On the neural mechanisms of reduced behavior in people with cognitive decline
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 1

General introduction
General introduction

1.1. Summary

This thesis explores the neurocognitive mechanisms underlying apathy in patients with dementia probably due to late-onset Alzheimer’s disease (AD) or mild cognitive impairment (MCI), a possible precursor of AD. Although colloquially typified as a memory disorder, patients with AD commonly develop a variety of cognitive deficits (Amieva et al., 2008; Stopford, Snowden, Thompson, & Neary, 2008; Dickerson & Wolk, 2011; Scheltens et al., 2016) and behavioral symptoms (Mega, Cummings, Fiorello, & Gornbein, 1996; Benoit et al., 1999; Lyketsos et al., 2011). Among the various behavioral symptoms seen in AD, apathy is recognized to be of particular significance (Vilalta-Franch, Calvó-Pexas, Garre-Olmo, Turró-Garriga, & López-Pousa, 2013; van der Linde, Matthews, Dening, & Brayne, 2016; van der Linde, Dening, et al., 2016). This is because it develops in a substantial proportion of individuals in the early stages of AD and in these individuals, the risk for poor outcomes is found to be higher as compared to those without any behavioral symptoms (Palmer et al., 2010; Richard et al., 2012; Vilalta-Franch et al., 2013). Moreover, the cognitive mechanisms required to produce complex behavior, which is impaired in apathy, are likely to be better understood by studying its neural underpinnings.

Apathy is defined as reduced self-generated voluntary and purposeful behavior, and is characterized by symptoms such as loss of interest in activities and inability to perform actions out of own volition (Robert et al., 2009). As compared to the characteristic symptom of memory decline, apathy has been investigated less extensively in AD patients. This is especially the case with advanced imaging techniques that can probe functional mechanisms of a disorder. In the chapters of this thesis, we aimed to address this gap in knowledge by investigating the neural correlates of apathy in patients with AD and its early stages. To achieve this goal, we investigated neurochemical changes present in vivo and modelled brain activity in these patients using mathematical techniques. Results from these studies, accompanied by evidence from the literature, were used to propose a new neurocognitive model of apathy.

Cognitive decline in old age or due to AD occurs gradually over many years (Salthouse, 2009; Grober et al., 2008; Singh-Manoux et al., 2012). These changes are under various genetic and environmental influences (Deary et al., 2009; Sofi et al., 2011; Tangney et al., 2011), including neurohormonal influences (Ashpole, Sanders, Hodges, Yan, & Sonntag, 2015). Insulin-like growth factor-1 (IGF-1) is one such biological factor (Aleman & Torres-Alemán, 2009). The trophic function of IGF-1 is a canonical process, but the association between IGF-1, and normal and AD-related cognitive decline is not
clear due to contrasting findings (Deak & Sonntag, 2012; Hu, Yang, & Gong, 2016; Ostrowski, Barszczyk, Forstenpointner, Zheng, & Feng, 2016). Nevertheless, IGF-1 is of therapeutic interest (Gasparini & Xu, 2003; Vitiello et al., 2006) as changes in its serum concentration and cognition occur over overlapping timescales. Evidence for such an intervention is based mostly on cross-sectional studies, and the long term influence of IGF-1 on cognition is not well-understood (Ostrowski et al., 2016). To understand this long-term association, IGF-1 and cognitive function were investigated in healthy middle-aged and older men.

A detailed description of these topics is given in the remainder of this chapter, which is organized as follows: First, the conceptual and phenomenological basis of apathy and its impact is described. Next, an overview of current models that explain reduced behavior is provided. Following this, the cognitive and behavioral symptomatology of AD to provide the context in which apathy was studied is briefly described. After this, brain changes associated with apathy in AD are summarized. Lastly, studies reporting an influence of IGF-1 on cognitive ageing are described.

1.2. Apathy: Impaired generation of voluntary and purposeful behavior

Symptoms of apathy occur in a variety of neurological and psychiatric disorders (Chase, 2011). Besides AD, apathy is also seen in patients with Parkinson’s disease (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015), frontotemporal dementia (Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008), Huntington’s disease (Reedeker et al., 2011), progressive supranuclear palsy (Litvan, Mega, Cummings, & Fairbanks, 1996), traumatic brain injury (Andersson & Bergedalen, 2002), stroke (Caeiro, Ferro, & Costa, 2013), and in schizophrenia (Kiang, Christensen, Remington, & Kapur, 2003). Its occurrence in multiple disorders suggests that apathy does not have a single etiopathological origin, but may result from impairment of specific brain regions or networks.

Patients with apathy display a wide variety of symptoms, among which lack of initiative, flattening of affect, reduced responsiveness to stimuli, and in severe cases, indifference to their own needs are prominent (Marin, 1990; Chase, 2011). In severe cases, patients are passive to an extent that they allow themselves to be fed and dressed by caretakers without any apparent reaction (Nagaratnam, Nagaratnam, Ng, & Diu, 2004). They may not respond to questions posed or show inclination for any social contact. In milder but more common cases, patients find it difficult to initiate and complete tasks, lose interest in previously enjoyable activities, do not attempt to take actions to overcome problems, and do not show interest in gaining new experiences (Starkstein & Leentjens, 2008). They may also lack insight into their abnormal behavior (Starkstein, Brockman, Bruce, & Petracca, 2010). These symptoms result in observers
and caretakers perceiving patients to have lost interest in routine and new activities, lacking concern for their problems, and reduced enthusiasm for living in general (Colling, 2004; Schulz et al., 2012).

The definition of apathy has evolved over the past twenty-five years (Marin, 1990; Starkstein, 2000; Stuss, Van Reekum, & Murphy, 2000; Brown & Pluck, 2000; Sockeel et al., 2006; Levy & Dubois, 2006). The changes in its definition during this period reveal the trajectory of our understanding of this subtle but widely prevalent neuropsychiatric symptom. Apathy was first defined as a disorder of motivation and was stated to result from ‘diminished motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress’ (Marin, 1990). This early characterization provided impetus towards recognizing apathy as an independent syndrome and spurred interest into understanding its clinical correlates.

Another early view suggested that symptoms such as withdrawal from activities in the absence of other causative conditions such as impaired consciousness or intact motor functions can be interpreted as lacking the ‘will’ to act (Berrios & Gili, 1995). This has also been termed “avolition” in the neurological and psychiatric literature. As ‘motivation’ and ‘will’ are not easily measured and susceptible to subjective interpretations, an alternative definition for apathy was proposed. Apathy was defined as ‘absence in responsiveness to stimuli as demonstrated by lack of self-initiated action’ (Stuss et al., 2000). This definition laid stress upon externally observable features in the form of the patient’s responses. In addition, apathy was directly linked to lack of self-initiated action. In this definition and that proposed by Marin, apathy was divided into three subtypes that categorized symptoms according to impairments in affective, cognitive, and sensory-motor domains (Marin, 1996; Stuss et al., 2000). Moreover, each subtype was linked to independent neural deficits in the circuits of the forebrain and brainstem.

In addition to proposing a definition for apathy, Marin postulated that the amotivational state of apathy is a result of impaired goal-directed behavior (GDB) (Marin, 1996). For understanding the basis of reduced motivation or self-initiated action, the concept of GDB provides a neuropsychological framework that describes various processes needed to perform purposeful actions oriented towards achieving a goal. Note that reflexive actions in response to stimuli, even if complex are not considered as GDB. GDB involves the selection of a goal on the basis of internal or external stimuli, making a plan of action comprising of sub-goals, and orderly execution of planned actions towards achieving the overall objective (Dickinson & Balleine, 1994; Brown & Pluck, 2000). For example, seeking treatment in a hospital for symptoms (like pain) and with the objective of curing the ailment. In this scenario, an individual would determine a series of sub-goals such as planning appointments, arranging transport to the hospital, consulting
doctors, and following the treatment regimen. The need for elaborate planning and execution calls upon a number of neural functions. The inability to perform such goal-directed actions is suggested to result in symptoms of apathy.

For successful GDB, several neural processes are needed to transform a motivating stimulus into plans and actions. Using a simplified framework of GDB, Brown and Pluck (2000) proposed that symptoms of apathy can be divided into three subtypes - affective, cognitive, and motor, following Marin’s (1990) earlier categorization. Each subtype is said to result from deficits in separate neural circuits that link the cortico-striato-thalamic regions. Other authors have also suggested a similar three-subtype division of apathy (Cummings et al., 1994; Robert et al., 2002; Levy & Dubois, 2006; Starkstein & Leentjens, 2008). However, further subdivisions may be possible. Sockeel and colleagues (2006) conducted a principal component analysis on a 33-item questionnaire and found four clusters of symptoms that were grouped as (lack of) a) Intellectual curiosity, b) Action initiation, c) Emotion, and d) Self-awareness.

The most widely used definition states that apathy is a ‘quantitative reduction in self-generated voluntary and purposeful behavior’ (Levy & Dubois, 2006). In this definition too, dysfunctional GDB was posited to be the basis of apathetic symptoms. As in Stuss et al. (2000) and Brown and Pluck (2000), three mechanisms localized to the prefrontal cortex and basal ganglia were proposed to underlie apathy by Levy & Dubois (2006). An emotional-affective type was related to the orbitofrontal and medial prefrontal cortex, and ventral striatum and ventral pallidum in the basal ganglia. The deficits proposed to be associated with this subtype were an inability to process affect and link it to behavior, and assign accurate reward value to actions. A second subtype proposed that deficits in the dorsolateral prefrontal cortex, dorsal caudate nucleus, and part of the thalamus led to apathy. Termed cognitive type, executive functions such as planning, rule-learning, and set-shifting were expected to be deficient. The third mechanism was related to a deficit in auto-activation, in which lesions mainly in the basal ganglia were considered to be the underlying mechanism. The features of this type were expected to be a relative sparing of externally-driven actions along with a severe reduction in spontaneous thoughts and actions. While this categorization is based on well-known functions of neural circuits, empirical evidence for subtypes of apathy is weak. While studies have linked apathy to individual cognitive functions (Chau, Chung, Herrmann, Eizenman, & Lanctôt, 2016; Fazio et al., 2016; Martinez-Horta, Pagonabarraga, Fernández de Bobadilla, García-Sanchez, & Kulisevsky, 2013; Rochat et al., 2013), a comprehensive assessment of goal-directed behavior and the circuits involved is currently lacking.

Taken together, the various definitions concur that GDB is impaired in apathy but its neural substrates are not established. For this, better assessment of apathy and further
analysis of associated brain changes are needed. Several instruments are used to assess symptoms of apathy including (but not limited to) the neuropsychiatric inventory (NPI) (Cummings et al., 1994), apathy evaluation scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991), apathy inventory (Robert et al., 2002), apathy scale (Starkstein et al., 1992), and Lille apathy rating scale (Sockeel et al., 2006). Here the NPI and AES are described. The NPI is the most commonly used instrument to assess apathy and other behavioral symptoms (Clarke et al., 2011). A caretaker or an informant who knows the patient well is asked whether the patient seems to be less interested in activities, lacks motivation for starting new activities, or is more difficult to engage in a conversation. A score is assigned for the symptom by multiplying the frequency (in four levels) by the severity (in three levels) (Cummings et al., 1994). Although used widely, the NPI is not specifically designed to assess apathy. It does not assess the degree of apathy or the domains that may be affected. These limitations are addressed by the apathy evaluation scale (AES), which is an 18-item questionnaire, scored using 4-point Likert scale with higher scores indicating greater apathy. In addition, the AES has been shown to discriminate apathy from depression and the clinician-rated AES was found to be more reliable than the informant-rated and self-rated versions (Clarke et al., 2007).

On the basis of accumulating evidence that indicates apathy is a distinct syndrome with underlying neural correlates, clinical criteria for its diagnosis have been established (Robert et al., 2009). A consensus group proposed that for a diagnosis of apathy, the following conditions must be present – the symptoms must be present for at least four weeks, impairment must be present in two of the three domains (goal-directed behavior, goal-directed cognitive activity, and emotions), the impairment affects functioning, and no other exclusionary causes of apathy such as physical disability or medication-induced changes must be present (Robert et al., 2009) (See Box 1.1 for full definition). Notably, these criteria require impairment in at least two domains, which from a neural viewpoint would entail deficits in two of the three proposed circuits. Also, no threshold score on any instrument is prescribed or recommended for a diagnosis.
BOX 1.1: Diagnostic criteria for apathy

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D

A] Loss of or diminished motivation in comparison to the patient’s previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

B) Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time

Domain B1: Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:
- Loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
- Loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)

Domain B2: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
- Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).
- Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person’s residence, neighbourhood or community)

Domain B3: Loss of, or diminished, emotion as evidenced by at least one of the following:
- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
- Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)

C] These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D] The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

(from Robert et al., 2009)
1.3. Apathy in Alzheimer’s disease dementia

AD is typically characterized by memory deficits (McKhann et al., 2011). Symptoms such as forgetting a familiar route to one’s home or asking the same question multiple times within the span of a single conversation are suggestive of probable AD (Budson & Solomon, 2011). Less relevant are other forms of forgetfulness that are common in older individuals. An example of benign forgetfulness is an inability to remember where keys or eye glasses were last kept. Thus, not all memory loss occurring with age is of concern but forgetting important facets of one’s personal life is an indicator of AD. Clinically, the failure to store and consolidate new information is considered suggestive of declining memory. As memory and other cognitive functions decline over time at a higher rate than normal, the individual is no longer capable of functioning independently, warranting a diagnosis of probable Alzheimer’s disease (McKhann et al., 2011).

The early identification of individuals at risk for AD is an important research priority because by the time a clinical diagnosis of AD is possible, extensive atrophy or loss of brain tissue is already present (Petersen et al., 1999). As lost neuronal tissue cannot be replaced, identifying those likely to develop AD before atrophy occurs is a key goal. Interventions at this stage are more likely to be successful. Accordingly, an early stage of AD was defined and termed ‘MCI due to AD’ (Albert et al., 2011). Typically, those who progress to AD are more likely to have deficits in episodic memory. Hereafter termed amnestic MCI (aMCI), the primary criteria for identifying these patients are a subjective concern of memory decline and objective deficit in episodic memory tests (Albert et al., 2011) (See Box 1.2 for a complete definition). In this state, minimal atrophy, typically restricted to the medial temporal lobe is observed (Visser et al., 1999; Killiany et al., 2000; Ferreira, Diniz, Forlenza, Busatto, & Zanetti, 2011).

The prevalence of aMCI in the population is estimated at approximately 7% (Ward et al., 2012) and the rate of progression to AD in this cohort is estimated at 10-15% per year as opposed to 1-2% in the general population (Petersen et al., 1999; Larrieu et al., 2002; Visser, Kester, Jolles, & Verhey, 2006; Mitchell & Shir-I-Feshki, 2009; Brodaty et al., 2013). However, aMCI has proven to be a heterogeneous state (Petersen et al., 2014). About 67% remains stable at 2 years and about 24% may revert back to a cognitively normal state (Brodaty et al., 2013; Canneveli et al., 2016). Over longer periods, the annual rate of reversion of 18.6% has been reported (Gao et al., 2014) but even those who revert show a higher risk of progressing to dementia subsequently (Roberts et al., 2014).
Although impaired memory is more specific for AD compared to other symptoms, the complete clinical picture in aMCI and AD is complex. Nearly all patients with advanced AD develop one or more neuropsychiatric symptoms (NPS) that are usually persistent and become more severe over time (Lyketsos et al., 2002; Apostolova & Cummings, 2008; Steinberg et al., 2008). Some of the NPS such as apathy are more likely to develop earlier in the aMCI stage or even in cognitively normal older adults, although at a low prevalence rate.

Several large population studies have estimated the prevalence of apathy and other NPS in AD (Burns, Jacoby, & Levy, 1990; Mega et al., 1996; Lyketsos et al., 2002; Aalten et al., 2007; Van der Mussele et al., 2013). Among 178 AD patients, apathy was present in 41% (Burns et al., 1990). A larger population-based study found apathy to be the most common NPS at 28.5% in AD (Lyketsos et al., 2002). Within the same study population, apathy in all-cause dementia increased from 20% at baseline to 51% after 5 years. Moreover, nearly three-fourths of the sample had apathy at some point during the five years of follow-up. In this study, apathy was also found to have the highest severity score (Steinberg et al., 2008). A recent meta-analysis found that, at 49%, apathy was the most prevalent NPS in AD (Zhao et al., 2016). In aMCI patients, large population-based studies estimate that 15% (Lyketsos et al., 2002; Okura et al., 2010) to 21% (Geda et al., 2008) of this cohort shows apathetic symptoms. Other studies have reported prevalence figures of 39% (Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004), 10.7% (Palmer et al., 2010), and 29% (Vicini Chilovi et al., 2009). Apathy also occurs in community-dwelling, cognitively normal older adults where expectedly lower prevalence rates are found, with estimates of 4.8% (Geda et al., 2014), 5% (Forrester, Gallo, Smith, & Leoutsakos, 2016), and 12.1% (Savva et al., 2009) being reported.

In several studies, the estimated risk of progression to AD in those with aMCI and apathy symptoms was approximately 1.85 to 7 times higher than those without apathy (Teng, Lu, & Cummings, 2007; Robert et al., 2008; Vicini Chilovi et al., 2009; Palmer et al., 2010; Richard et al., 2012; Pink et al., 2015). The combination of high prevalence in aMCI patients and increased risk for progression to AD gives apathy the highest population attributable risk among all NPS. Notably, cognitively normal older adults with apathy were also twice as likely to develop MCI as compared to those without apathy and this risk was greater than that associated with hippocampal size in the same population (Geda et al., 2014). These findings provide a strong basis to consider apathy as a marker for identifying those at risk of developing AD (Lanctôt et al., 2016).

While this epidemiological profile of apathy establishes its significance in the clinical trajectory of AD, the underlying neural mechanisms are not clear. Its mechanisms are of interest as the increased risk suggests that the pattern of neural changes underlying the development of apathy influence the pathophysiological process of AD.
1.4. Distinguishing apathy from depression in AD

The symptomatologies of apathy and depression show considerable overlap (Marin, Firinciogullari, & Biedrzycki, 1993). Due to this, whether apathy and depression are independent has been debated (Levy et al., 1998; Tagariello, Girardi, & Amore, 2009; Zahodne et al., 2013). The similarities in observed symptoms, for example, withdrawal from regular activities, make it difficult to distinguish the two syndromes. It should be noted though, that a clear difference between the two is that depression is characterized by depressed mood and negative attentional biases (including low self-esteem), which are not characteristic of apathy proper. Rather than having negative cognitions, people with an apathy syndrome are characterized by being callous. Apathy is not recognized as an independent entity in the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5; American Psychiatric Association, 2013), perhaps because it is considered to be a correlate of other psychiatric or neurological problems. In DSM-5, apathy is included in criteria for diagnosing neurocognitive disorders but a clear definition is not provided (American Psychiatric Association, 2013). In earlier editions, symptoms of apathy such as lack of interest and flat affect were included in diagnostic criteria without terming such symptoms as part of an apathy syndrome (American Psychiatric Association, 2000). On the other hand, DSM-5 characterizes depression or major depressive disorder by depressed mood (affect) and loss of interest or pleasure (American Psychiatric Association, 2013). A closer reading of the nine symptoms comprising the diagnostic criteria for major depressive disorder suggests that two of the criteria show symptomatic overlap with those of apathy. These two symptoms of depression are i) ‘Markedly diminished interest or pleasure in all, or almost all, activities...’, and ii) ‘psychomotor retardation or agitation, nearly every day’. It is likely that clinical or caregiver observations of externally manifested reduction in interest or psychomotor activity do not provide information about internal unobservable factors that produce these symptoms. In short, positive affect and hedonic responses are reduced in depression whereas in apathy, the generation of voluntary behavior is reduced.

In addition to the phenomenological differences, numerous studies have shown apathy to exist independently of depression in a wide range of disorders, e.g. Parkinson’s Disease (Kirsch-Darrow et al., 2006; Oguru, Tachibana, Toda, Okuda, & Oka, 2010), Alzheimer’s Disease (Levy et al., 1998; Palmer et al., 2010; Starkstein, Jorge, Mizrahi, & Robinson, 2006), and schizophrenia (Kiang et al., 2003; Shaffer et al., 2015; Simon et al., 2010). In MCI and AD, apathy and depression show different clinical profiles such as different prevalence rates (Apostolova & Cummings, 2008), risk for disease progression (Richard et al., 2012), and responses of medication (Wongpakaran, van Reekum, Wongpakaran, & Clarke, 2007). Studies have also attempted to distinguish between their neural correlates (Bruen, McGeown, Shanks, & Venneri, 2008). However,
both syndromes are often comorbid and their individual neural mechanisms have not been conclusively established. Further discussion on the separation of depression and apathy is beyond the scope of this thesis (See Mortby, Maercker, & Forstmeier, 2012 for a recent review).

1.5. Brain changes associated with apathy in aMCI/AD

Several studies investigating the neural correlates of apathy in AD and MCI patients, have used brain imaging methods such as single-photon emission computed tomography (SPECT) to measure changes in regional blood flow, positron emission tomography (PET) to measure specific ligands, and magnetic resonance imaging (MRI) to measure changes in brain structure and function. The findings of these studies have been reviewed recently (Kos, van Tol, Marsman, Knegtering, & Aleman, 2016; Stella et al., 2014; Theleritis, Politis, Siarkos, & Lyketsos, 2014) and are briefly summarized below.

The systematic reviews show that across imaging modalities, the dorsal anterior cingulate cortex has been consistently associated with apathy in AD patients. In addition, other regions such as the orbitofrontal and medial prefrontal cortex have been associated with apathy in this patient group. The changes in these regions associated with apathy include reduced perfusion (Migneco et al., 2001; Benoit et al., 1999, 2002, 2004; Robert et al., 2006; Lanctôt et al., 2007), lower glucose metabolism (Holthoff et al., 2005; Marshall et al., 2007), and loss of grey matter (Apostolova et al., 2007; Bruen et al., 2008; Tunnard et al., 2011). Moreover, white matter changes in these regions have also been found (Starkstein et al., 2009), with a notable loss of integrity of the cingulum bundle, which passes through the cingulate cortex (Kim et al., 2011; Ota, Sato, Nakata, Arima, & Uno, 2012; Tighe et al., 2012; Hahn et al., 2013). These findings are strengthened by the association of apathy in these patients with amyloid deposition (Marshall et al., 2013; Mori et al., 2014) and neurofibrillary tangle counts (Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2006), both of which are hallmarks of AD, in the anterior cingulate cortex.

In contrast with the consistent association between changes in the anterior cingulate cortex and prefrontal cortex with apathy in AD patients, the link between particular brain regions and apathy in aMCI patients is less robust. Studies assessing cortical thickness have not found any association between any brain region and apathy at baseline in aMCI patients (Donovan et al., 2014; Zahodne et al., 2013), whereas future severity of apathy was predicted by thinning in the inferior temporal cortex (Donovan et al., 2014). Reduced cortical thickness in the same region was associated with apathy at baseline in these patients when the apathy evaluation scale was used for assessment (Guercio et al., 2015).
### BOX 1.2: Diagnostic criteria for aMCI due to AD

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<tr>
<td>1.</td>
<td>Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time).</td>
</tr>
<tr>
<td>2.</td>
<td>Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains). There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient’s age and educational background. As a guideline, scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data.</td>
</tr>
</tbody>
</table>
| 3. | Preservation of independence in functional abilities
Persons with MCI commonly have mild problems performing complex functional tasks, which they used to perform previously, such as paying bills, preparing a meal, or shopping. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. |
| 4. | Not demented
These cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning. |

(from Albert et al., 2011)
Recently, functional connectivity in brain networks has also been assessed with respect to apathy. Whereas one study in AD patients did not find any association between apathy and a limited number of brain networks (Balthazar et al., 2014), other preliminary findings suggest that apathy in aMCI patients may be associated with reduced connectivity in the frontoparietal network (Joo, Lee, & Lim, 2017; Munro et al., 2015).

Overall, the evidence suggests that apathy is associated with dorsal anterior cingulate cortex and prefrontal cortex in AD patients, and with the temporo-parietal regions in aMCI patients. The systematic reviews also show that only a few studies of apathy have used advanced methods or other imaging modalities that investigate aspects of brain function other than changes in structure and perfusion. Addressing these limitations in this thesis, we investigated apathy in AD and aMCI patients with proton magnetic resonance spectroscopy (1H-MRS) and whole-brain functional connectivity.

1.6. Techniques used to assess functional properties of the brain

1H-MRS quantifies neurometabolites, which are markers for various processes, in the brain in vivo (Alger, 2010). Similar to structural MRI scans, 1H-MRS quantifies substances that have a net magnetic moment and are present in adequate amounts in the tissue (Alger, 2010). While structural scans quantify the signal from proton ions of water, 1H-MRS is optimized to detect other substances that possess protons with a net magnetic moment. Due to the relative abundance of water (nearly 10000 times higher as compared to neurometabolites), structural scans provide high quality images of 1 x 1 x 1 mm resolution. In contrast, conventional 1H-MRS scans acquire signals of neurometabolites from 20 x 20 x 20 mm voxels in a clinically reasonable amount of time.

The most abundant neurometabolites in the brain include N-acetyl aspartate (NAA), Choline (Cho), myo-inositol (mI), creatine (Cr), and glutamate and glutamine (Glx) (Soares & Law, 2009). Each of these metabolites are enriched in particular neural compartments or are indicators of specific metabolic functions, and hence can be used as biomarkers for various diseases (Öz et al., 2014). For example, NAA is considered as a marker of neuronal health as it is localized primarily to neurons, whereas mI is localized to glial cells and an elevated level is considered to represent increased glial activity indicating inflammatory changes. Cho measures free choline, which is derived from cell membranes and also to a small extent from the neurotransmitter acetylcholine, while Cr is considered to be an indicator of energy metabolism. The Glx signal indicates the level of the excitatory neurotransmitter glutamate and its metabolite glycine.
In AD patients, lower levels of NAA and higher levels of mI have consistently been reported in the posterior cingulate cortex, a major locus of degenerative changes in AD (Adalsteinsson, Sullivan, Kleinhans, Spielman, & Pfefferbaum, 2000; Kantarci et al., 2000; Catani et al., 2001). These changes were also linked to neuronal loss and increased inflammation in the posterior cingulate cortex (Murray et al., 2014). In asymptomatic individuals at risk for developing AD, mI and Cho levels were found to be elevated in this region (Kantarci et al., 2011). Hence, it was suggested that inflammatory changes and breakdown of cell membranes precede the decline observed in NAA level. Together, these results show that 1H-MRS can be used to improve our understanding of pathophysiological processes in the brain. In this thesis, we sought to determine changes in these processes in relation to apathy in aMCI patients.

In addition to 1H-MRS, we also analyzed whole-brain functional connectivity and its association with apathy and AD. Functional connectivity is measured by fMRI scans that are sensitive to what is termed as the blood-oxygen level dependent (BOLD) signal (Huettel, Song, & McCarthy, 2014). This signal is an indirect measure of neuronal activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Neuronal firing triggers increased local blood flow, which leads to more oxygen-rich hemoglobin locally. The increased hemoglobin produces a larger BOLD signal than when no neuronal firing occurs and is inferred as presence of local neuronal activity. In standard fMRI scanning sequences, a BOLD signal from approximately 3 x 3 x 3 mm voxels spread all over the brain is acquired every 2 seconds. In chapter 4, such scans were acquired when a subject was lying in a quiet, awake and restful state. Termed resting state fMRI, it is of particular interest as these scans are easily acquired in a standardized format with minimum problems in following scan procedures, especially for patients. This method is increasingly being used to understand normal and abnormal brain function, catalyzed by the discovery of functional brain networks (van den Heuvel & Hulshoff Pol, 2010).

In functional networks, the activity of the BOLD signal in distant brain areas is correlated (Biswal, Yetkin, Haughton, & Hyde, 1995). For example, the default mode network comprises cortical midline regions and the inferior parietal lobule and dysfunction in this network has been associated with various disorders (Raichle et al., 2001). Specifically in AD, connectivity within this network is progressively reduced (Greicius, Srivastava, Reiss, & Menon, 2004; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). Other canonical networks include the frontoparietal network and the salience network that are implicated in executive functions and in directing attention towards relevant stimuli, respectively (Seeley et al., 2007). Both these networks have not consistently been linked to AD, but it may be that specific symptoms are associated with changes in particular networks.
Standard methods of analysis investigate mean connectivity within a few large networks, which effectively ‘blurs’ functional connectivity data (Biswal et al., 1995; Fox et al., 2005). Such methods do not typically investigate functional connectivity across the whole brain or between networks. A new method, graph theory, has been used though to assess brain-wide functional connectivity with a small number of summary measures. This method describes the brain as a topological network consisting of regions of interest called nodes. Nodes may be connected to one another by edges, thus forming a topological map. An edge (or connection between two regions) is considered to be present if the correlation in the BOLD activity between the regions is above a certain (arbitrary) threshold. It is observed that real-world networks form optimum connectivity profiles, which can be assessed by various measures of graph theory (Bullmore & Sporns, 2009). For example, path length of a node is given by the number of edges between that node and every other node. In AD, path length is found to be increased, leading to reduced efficiency of functional connectivity (Sanz-Arigita et al., 2010). As of yet, no such detailed studies of functional connectivity have been reported in AD/aMCI patients with apathy. We aimed to fill this gap in knowledge about the changes in functional connectivity underlying apathy in AD/aMCI.

1.7. Insulin-like Growth Factor-1: link to cognition

In the second part of this thesis, we will examine the influence of a biological factor on cognitive function. Cognitive decline in older individuals occurs gradually over prolonged durations (Salthouse, 2009). Moreover, age is the strongest predictor of cognitive status in both normal ageing and pathological conditions like AD (Deary et al., 2009). Recent studies in AD have found that biological changes precede cognitive decline by several years (Sperling et al., 2011; Jack et al., 2013). Therefore, it is possible that biological factors affecting the general ageing process also independently affect cognition. Consistent with this hypothesis, early interventions have been called for that can slow the progress of biological changes and delay the development of clinically significant symptoms of cognitive decline (Torres-Alemán, 2007).

IGF-1 has been suggested as a potential endogenous molecule affecting neuronal resilience, and hence, cognitive function (Sonntag, Ramsey, & Carter, 2005; Aleman & Torres-Alemán, 2009). It is an evolutionarily conserved systemic somatotrophic factor, which partly mediates the actions of growth hormone on the body and regulates the process of aging (Deak & Sonntag, 2012). Researchers have sought to determine whether variations in the serum concentration of IGF-1 are associated with differences in cognitive performance. Several early studies found that low IGF-1 levels in older adults, as compared to those with high levels, were associated with worse cognitive function (Morley et al., 1997; Rollero et al., 1998; Aleman et al., 1999). This result was replicated in larger samples of older adults (Dik et al., 2003; Okereke, Kang,
Ma, Gaziano, & Grodstein, 2006) and it was suggested that raising IGF-1 levels therapeutically may delay the onset of cognitive decline in these individuals. A single clinical trial found that raising IGF-1 levels (by administering growth hormone releasing hormone) appeared to improve cognition in MCI patients (Baker et al., 2012). However, the evidence for such interventions is not unequivocal as seen in a recent meta-analysis that did not find any difference in serum IGF-1 levels between AD patients and control subjects (Hu et al., 2016). Furthermore, no association was found between IGF-1 and cognition in healthy middle-aged subjects. A better understanding of these contrasting results and the role of IGF-1 in cognitive function is needed to reveal how IGF-1 affects cognition and inform its therapeutic possibilities.

Extensive studies in animals show that IGF-1 has a complex regulatory function that has also been described as paradoxical (Fernandez & Torres-Alemán, 2012). It is likely that the influence on cognition in humans is also complex and apparently paradoxical. This is illustrated by a study in centenarians in whom mutations were found in genes for receptors of IGF-1 that lowered the bioactivity of IGF-1, which putatively contributed to increased lifespans (Suh et al., 2008). As this effect was limited to females, it indicates that the influence of IGF-1 may be gender-specific, in addition to being related to age. A particular gap in the literature on IGF-1 and cognition in humans pertains to its influence on long-term cognition. Cross-sectional studies find a small but significant negative association between IGF-1 and cognition in older adults (Dik et al., 2003) but not in middle-aged adults (Licht et al., 2014). An association was found in middle-aged adults in a longitudinal study approximately twenty years after serum IGF-1 levels were determined (Okereke et al., 2006). A limitation of this study was the use of a rather brief cognitive measurement. To better understand this relationship, we examined cognitive functions in detail in middle-aged and older men at two time points approximately eight years apart and estimated the association with serum IGF-1 at the baseline measurement. The aim was to determine whether the cross-sectional association between cognition and IGF-1 in older adults is also present prospectively.

1.8. Overview of studies

This thesis comprises of two broad overlapping themes. In the first part, we used the approach of cognitive neuropsychiatry, which models symptoms of a disorder based on the cognitive and neural deficits present (Halligan & David, 2001). Such models are based on evidence of deficient neuropsychological performance and associated changes in brain function. Thus, complex symptoms can be interpreted as resulting from deficits in specific cognitive functions and associated brain regions. The second part of this theses focuses on the biological mechanisms in the brain and the periphery that influence cognitive decline. In chapter 2, we conducted a meta-analysis of neurometabolite changes in ¹H-MRS studies in MCI patients. In chapter 3 and 4, we
aimed to understand the neural basis of apathy in the context of AD. Current knowledge on this topic is based on structural MRI studies, PET studies that measure metabolic activity or toxic amyloid deposits characteristic of AD, and SPECT studies that measure blood flow. In chapter 3, we investigated the association between apathy in aMCI patients and neurometabolite changes on $^1$H-MRS from various regions that may underlie symptoms in these patients. Studies using fMRI are limited in number and have investigated functional connectivity within a few pre-defined networks. In chapter 4, we conducted a comprehensive investigation of functional connectivity to determine global and network-level connectivity changes in those with apathy in aMCI/AD. In chapter 5, the findings from chapters 3 and 4 are integrated with a critical review of literature and a new neurocognitive model of apathy is proposed with a focus on the parietal cortex. Chapter 6 describes the longitudinal association between serum IGF-1 and cognition in middle-aged and older men. In chapter 7, an integrated view of the findings along with their implications and future research directions are discussed.