD dementia has been suggested, as both conditions share common risk factors, often co-exist in older individuals and are considered contributors to cognitive decline and dementia. However, a clear understanding of the interaction between vascular pathology and AD is lacking. A particular interesting measure to investigate this interaction is CBF. CBF depends on a wide range of physiological factors (Figure 1), including arterial blood pressure, vasoreactivity and the status of cerebral autoregulation, and the majority of these factors have also been linked to AD and dementia. Studies with ASL show a reduction in CBF in patients with AD dementia, compared to controls. Currently, there is an ongoing debate about the role of reduced CBF in the pathogenesis.
of cognitive impairment and AD. The underlying mechanism for the decline in CBF in AD is poorly understood and the question is whether reduced CBF is more a reflection of AD pathology or of vascular pathology (Figure 1).

Reduced CBF as a reflection of AD pathology

Some studies indicate that a reduction in CBF is intrinsic to AD pathophysiology. Increased stiffness of the small cerebral vessel walls in the brain challenge the cerebral blood supply in the brain and might attenuate amyloid clearance and thereby accelerate amyloid deposition and resulting tauopathy. The association between amyloid deposition (measured with amyloid-PET imaging) and CBF has been investigated in healthy controls, MCI and patients with AD. It was found that amyloid deposition was associated with reduced CBF in several brain regions, already in the stage of preclinical AD. In addition, results showed that amyloid deposition was more associated with reduced CBF than with brain volume. A study in late-onset AD patients using a data-driven approach found that reduced CBF preceded the accumulation of amyloid pathology. These studies suggest that (functional) changes in CBF are an early event in the pathophysiology of AD and that reduced CBF might precede and contribute to the presence of amyloid pathology and neurodegeneration. Earlier work from our center, however, showed that CBF does not decrease until both amyloid-beta and total-tau, the Alzheimer biomarkers, in the cerebrospinal fluid (CSF) were abnormal. The first signs of neurodegeneration are likely to occur years, or even decades, before the diagnosis of dementia, and changes in CBF may consequently occur well before the presence of cognitive impairment. To investigate a potential temporal relationship between CBF and the presence of cognitive impairment, it is important to study the association between CBF and cognitive functioning in different stages of the disease. However, studies on this relationship are scarce. In chapter 4 we found associations between reduced CBF and worse cognitive functioning, but only in the group of patients with dementia. Furthermore, in chapter 5 we showed in a longitudinal study that AD dementia patients with reduced CBF have a more rapid decline in global cognition after a diagnosis of dementia. Results of this thesis indicate modest associations between CBF and cognitive functioning in memory clinic patients. We concluded that reduced CBF could be a measure of disease severity, particularly in the more advanced stages of the disease. Contrary to earlier studies, we found no indication that reduced CBF might precede the presence of cognitive impairment.
Figure 1. Conceptual framework of the role of reduced cerebral blood flow in Alzheimer’s disease, as studied in this thesis.

**CBF as a neurodegenerative or vascular measure**

Recently, the Rotterdam Study found that reduced CBF was associated with accelerated cognitive decline and increased risk of dementia in the general population. They found that this association was most profound in patients with vascular brain injury or higher blood pressure at baseline, suggesting the possibility of reduced CBF as a vascular measure. In a previous study in the Amsterdam Dementia Cohort we found that reduced CBF was associated with both larger WMH volumes as small brain volumes, suggesting that reduced CBF reflects both neurodegenerative as vascular changes. In chapter 6 we found only modest associations between CBF and cognitive functioning in a community-based multi-ethnic cohort with a high prevalence of adverse vascular risk factors, which could indicate that changes in CBF are less dependent on vascular factors and that changes in CBF are less sensitive in the early stages of cognitive impairment and dementia. In addition, in chapter 7 we showed that the profile of cognitive impairment is similar in patients with diseases along the heart-brain axis, which suggests a similar underlying mechanism. In chapter 8 we investigated the association between CBF and cognitive functioning in a clinical heart-brain axis study and we found that the overall effect of CBF on cognitive functioning in patients with diseases along the heart-brain axis appeared to be scarce. Our results indicate that reduced CBF, whether brought on by cardiovascular disease or vascular brain injury, plays a limited role in cognitive functioning.

Overall, we found modest associations between CBF and cognitive functioning in several different cohorts. The most profound association between CBF and cognitive functioning was in patients with AD dementia, indicating that reduced CBF is likely to be more a reflection of AD pathology instead of a vascular measure. The results in
this thesis suggest that CBF, measured with ASL, is not a sufficient measure to identify patients at risk for AD dementia in secondary prevention trials. However, our results in patients with AD dementia suggest that ASL is a potential imaging marker or outcome measure in clinical trials in patients in the more advanced stages of the disease. Our findings in the Heart-Brain study indicate that haemodynamic factors may play a role in cognitive decline in patients with cardiovascular disease, but that CBF is not a contributing factor in this. Other potential mechanisms are the disruption of cerebral autoregulation, reduced cardiac output or the presence of Alzheimer pathology. To understand more about the role of these factors and the temporal relationship between CBF and dementia, we need studies with repeated measurements of CBF and cognitive functioning. Further studies on the haemodynamic complications of disorders along the heart-brain axis will enhance our understanding of how the heart affects the brain under pathophysiological conditions. The structural and functional measurements of the heart and brain and longitudinal measurements of CBF and cognitive functioning in the Heart-Brain study (chapter 2) will help unravel the pathophysiology of dementia.

Neuropsychiatric symptoms in patients with dementia

Depressive symptoms at older age can be difficult to recognize. Depressive symptoms may occur as a comorbidity to co-existing diseases or as a natural consequence of life events and illnesses. In addition, depressive symptoms could also be the earliest symptom of a neurodegenerative disease as AD. The ‘vascular depression hypothesis’ states that vascular brain injury may predispose, precipitate or perpetuate depressive symptoms in older people. This hypothesis proposed a number of clinical features that are unique to vascular depression and these include a late age of onset, increased prevalence of cognitive deficit, presence of psychomotor deficit and lack of insight. The vascular depression hypothesis has been investigated intensively in population-based studies and in patients with major depressive disorder. In this thesis, we investigated the ‘vascular depression hypothesis’ in memory clinic patients. As described in this thesis, we found that the location and severity of WMH in depressive symptoms appeared to be particularly important in patients with SCD, but not in patients with dementia. Our results could suggest that the vascular depression hypothesis is limited to cognitively healthy participants, in older people without cognitive impairment. However, we did find more depressive symptoms in patients with AD dementia and microbleeds. The presence of microbleeds could indicate cerebral amyloid angiopathy (CAA). CAA is closely related to AD, but also frequently presents with vascular brain injury. As we found modest associations between vascular brain injury and depressive symptoms in AD dementia, this would suggest that other determinants play a role in the presence of depressive symptoms in patients with AD, as neurodegeneration and
amyloid pathology. Future research could focus on the relation between AD pathology and depressive symptoms and help to clarify the mechanism involved in the presence of neuropsychiatric symptoms as depression in memory clinic patients.

METHODOLOGICAL CONSIDERATIONS

There are some methodological considerations that have to be considered when interpreting the results presented in this thesis.

Selection of study population
A strong aspect of this thesis is the use of different cohorts, including a memory-clinic population, a population-based cohort and a large prospective observational cohort. An important advantage of the use of cohort studies is that all patients and participants within a specific cohort underwent a standardized work-up, with for example a standardized extensive neuropsychological assessment covering several cognitive domains and a standardized imaging protocol. In the population-based SABRE cohort we investigated the association between CBF and cognitive functioning in participants with a cardiovascular profile (chapter 6). However, the study of diseases is more efficient in a clinic-based cohort, as the Amsterdam Dementia Cohort (ADC), the TRACE-VCI or Heart-Brain study cohort (chapter 4, 5, 7-10). Although the clinic-based observational design may have induced a selection bias, at the same time it enhances the relevance of our findings in a clinical setting. A potential limitation of using data from ADC and TRACE-VCI is that patients were included at tertiary referral centers. Both ADC as TRACE-VCI and the Heart-Brain study have included relatively young patients, which may limit the generalizability of findings. However, the inclusion of these relatively young patients is also an advantage as dementia at a younger age is often thought to be more ‘pure’, with less mixed pathology.

Arterial spin labeling
In this thesis we used ASL to measure CBF. ASL is particularly useful in clinical practice due to the non-invasiveness: it does not need a contrast agent or a radioactively labeled tracer. In addition, ASL has a short acquisition time and can be derived during the same scanning session as structural images. Therefore, the measurement can be applied in vulnerable populations such as a memory clinic population and it is possible to repeat the CBF measurements as frequently as desired. However, the presence of cortical atrophy, an important characteristic of AD, could affect functional MRI measures (i.e. ASL) through partial volume effects. The main drawback is that there is
no consensus on which method is best to correct for partial volume effects or cortical atrophy. For this reason, we chose to report both uncorrected CBF as partial volume corrected ASL (PVC-ASL). For most studies, both measures of CBF yielded comparable results (chapter 4, 6 and 8). However, we did find conflicting results between the uncorrected and PVC CBF results in our longitudinal study (chapter 5). This would suggest that the PVC method we used in our memory clinic cohort is not the most optimal method to correct for atrophy. Second, ASL measurements in this thesis were not acquired using several delay times to account for between-group differences in transit time. Transit time is the duration for the magnetically labeled arterial blood water to travel from the labeling region in the neck to the tissue of interest. Transit time varies across the brain and is dependent on age, arterial size, stiffness, presence of vascular risk factors and the cardiac output fraction. For example, healthy older people have prolonged transit times and longer transit delays compared to healthy younger people. This is similar for a patient with vascular brain injury compared to a patient without vascular brain injury. The influence of transit time is in particular of interest in patients with changes in haemodynamic status, i.e. patients with vascular cognitive impairment (VCI). To account for a variation in transit time in memory clinic patients (chapter 4 and 5), we used a delay time of 2.0s, which is recommended for a memory clinic population and is assumed to be suitable to account for differences in transit time. CBF measurements in the SABRE study (chapter 6) and the Heart-Brain study (chapter 8) used the common delay time of 1.8s. To alleviate the effect of transit time, in the MRI protocol of ExCersion-VCI (chapter 3) we added a multiphase ASL with multiple postlabel delay acquisitions to measure transit time. Third, in this thesis we did not apply a correction for possible perfusion confounders as smoking habits, medication and recent caffeine intake. However, in the design of ExCersion-VCI (chapter 3) we tried to minimize physiological perfusion fluctuations and instruct participants who undergo ASL measurements to refrain from alcohol during 24 hours prior to scanning, from caffeine and smoking during the preceding 6 hours and from eating 1 hour before the MRI measurement. Fourth, all studies on ASL and cognitive functioning in this thesis were performed on a group level, making these findings not necessarily generalizable to individual patients. Future studies are necessary to confirm the additional value of ASL on the individual level. And finally, a much-heard disadvantage of ASL for patients is the production of a highly uncomfortable sound. Future research could investigate if a more patient-friendly sound is possible, as patients have to lie still for a prolonged period of time during the MRI-acquisition.

Assessment of neuropsychiatric symptoms in memory-clinic patients
Neuropsychiatric symptoms including depression, apathy, agitation, psychosis and sleep disturbances are common in patients with cognitive impairment and dementia.
However, the prevalence of neuropsychiatric symptoms is variable among studies.\textsuperscript{24} The assessment of neuropsychiatric symptoms is challenging in patients with cognitive impairment or dementia, especially in the absence of biological markers and reliance on the clinical examination. Using valid and reliable measurements in the accurate assessment of neuropsychiatric symptoms is critical. In addition, other important requirements of measurements of neuropsychiatric symptoms are that they are clinically interpretable, brief and simple to use.\textsuperscript{25} The psychometric properties or the validity of a measurement could be influenced by decreasing levels of cognitive functioning.\textsuperscript{26} In the clinical setting and in research, many questionnaires or (semi-) structured interviews to measure neuropsychiatric symptoms are available.\textsuperscript{26} In this thesis, we used the Geriatric Depression Scale (GDS)-15 as an instrument to measure depressive symptoms. The GDS-15 is a questionnaire that can be self-administered or presented as an interview. The questions have a yes/no format which makes the GDS easy to use. In \textbf{chapter 9} we used a cut-off of 5 on the GDS as indicator for depressive symptoms, in \textbf{chapter 10} we used the continuous GDS score. We chose a cut-off of 5 as this is frequently used in research and has a high sensitivity and specificity.\textsuperscript{27} However, the cut-off of 5 may have been too low, which may have led to an overestimation of patients having depressive symptoms. A limitation of the GDS and other questionnaires is that it relies on the ability of the patient to recall their recent mood state, which could be difficult for patients with dementia. A recent meta-analysis showed that questionnaires that incorporate an interview with both the patient with dementia and the caregiver have a higher sensitivity to detect depressive symptoms, compared to the GDS.\textsuperscript{28} In this thesis we did not use a scale that depends on a caregiver or proxy to report (changes in) neuropsychiatric symptoms, suggesting a potential underestimation of patients having depressive symptoms. A widely used scale on neuropsychiatric symptoms, obtained from a caregiver or proxy, is the Neuropsychiatric Inventory (NPI).\textsuperscript{29} The NPI focuses on 12 existing neuropsychiatric symptoms and is entirely based on input of the caregiver. The NPI is a clinical interview and is easy to administer. A main disadvantage of the NPI is that it is a retrospective measurement and not based on direct patient observations.\textsuperscript{30} A recently developed new version is the Neuropsychiatric Inventory-clinician rating (NPI-C), which incorporates information from the patient and caregiver and also allows the clinician’s judgment to be factored into the assessment.\textsuperscript{31} Patient and caregiver rate the frequency, severity and distress of each neuropsychiatric symptom, and the clinician makes a final rating, which brings additional strength to the measurement compared to the original NPI. The NPI-C has better inter-rater reliability compared to the original NPI.\textsuperscript{31} A small study in patients with cognitive impairment and dementia showed that the agreement of symptom severity varied across the range of cognitive impairment.\textsuperscript{32} Future research could investigate to what extent reports
on neuropsychiatric symptoms by the caregiver or a proxy are congruent with the report of the patient. The NPI-C could be a useful tool to investigate neuropsychiatric symptoms in memory clinic patients.

**Implications and future directions**

In this paragraph possible implications and future directions of our work are discussed.

**Understanding the pathophysiology of cognitive impairment and dementia**

Although the results in this thesis have provided novel insights in the role of reduced CBF in cognitive impairment and dementia, many questions remain. Besides CBF, other factors that determine vascular health, for example blood pressure, cerebrovascular reactivity and dynamics of cerebral perfusion, together with the impact of comorbidities receive increasing attention as potential contributors to cognitive impairment and dementia. Future studies to the role of these haemodynamic factors are needed to increase understanding of the pathophysiology of VCI and AD. Another important development is the increasing awareness of the impact of comorbidities and mixed etiologies in VCI. First, at the level of the heart, atrial fibrillation is an important comorbidity in VCI. The mechanism how atrial fibrillation is associated with cognitive impairment and dementia is still unknown. In the Heart-Brain study (chapter 2), we excluded patients with atrial fibrillation because this could interfere with the cardiac MRI measurement. However, the presence of atrial fibrillation could be an important vulnerability factor for the development of VCI. Investigating the relation between severity of atrial fibrillation, cognitive functioning and the presence of vascular brain injury and neurodegeneration on brain MRI might increase our knowledge about the role of atrial fibrillation contributing to VCI. Second, despite the fact that mixed etiologies (i.e. Alzheimer’s disease and vascular brain injury) are so common, we know little about their interplay. Earlier studies showed that AD pathology and vascular brain injury act independently and have additive effects on cognitive functioning.\(^{33,34}\) In addition, recent studies suggest that the presence of vascular brain injury may lower the threshold at which AD pathology leads to cognitive impairment.\(^{35–37}\) Patients with both a high vascular risk and presence of AD pathology showed the steepest decline on cognitive functioning. Further work is needed to examine potential interactions between both pathologies and the individual importance of both pathologies to the presence of cognitive impairment. In addition, investigating whether the presence of amyloid deposition modifies the association between CBF and cognitive functioning will lead to more knowledge about the role of CBF in the pathophysiology in AD.
Implementation of heart-brain clinics
The implementation of so-called in-house heart-brain clinics in clinical care, staffed by a multidisciplinary team made up of neurologists, cardiologists, internist-geriatricians and neuropsychologists, results in a systematic focus on both heart and brain, instead of focusing on one specific organ. In addition, the multidisciplinary approach will lead to better risk stratification and medical decision-making. The heart-brain clinic can help in the early detection of brain dysfunction or cognitive impairment in patients with cardiovascular disease (e.g. heart failure and atrial fibrillation) and the detection of cardiovascular conditions as potential determinants of cognitive decline in patients with VCI. Early detection, control and prevention of vascular risk factors could change the course of dementia: it can potentially slow or delay the onset of Alzheimer’s disease (AD) and other forms of dementia. Most risk factors are modifiable, especially if they are detected early. As time may be a deciding factor in the eventual reversibility of cognitive impairment in these patients, an important advantage of this multidisciplinary approach is that the modifying intervention can be applied early in the development of cognitive decline. The early recognition of brain dysfunction in patients with disorders along the heart-brain axis or chronic cardiovascular disease would lead to proper medical treatment strategies and supportive care which may decrease the impact of cardiovascular disease on cognition and potentially prevent further decline in brain function.

All patients visiting the Heart-Brain clinic will undergo a standardized heart-brain protocol as developed in the Heart-Brain Study, consisting of a neuropsychological assessment, blood pressure and orthostatic measurements, blood sampling, ECG and MRI of the brain. Future implementation of amyloid measurement in the heart-brain clinic could lead to more knowledge about the potential role of amyloid as determinant of cognitive impairment in patients with diseases along the heart-brain axis. In addition, implementation of amyloid measurement could lead to early recognition of the patient at elevated risk for cognitive impairment.

Dementia research in multi-ethnic cohorts
Studies in this thesis were mostly focused on European-origin populations, but in chapter 6 we have investigated the association between CBF and cognitive functioning in a community-based multi-ethnic cohort. The current population of the Netherlands and of other Western countries will become increasingly diverse. However, in dementia research, studies in multi-ethnic cohorts are scarce. The investigation of ethnic variations in dementia rates has great implications for etiological research on AD. Currently, it is not clear whether the prevalence of cognitive impairment and dementia differs among ethnic groups. The use of similar cognitive tests among ethnic groups may skew prevalence numbers of cognitive impairment and dementia,
as some of them will underperform on those tests as a result of growing up with educational disparities. In addition, the underrepresentation of ethnic minorities in observational studies and in clinical trials has led to a lack of data on whether the mechanism and pathophysiology of AD operate the same or differently in racial and ethnic minorities. Research on the prevalence of cardiovascular risk factors (diabetes, smoking, systolic blood pressure, use of antihypertensive drugs, total cholesterol) showed differences between ethnic groups. In addition, important repercussions of research on ethnic variations are differences in genetic and environmental factors, including lifestyle, social and cultural factors (e.g. diet, nutrition, physical, mental and social activities), as well as their complex interactions. Future research in large longitudinal cohorts that track both vascular as AD biomarkers in multi-ethnic groups will increase the understanding of diversity in AD.

**Depressive symptom profiles in memory clinic patients**

Depression comprises many combinations of clinical symptoms and is a heterogeneous condition. In studies on depression, the difference between atypical and melancholic depression is increasingly recognized. It has been shown that specific depressive symptom patterns are associated with distinct characteristics (i.e. clinical psychiatric, psychosocial and physical health factors), which point to differential potential neurobiological markers and substrates. In addition, these different depressive subtypes responded differently to antidepressant medication. In this thesis, we investigated the vascular depression hypothesis in memory clinic patients. We used the total score of the GDS, which limits us to investigate patterns of self-reported depressive symptoms. Future research to different symptom profiles and the underlying etiologic mechanism in memory clinic patients could potentially lead to critical information about treatment (personalized therapy) and care to physicians and caregivers. As the GDS does not examine key vegetative symptoms of depression, as sleep, weight, psychomotor problems and appetite, the implementation of a standardized work-up of multiple neuropsychiatric measures in the memory clinic is needed for the characterization of these subtypes.
CONCLUSIONS

In this thesis, we have investigated cerebrovascular aspects of cognitive functioning and neuropsychiatric symptoms. First, we have investigated the relationship between CBF and cognitive functioning and we found that:

- The association between CBF and cognitive functioning in a multi-ethnic population-based cohort, with a high prevalence of cardiovascular risk factors, was modest;
- Reduced CBF, measured with ASL-MRI, is associated with worse cognitive functioning in all cognitive domains in patients with AD dementia, but not in MCI or SCD;
- Reduced CBF in the posterior brain-regions is associated with cognitive decline over time in patients with AD dementia;
- The results in this thesis suggest that CBF has potential as a measure of disease severity, but only in the more advanced stages of the disease.

Second, we have investigated the role of haemodynamics along the heart-brain axis in cognitive functioning and found that:

- A substantial part of patients with heart failure and carotid occlusive disease have cognitive impairment, with memory and attention-psychomotor speed as most impaired cognitive domains.
- Early detection of brain dysfunction in patients with diseases along the heart-brain axis is important;
- The association between CBF and cognitive functioning in patients with diseases along the heart-brain axis appeared to be absent, indicating that the predisposition of cognitive impairment in those patients is likely to be driven by other mechanisms than CBF.

Finally, we have investigated the implication of small vessel disease on depressive symptoms and our results showed that:

- Depressive symptoms are common in a memory clinic population, but are only modestly associated with WMH, particularly in patients with SCD.
- The presence of cerebral microbleeds is associated with a higher prevalence of depressive symptoms in patients with AD dementia.
REFERENCES


