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Keeping the heart in mind: Cardiovascular determinants of neurocognitive functioning in old age

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Chapter 1

General introduction

Neurocognitive functioning in older people

The clinical picture of patients with dementia is particularly associated with a decline in memory function. However, memory is merely one of the cognitive domains that can deteriorate to interfere significantly with daily functioning, the latter being imperative for the diagnosis of dementia[1]. Patients can also lose the ability to organize their finances (executive dysfunction), have trouble finding the right words to express themselves (language problems), or exhibit disturbed behavior that could severely damage their relationships with loved ones (problems with social cognition). By recognizing the full clinical picture of cognitive decline or dementia, scientific research can target those problems that are of consequence for real-life patients.

To describe this broader clinical spectrum of cognitive decline, the Diagnostic and Statistical Manual (DSM)-5 of Mental Disorders, which is being used as a uniform classification system for clinical practice and research in psychiatry, introduced the term 'major neurocognitive disorder' (NCD) to replace the term dementia[1]. Apart from the domain memory and learning, the cognitive domains comprise complex attention, executive dysfunction, language, perceptual motor function, and social cognition. Besides cognitive decline, patients can present with what the DSM-5 classifies as auxiliary 'behavioral disturbances' such as mood symptoms, apathy, irritability, sleep and eating disturbances, and psychotic symptoms[1]. These behavioral disturbances, in the literature often referred to as neuropsychiatric symptoms, are highly prevalent [2-4], can be particularly burdensome[5, 6], and can also occur outside the scope of cognitive dysfunction[7]. However, as research often focusses primarily on cognitive decline and dysfunction in the different cognitive domains, much less is known of specific risk factors and potential targets for treatment for these disabling neuropsychiatric symptoms. To capture the array of symptoms older patients can present with, in this thesis, the term 'neurocognitive functioning' will be used as an umbrella term for both cognitive (dys)functioning and neuropsychiatric symptoms. Phenomena of apathy and depression are among the most prevalent symptoms[2-4], and, together with cognitive dysfunction[8], these are most frequently associated with cardiovascular factors[9, 10]. Therefore, this thesis will focus on cognitive dysfunction as well as symptoms of apathy and depression as primary outcomes of interest.

Apathy, depression, and cognition in old age

Apathy as a clinical syndrome, distinct from depression and cognitive dysfunction

Apathy, defined as reduced motivation and goal directed behavior, diminished emotions, and less engagement in social interaction[11], can be part of depression[12] but is increasingly regarded as a symptom in its own right[13]. The two key symptoms of depression are a depressed mood and loss of interest. Clinicians noted that a marked proportion of older persons presented especially with this loss of interest and lack of motivation, but with no altered mood and with few of the other typical depressive symptoms such as hopelessness, weight and sleep changes, and suicidal thoughts[14]. As results from antidepressant treatment were also disappointing in these patients, it was proposed that these patients did not suffer from depression but rather from apathy as a distinct clinical syndrome[14]. When regarded as such, apathy is a frequent and disabling symptom in patients with major NCD (= dementia)[4] , but also occurs in those with minor NCD (=mild cognitive impairment)[3] and even in community dwelling older persons without cognitive dysfunction[7, 15, 16]. This implies a symptom overlap not only with depression, but also with cognitive dysfunction. Figure 1.1 not only shows the overlapping, but also the distinct symptoms of apathy, depression, and cognitive dysfunction, which is of relevance to both clinical practice and research.

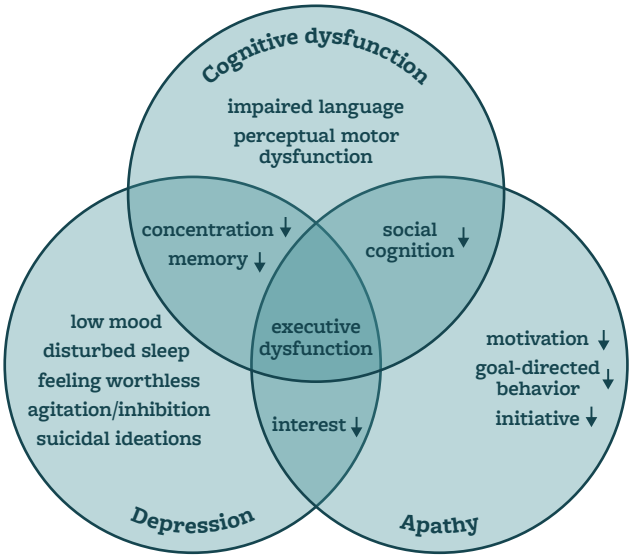

Figure 1.1 Overlap between cognitive dysfunction, depression, and apathy

It is important to correctly diagnose an older patient presenting with loss of interest, for this determines which treatment strategy a clinician proposes (e.g., psychotherapy and/or pharmacological antidepressant treatment in case of a clinical depression) or what psychoeducation she gives on the prognosis of disease progression (e.g., in the case of a diagnosis of major NCD). To enable clinicians to provide patients and their families with the correct information, researchers have to distinguish apathy from depression and cognitive dysfunction when investigating specific modifiable risk factors, studying treatment strategies, and determining symptom courses over time. It is especially important to separately address apathy, since far less is known on its specific risk factors in old age while it is associated with a high care giver burden[17], poor functional ability[18], and even mortality[19].

Measurement of symptoms of apathy in research settings

To investigate modifiable risk factors and potential treatment strategies, it is pivotal that apathy is adequately assessed in research settings. While symptoms of depression are frequently measured in large observational studies[20-22], a specific instrument for apathy such as the Apathy Scale[23] is scarcely being administered. Because apathy is increasingly prioritized in recent studies among older people, researchers have explored proxy instruments. The Geriatric Depression Scale (GDS)-15 is often used to screen for late-life depressive symptoms in research as well as in clinical practice, and has a good validity and inter rater reliability[24]. Factor analyses[25, 26] and expert panels[26] have identified three questions of the GDS-15 that assess symptoms of apathy, namely (1) have you dropped many of your activities and interests?; (2) do you prefer to stay at home, rather than go out and doing new things?; and (3) do you feel full of energy?. This subset, the GDS-3A, was first used by Van der Mast *et al.* to investigate risk factors for apathy and has been increasingly used since[16, 22, 26]. However, research into the scale properties of the GDS-3A is limited[26]. It is, therefore, important to know the epidemiological test characteristics such as sensitivity and specificity to determine the validity of the use of the GDS-3A to study potentially modifiable risk factors for apathy.

Cardiovascular determinants and neurocognitive functioning

Cognitive dysfunction, symptoms of apathy, and depressive symptoms in late life may have distinct risk factor patterns, and cardiovascular determinants may play an important role in all three. While the association between cardiovascular disease and cognitive dysfunction has been well established and consolidated in the clinically widely used diagnosis of *vascular cognitive impairment*[27], the link with symptoms of depression and apathy to date is less straightforward[28-31].

Vascular depression?

In the late 1990s, the concept of a vascular depression was postulated[32]. Clinicians observed a phenotype of late-life depression in which lack of initiative and motivation, as well as executive dysfunction, were more prominently present than purely 'mood' symptoms such as feelings of worthlessness and suicidal ideations. In the era of the rising use of neuro-imaging techniques, researchers observed that this particular phenotype was more often accompanied by vascular damage on computer tomography (CT) images of the brain, and the term vascular depression was coined[32]. At the same time, it was also observed that these depressive symptoms were more often associated with the presence of cardiovascular risk factors[32]. However, the temporality of these associations has been debated, as studies have shown both an increased risk of future depression in those with a higher burden of cardiovascular risk factors[30], as an increased risk of future myocardial infarction in patients with a depression[31]. Moreover, since depression measures often include items that represent apathy, it could be hypothesized that these studies have assessed associations with apathy rather than depression.

Vascular apathy?

In recent years, it has been suggested that the syndrome of vascular depression might actually be more accurately described as vascular apathy[10, 22, 26]. Exactly those symptoms that were most prominently seen in 'vascular depression', namely lack of interest and motivation in the absence of a depressed mood, are considered part of the apathy syndrome[11]. Further, studies have shown that cardiovascular factors and diseases were more often linked to symptoms of apathy than of a depressed mood[25, 26] and a recent review described how cerebral small vessel disease (CSVD) is increasingly found to be associated with apathy[10]. However, also for apathy a bidirectional association with cardiovascular disease has been described[22]. Thus, the exact mechanisms behind these associations have yet to be elucidated.

Taylor *et al.*[9] proposed a model for the pathogenesis of vascular depression (Figure 1.2) and described a pathway from cardiovascular determinants to depression, both through direct structural cerebrovascular damage and through impaired cerebral perfusion. This model, while not claimed to be conclusive, might also apply to cognitive impairment and apathy. Alternatively, specific risk factors might be differentially associated with these distinct outcomes. However, few studies have incorporated cognitive impairment, depressive symptoms, and apathy in one study design, hampering direct conclusions on specific risk factor patterns.

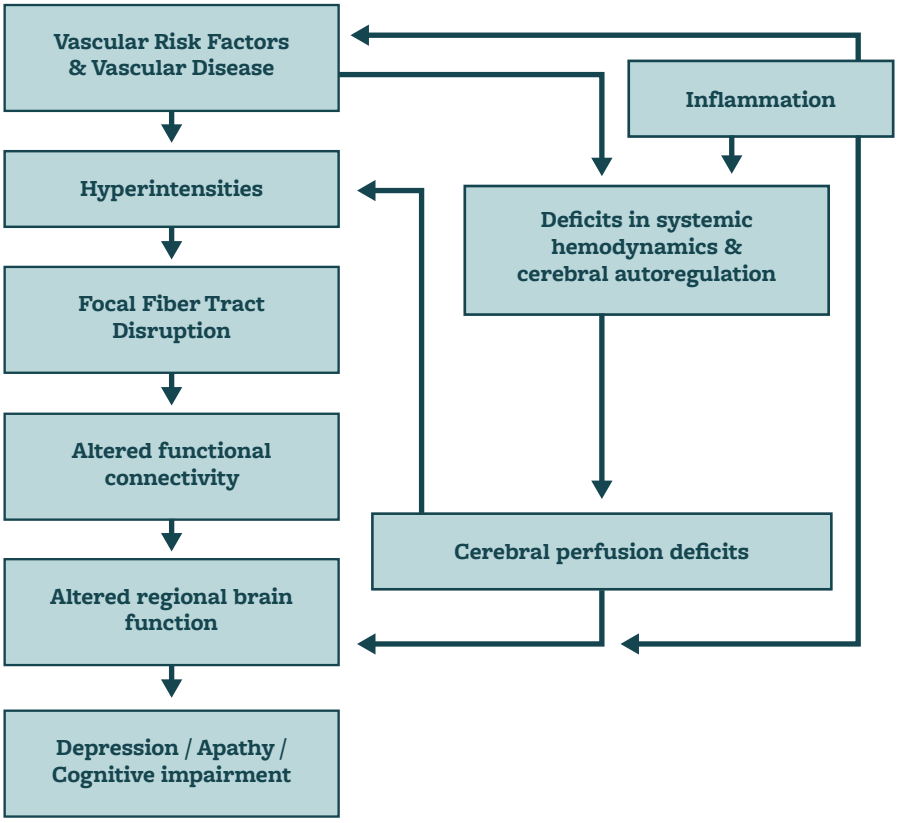

Figure 1.2 Proposed mechanisms for cardiovascular determinants of neurocognitive functioning

With permission adapted from Taylor et al. Molecular Psychiatry (2013) 18, 963–974.

There is increasing evidence that cardiac disease in particular might play an important role in adverse brain outcomes[33-35]. To establish the presence and degree of cardiac disease, serum cardiac markers such as natriuretic peptides and cardiac troponins are frequently measured in clinical practice. While the clinical role of high sensitivity cardiac troponin T (hs-c-TnT) lies mainly in the diagnostic work up for myocardial infarction[36], there is increasing evidence that also in the absence of acute myocardial infarction, higher levels of hs-cTnT are related to a higher cardiovascular morbidity and mortality[37]. Higher levels of hs-cTnT have also been related to adverse brain outcomes including cognitive decline[38, 39], but these studies have included mainly middle-aged or younger-old persons. Moreover, these studies have not looked into a possible association between hs-cTnT and symptoms of depression and apathy, and have not specifically addressed the role of overt cardiac disease in these associations.

Blood pressure and neurocognitive functioning

While vascular risk factors could lead to worse neurocognitive functioning through direct cerebrovascular damage, deficits in systemic hemodynamics and cerebral perfusion might also play an important role, as shown in Figure 1.2[9]. In this respect, it is important to consider the role of systemic blood pressure since it can be readily measured and rather easily be intervened upon, making it a potentially modifiable risk factor. The detrimental effect of midlife hypertension (commonly defined as a systolic blood pressure of <140 mmHg and/or a diastolic blood pressure of >90 mmHg) has been well-established. Not only does hypertension have a role in the risk of classical cardiovascular diseases such as myocardial infarction[40], but it has also been widely acknowledged that hypertension in midlife is associated with cognitive decline and dementia in older age[8, 41, 42]. However, the association between late-life blood pressure and adverse outcomes is less straight forward. Several observational studies found that lower rather than higher late-life (≥75 years) blood pressure was related to adverse brain outcomes including worse cognitive function[43-45]. In contrast, the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE)-Study Leiden, a randomized clinical trial among older persons (≥75 years) with mild cognitive deficits, did not find a favorable effect of elevating blood pressure on neurocognitive functioning[46]. Heterogeneity in population characteristics might underlie these contrasting findings[47]. Indeed, both cross-sectional[48] and longitudinal studies[49, 50] have shown that lower blood pressure was particularly related to worse cognitive function in those older persons with worse functional ability. Thus far, the few studies among relatively younger older persons that have investigated apathy, found however that higher and not lower blood pressure was a risk factor[25, 51], whereas both a higher[52] and a lower blood pressure[53, 54] have been associated with depressive symptoms in later life. It has yet to be investigated whether population characteristics such as functional ability also play a role in the relation between late-life blood pressure and symptoms of apathy and depression.

A role for cerebral small vessel disease in neurocognitive functioning?

One of the proposed mechanisms through which lower late-life blood pressure might lead to worse neurocognitive functioning in older persons with worse functional ability, is through reduced cerebral blood flow in brain areas involved in regulating cognitive function, mood, and motivation[55]. While the healthy brain is able to keep cerebral blood flow constant during changes in systemic blood pressure[56], this mechanism of cerebral autoregulation might be impaired by vascular damage[57, 58], which hypothetically may lead to reduced cerebral blood flow[59]. Although the exact mechanism has yet to be elucidated, it has therefore been hypothesized that lower

systemic blood pressure might impair neurocognitive functioning specifically in individuals with more vascular brain damage[55]. This vascular brain damage may clinically be reflected by worse functional ability[60, 61], which could explain why particularly in these older persons an association between lower blood pressure and worse cognitive function has been repeatedly found[48-50].

In studies with available magnetic resonance imaging (MRI), (subclinical) damage to the arterioles and smaller vessels of the brain can be measured as features of cerebral small vessel disease (CSVD). These features comprise white matter hyperintensities, lacunar infarcts, cerebral microbleeds, and enlarged perivascular spaces, also known as Virchow-Robin spaces[62]. With technical and clinical aspects, e.g. MRI field strength and radiological definitions of CSVD features, differing between studies and hospitals[62], as of yet no widely practiced definition of clinically relevant CSVD is in use. Further, it is still under debate whether brain atrophy is a distinct feature of CSVD or whether it is a consequence of it[62].

Regarding individual markers, white matter hyperintensities have been most widely studied and associated with worse neurocognitive functioning, while increasing evidence suggests that also microbleeds and lacunar infarcts may play a role[63,64]. While it can easily be reasoned why specific lesion locations would relate to specific symptoms based on knowledge of brain structure and function, it appears that not only individual features but also the total burden of features of CSVD is of importance, as a higher total CSVD burden has been related to worse cognitive and daily functioning[61, 65] and to more depressive symptoms[66] and symptoms of apathy[10]. As of yet, it has not been studied whether vascular brain pathologies as reflected by CSVD, have a role in the relation between blood pressure and neurocognitive functioning.

General aim and outline of this thesis

The aim of this thesis is to investigate cardiovascular determinants of neurocognitive functioning in old age, in particular cognitive dysfunction, depressive symptoms, and apathy.

First, we seek to investigate whether the GDS-3A, a sub set of the frequently used GDS-15, can be used to measure symptoms of apathy in research settings. In **chapter 2,** we therefore investigate the scale properties of the GDS-3A compared to the Apathy Scale in both the DANTE Study Leiden and the PROMODE Study.

Next, we aim to explore the relation between cardiac biomarkers and neurocognitive functioning. Therefore, in **chapter 3**, we study the longitudinal association between high sensitivity troponin T and neurocognitive functioning in the oldest old, using data from the Leiden 85-Plus Study.

The subsequent chapters focus on the role of markers of (vascular) brain damage in the association between blood pressure and neurocognitive functioning. In **chapter 4,** we investigate in the DANTE Study Leiden whether the association between blood pressure and symptoms of apathy and depression is different for older persons with varying levels of functional ability. In **chapter 5,** we study the role of cerebral small vessel disease in the association between blood pressure and symptoms of apathy and depression in the DANTE Study Leiden. These analyses were extended to cognitive function and the AGES-Reykjavik population in **chapter 6.** We hypothesize that lower blood pressure is related to worse neurocognitive functioning in sub groups of older persons with more (vascular) brain damage.
To conclude, **chapter 7** provides a general discussion of the main findings of this thesis and perspectives for future research. In **chapter 8**, the main findings are summarized.

Description of studies in this thesis

To test our hypotheses and answer our research questions we use data from four different population-based study cohorts that included older people.

The DANTE Study Leiden

The Discontinuation of ANtihypertensive Treatment in the Elderly (DANTE) Study Leiden included community dwelling older persons (aged 75 and older from the Leiden area, the Netherlands) with mild cognitive deficits (MMSE score 21-27, no diagnosis of dementia), using antihypertensive medication, and without a history of major cardiovascular disease[46]. The main aim of the DANTE Study Leiden was to investigate the effect of discontinuation of antihypertensive treatment on cognitive disfunction in a randomized controlled trial design. A baseline measurement including blood pressure and neurocognitive functioning (cognitive tests, GDS-15, Apathy Scale) was performed in 430 participants, and 210 of those also underwent MRI at baseline.

The PROMODE Study

The PROactive Management Of Depression in the Elderly (PROMODE) Study investigated the effect of a stepped-care intervention program among older persons (aged 75 years and older from the western part of the Netherlands) with depressive symptoms, but without a current treatment for depression or a diagnosis of dementia[67] in the western part of the Netherlands. A baseline measurement including the GDS-15 and Apathy Scale was performed in 1118 participants.

The Leiden 85-Plus Study

The Leiden 85-Plus Study invited all inhabitants of the city of Leiden (the Netherlands) who reached the age of 85 between 1997 and 1999, without applying eligibility criteria[68]. Hs-cTnT was determined at the age of 86, which we considered the baseline for our study. The 455 participants with available data on neurocognitive functioning (cognitive tests, GDS-15), hs-cTnT, and covariates at the age of 86 were selected for our analyses.

The AGES-Reykjavik Study

The Age Gene/Environment Susceptibility (AGES)-Reykjavik Study is a population based cohort study among community dwelling older persons (aged 75 years and older from Reykjavik, Iceland)[20]. A baseline assessment including blood pressure, neurocognitive functioning (cognitive tests, GDS-15), and MRI was performed in 4,014 participants, excluding those with a diagnosis of dementia.

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