GENERAL INTRODUCTION

Chapter 1
What is apathy?

Sometimes it can be difficult to get yourself together and go outside, take a walk, go to the supermarket, or for example to fulfill regular household activities. Probably every one of us has experienced these difficulties, at some point in their lives, maybe in the aftermath of a heavy flu or just on a lazy Sunday afternoon. However, some people experience these problems on a day-to-day basis. It is often seen in people with certain psychiatric problems, patients with brain injury, or for example in those who are diagnosed with a neurodegenerative disorder. Although the will to engage and to enjoy activities can be present, the actual undertaking of actions appears to be severely compromised. To their friends and families, the person can appear listless, indifferent, insensible, or just lazy. This reduction in voluntary and goal-directed behavior can be described as apathy. Apathy can be highly debilitating in the development and maintenance of social interactions and fulfilling basic tasks in daily practice. Furthermore, across various disorders, apathy has been indicated as a strong predictor of worse clinical, functional and occupational outcome. Therefore, it can be of great burden to those who suffer from it, but also to those in their surroundings. Understanding underlying mechanisms and developing better treatment options for apathy is highly relevant in improving clinical outcome of people suffering from apathy as part of psychiatric, neurodevelopmental, and neurodegenerative disorders.

Apathy is derived from the ancient Greek word apatheia, meaning ‘without feelings’. It refers to being free of pathos, or passions. In this state of being there is no fear, pain or desire. Apathy was regarded as a highly desirable state of being by the ancient Greek; the only way to live a ‘virtuous and happy live’, because it allowed rational thoughts or clear thinking (Starkstein & Leentjens, 2008). From the mid-19th century onwards the term ‘apathy’ has been used to describe an undesirable state of being, indicating unresponsiveness and insensitivity (Arts, 2013). At that point in time, apathy was described as a disorder of emotions, including a lack of feelings, lack of emotions, and interests, which was commonly found in various patient populations (Arts, 2013). This definition was however incongruent with the observation that certain patients could appear apathetic because of a lack of motivation and interest, but on the other hand could be hostile or anxious at the same time (Marin, 1990). In order to differentiate apathy from related concepts, but at the same time acknowledge the similarity of symptoms found in various patient populations, Marin (1990) proposed to define apathy as a state of diminished motivation. Of note, the motivational impairment was assumed not to be due to a ‘diminished level of consciousness, intellectual deficit, or emotional distress’ (Marin, 1990). To date, apathy has been described as an independent syndrome on its own, but also as part of various syndromes (Marin, 1991; Marin, Fogel, Hawkins, Duffy, & Krupp, 1995; Starkstein, Petracco, Chemerinski, & Kremer, 2001). Apathy as an independent syndrome can be considered to be at the extreme end of a distribution of otherwise normal variation in the propensity to execute self-initiated and goal-directed behavior; a variation in behavior that is also present in the healthy population (Bonnelle et al., 2016). Moreover, Marin (1991) and Starkstein (2001) advocated that apathy can also be described as a cluster of related but also varying symptoms (such as lack of feeling, interest, concern or motivation) with its own pathophysiology, which is reliably measurable, and that is clinically relevant.

The notion of apathy as a separate syndrome of impaired motivation and/or loss of initiative has been studied in different fields of research, e.g. neurodegenerative, lesion, and psychiatry studies. Moreover, multiple factor analyses have identified apathy as a separate syndrome in various populations (Aalten et al., 2008; Zuidema, de Jonghe, Verhey, & Koopmans, 2007), but also as a separate
construct in measurement scales of psychiatric symptomatology (Liemburg et al., 2013). Despite this, apathy has not been described as a separate syndrome in any of the diagnostic manuals. Nevertheless, based upon the work of Marin (1990; 1991) and Starkstein (2001), international consensus criteria for a diagnosis of apathy have been established (Robert et al., 2009). According to this international consensus, apathy is regarded as a syndrome of diminished motivation that is persistent over time (criterion A). In order to diagnose apathy, symptoms within two of three dimensions, i.e. loss of goal-directed behavior, goal-directed cognitive activity (for example, loss of ideas and curiosity for new events), and loss of emotions, should be present (criterion B). Furthermore, according to these diagnostic criteria, apathy should be characterized by multiple functional losses leading to clinically relevant impairments in daily life (criterion C). Lastly, these symptoms cannot be exclusively explained by physical or motor disabilities, or diminished levels of consciousness (criterion D).

According to the international consensus criteria of Robert et al. (2009), apathy can be described as a disorder of motivation. While Galderisi and coworkers (2016) emphasize the importance of internal experiences in measuring apathy, others have argued that a motivational disturbance is difficult to measure. Difficulties could arise because motivation is not an objective and observable behavioral state, but a psychological interpretation of observed or reported behavior (Levy & Dubois, 2006; Stuss, van Reekum, & Murphy, 2000). Therefore, it has been proposed to define apathy as a behavioral syndrome involving a lack of self-initiated, goal-directed behaviors (Levy & Dubois, 2006; Stuss et al., 2000; van Reekum, Stuss, & Ostrander, 2005). In this way, apathy can be measured independent of a psychological interpretation (Levy & Dubois, 2006). For this reason, in this dissertation, the definition of apathy as provided by Levy & Dubois (2006) will be adhered, as it acknowledges apathy as a loss of observable (i.e. quantifiable) goal-directed behaviors. More specifically, throughout this dissertation, apathy is regarded as a behavioral characteristic reflecting reduced self-initiated goal-directed behavior that can be present to differing degrees (along a continuum).

Apathy-related concepts

Even though international criteria have been proposed to classify apathy as a separate syndrome, there is still a debate going on about the exact definition. The presence of various related terms illustrates the lack of consensus and complicates research. Two of the most closely related concepts are avolition and amotivation. Avolition can be defined as “a severe problem with initiation, volitional, or willed action, and production of goal-directed behavior”. Which “may reflect in a general lack of motivation and drive” (Piryatinsky & Malloy, 2011). Amotivation yields a similar description: “the inability to initiate and sustain goal-directed activity, related to a diminished sense of drive” (Fervaha, Foussias, Agid, & Remington, 2015). Indeed, these terms are often used interchangeably. Though, avolition, amotivation, and apathy describe similar or identical symptomatology, avolition and amotivation appear to be more often used than apathy in patients with schizophrenia (Fervaha et al., 2013). Abulia is another term used to describe disorders of ‘the will’, however it was more often used in the beginning of the 20th century (Arts, 2013). Abulia describes a lack of will, or an inability to decide, causing an absolute inactivity (Arts, 2013; Marin, 1990). According to Marin (1990) abulia (‘a lack of will’) and apathy (‘a lack of motivation’) are on a continuum, with abulia being more severe, referring to awake but unresponsive patients. Within clinical practice this continuum and distinction in symptom severity is however not always acknowledged and terms are used interchangeably (Vijayaraghavan, Krishnamoorthy, Brown, & Trimble, 2002).
It may be difficult to demarcate apathy from depression. Overlapping symptoms include inactivity, reduced social behavior, affective flattening, and loss of interests in activities that were previously enjoyed (Drijgers, Aalten, Leentjens, & Verhey, 2010; Marin, 1990). However, depression is distinct from apathy in a way that patients with depression actively avoid certain tasks, places or people, instead of being more passive or ignorant, as what is often seen in apathy. Furthermore, patients with depression are often more emotionally distressed. Whereas apathy is associated with insensibility, depression is characterized by high levels of distressing emotions. People with depression can be sad, feel worthless, and can even be suicidal, which clearly reflects despair and negativism (Marin, 1990). Another core symptom of depression is anhedonia, or an inability to experience pleasure (Drijgers et al., 2010; Ribot, 1882). In patients with apathy, anhedonia can be present, and is often suspected to be present, however various studies have demonstrated an intact experience of pleasure in at least part of the patients with apathy (Gard, Gard, Kring, & John, 2006; Waltz et al., 2009). Indeed, studies in various patient populations demonstrated that apathy and depression can be present independently of each other, they involve separate neural correlates, and can independently predict functional outcome (e.g. Hama et al., 2007; Holthoff et al., 2005; Kang et al., 2012; Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007; Onoda & Yamaguchi, 2015; Simon et al., 2010; Skidmore et al., 2013; Starkstein et al., 2009). Taken together, apathy and depression can be regarded as separate constructs, that can co-occur but not by necessity. If one measures clinical apathy, it is therefore important to evaluate causes of reduced goal-directed behavior while prominent depressive symptoms need to be absent (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015).

A final cluster of symptoms that overlaps with apathy concerns “negative symptoms”, and is part of the disorder of schizophrenia. Negative symptoms indicate a loss of behaviors (Andreasen, 1982). Positive symptoms on the other hand, refer to new produced behavior, i.e. behaviors that are present in the affected schizophrenia population, such as hallucinations and delusions, while these are not present (or not as strong) in the healthy population (Crow, 1980). Primary negative symptoms, sometimes referred to as deficit symptoms, often occur before or after the onset of psychosis or positive symptoms, and include blunted affect, alogia (reduced speech), asociality, anhedonia, and apathy/avolition (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Apathy therefore is a narrower term compared to negative symptoms, the latter also including more general deficits such as alogia and anhedonia (Kirkpatrick Brian B, 2014-4). Within the most recent diagnostic manual for mental disorders, the negative symptom cluster is subdivided into at least two subdomains, which is in accordance with several factor analyses (e.g. Blanchard & Cohen, 2006; Liemburg et al., 2013). A first subdomain refers to reduced affective and linguistic expressions (blunted affect and alogia), and a second subdomain refers to apathy, encompassing avolition, anhedonia, and asociality.

**Apathy as a behavioral characteristic with multiple subdomains**

Undertaking goal-directed behavior requires thinking of and planning actions, the experience of (anticipatory) pleasure/reward or avoidance of aversive stimuli to engage in such actions (before the start of the action and during execution of actions), computation and willingness to exert the effort needed to perform the action, and to actually start the action and continue doing it while evaluating the outcomes and adapting your behavior to external circumstances (Hommel, 2016; Kring & Barch, 2014). In line with Criterion B of the international consensus criteria, emotional, cognitive, and behavioral/auto-activation subdomains of apathy have been proposed (Levy & Dubois, 2006; Stuss et al., 2000). A reduction or
inability to associate certain emotions or emotional states with planned or ongoing behavior could induce emotional apathy. In this case, the willingness and effort to engage in activities is diminished because motivational values are lacking (Levy & Dubois, 2006). Reduced goal-directed behavior has also been proposed to occur due to the inability to plan and execute behaviors, possibly affected by working memory deficits, reductions in cognitive flexibility or set-shifting and attentional control (Levy & Dubois, 2006). This domain of apathy is referred to as cognitive apathy. The behavioral or auto-activation component of apathy is described as the inability to activate thoughts or start a motor program. Even though these deficits could lead to severe inactivation, it has been suggested that goal-directed behavior could still be provoked in case of external stimulation (Levy & Dubois, 2006).

It is possible that certain symptom dimensions of apathy are more frequently present in specific patient populations or in specific illness phases. For example, in patients with Alzheimer’s disease apathy mostly occurs during the stage in which they experience confusion and are not capable of organizing and planning their activities, which in turn reduces goal-directed actions (Marin, 1990). In patients with traumatic brain lesions to the orbital and medial prefrontal cortex, a pronounced reduction in sensitivity to reward, and reduced emotional state is often observed, leading to a reduction in goal-directed behavior (Levy & Dubois, 2006). Even though these or similar types of apathy are acknowledged in a portion of the existing literature (Aleman, 2014; Levy & Dubois, 2006; Stuss et al., 2000; van Reekum et al., 2005), studies investigating apathy rarely specify apathetic symptoms or apathy domains occurring in patients. As stated earlier, in this dissertation, the definition of apathy as provided by Levy & Dubois (2006) will be adhered, acknowledging apathy as a multidimensional construct (including emotional, cognitive, and behavioral/auto-activation subdomains) leading to quantitative loss of goal-directed behaviors.

Epidemiology of apathy and prognosis
Apathy is commonly present in a wide range of diseases and disorders, including patients with Alzheimer’s disease (AD), Mild Cognitive Impairment (MCI), Parkinson’s disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Progressive Nuclear Palsy (PSP), traumatic brain injury, stroke, but also in patients with psychiatric disorders including schizophrenia and Major Depressive Disorder (MDD). There are no authoritative estimates available on the prevalence of apathy in general, but it has been suggested that approximately 60% of the patients suffering from AD also suffer from apathy (Clarke et al., 2011). Furthermore, in schizophrenia apathy is regarded as the most prevalent negative symptom, occurring in approximately 50% of the patients (Barch & Dowd, 2010; G. Fervaha et al., 2015; Foussias et al., 2015; Mulin et al., 2011). Apathy is not only common, but also clinically relevant: it is associated with adverse outcomes. Patients with apathy often show a general decrease in quality of life, reduced social interactions, lower employment, reduced medication compliance, and worse general health (Caeiro, Ferro, & Costa, 2013; Chase, 2011; Clarke et al., 2011; G. Fervaha et al., 2015; Ishii, Weintraub, & Mervis, 2009; Theleritis, Politis, Siarkos, & Lyketsos, 2014; van Reekum et al., 2005).

Apathy has also been reported to be present in a portion (approximately 24%) of the normal population (i.e. people without a psychiatric or neurological diagnosis, Clarke, Ko, Lyketsos, Rebok, & Eaton, 2010; Pardini et al., 2016). Apathy can result from a variety of causes including stressful changes in the social or physical environment of a person. A few studies on apathy in the normal
population indeed confirm that people who are functioning well at first sight (for example being able to fulfill high education), can also fulfill criteria for apathy in ranges comparable with apathy scores that are thought to be relevant in clinical populations. Of note, apathy in the normal population has been associated with reduced perceived quality of life (Pardini et al., 2016) and distress (G. Fervaha, Zakzanis, Foussias, Agid, & Remington, 2015). However, in the normal population, apathy symptoms might most often be present for a short period of time, while for patients, especially patients with schizophrenia it might be there for a lifetime.

Neuropathology underlying apathy

Structural neural correlates

The neuropathological basis of apathy has been investigated by means of various neuroimaging methods, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), and Near Infrared Spectroscopy (NIRS). Alterations in cerebral blood flow in addition to alterations in neural density and volume (i.e. gray matter structure) of specific brain regions, and connections between brain regions (i.e. white matter structure) are associated with apathy. Overall, these studies suggest that lesions or abnormalities underlying apathy are primarily located within prefrontal and subcortical (striatal) brain regions, or lesions involving white matter connections between these regions (for reviews see Benoit & Robert, 2011; Chase, 2011; Guimaraes, Levy, Teixeira, Beato, & Caramelli, 2008; Jorge, Starkstein, & Robinson, 2010; Kostic & Filippi, 2011; McIntosh, Rosselli, Uddin, & Antoni, 2015; Santangelo et al., 2013; Stella et al., 2014; Theleritis et al., 2014).

Abnormalities within separate fronto-striatal circuits have specifically been related to different clinical representations of apathy, including the emotional, cognitive, and auto-activation (behavioral) components (Levy, 2012; Pagonabarraga et al., 2015; Stuss et al., 2000). It has been suggested that because apathy can arise through abnormalities within one or more steps towards goal-directed behavior, a diversity of underlying neural deficits may be involved, caused by specific disrupted processes. Indeed, separate structural abnormalities have been reported in association with emotional-affective, cognitive and auto-activation components. Reductions in goal-directed behavior, i.e. apathy, in relation to disrupted emotional processing have been associated with abnormalities in the orbital and medial regions of the prefrontal cortex (PFC, (e.g. Bechara, Damasio, & Damasio, 2000)) and subcortical regions including putamen, globus pallidus and thalamus (Rochat et al., 2013); apathy related to disruptions in cognitive processing has been suggested to result from brain lesions in the dorsolateral PFC (Levy, 2012; Mega & Cummings, 1994); and apathy related to disruptions in auto-activation processing have been most often associated with cognitive and limbic regions of the basal ganglia, including large portions of the caudate nucleus, globus pallidus, and medial dorsal thalamus (Adam, Baulac, Hauw, Laplane, & Duyckaerts, 2008; Fukuoka et al., 2012; Laplane, Baulac, Widlocher, & Dubois, 1984). Disruptions in auto-activation have also been associated with lesions to the dorsomedial prefrontal regions, premotor medial frontal cortex, and dorsal part of the anterior cingulate cortex (Laplane & Degos, 1983; von Giesen et al., 1994).

Functional neural correlates

Most of the magnetic resonance studies investigating apathy focused on structural brain abnormalities, while functional neural correlates of apathy have hardly been investigated. Functional MRI (fMRI) refers to task-free or task-related imaging (i.e. imaging brain properties that reflect activation
of brain networks or certain brain regions in response to a certain task). Interestingly, fMRI could be very suitable for investigating the neural correlates of apathy or subcomponents of apathy. The small amount of fMRI studies that have been performed, primarily studied apathy in schizophrenia patients by means of reward related paradigms. Indeed, these studies report abnormalities within ventromedial regions of the prefrontal cortex, the anterior cingulate cortex, and ventral striatum in relation to higher levels of apathy (Park et al., 2015; Waltz et al., 2010; Waltz et al., 2013). These results are in accordance with previous studies on structural brain abnormalities and hypothesis described in the previous paragraph, further substantiating involvement of a cingulo-striatal network in reward-related motivational aspects of apathy in schizophrenia patients.

To our knowledge, higher order executive functioning in patients with schizophrenia and varying levels of apathy have only been investigated by our research group (Liemburg et al., 2013). Increased neural activation was found in the parietal cortex, within selective activations of regions in the temporal lobe, and in subcortical regions in relation to higher apathy (Liemburg et al., 2013). These results are in line with the hypothesis that apathy in schizophrenia patients can be associated with abnormalities in cognitive functioning and related neuronal networks. However, previously hypothesized involvement of the dorsolateral prefrontal regions in association with the cognitive subdomain of apathy was not confirmed by this study. Lastly, to our knowledge, fMRI studies investigating self-activating thoughts or self-initiated actions in relation to reduced goal-directed behavior have not been performed. Overall, it can be concluded that the limited number of fMRI studies have been performed particularly contribute to the understanding of emotional components of apathy and its neural basis, while cognitive and auto-activation components require further study.

**How to measure apathy**

Apathy is most frequently assessed by means of (self-rating) questionnaires or (clinical) interviews. Development of these assessment tools has been facilitated and stimulated by the introduction of the apathy definition wherein apathy is described as a reduction in motivation and self-initiated behavior (Clarke et al., 2011). Several questionnaires are especially designed to measure apathy, but there are also other more general instruments that include a small range or a single question on apathy, and which can better be used for screening purposes. A portion of the available instruments can be used in all patient populations, while others are specifically designed for a certain group, for instance taking factors into account that might mimic apathy. Although most of the scales that are used to measure apathy are reliable, valid, and feasible to use in different settings, an appropriate cutoff score for the presence of the apathy syndrome or clinically relevant apathy is missing (van Reekum et al., 2005). Furthermore, current instruments assess apathy only at a certain point in time (including a time range of 4 weeks), while it can also be informative to know if apathetic symptoms were present throughout someone’s life span or if it occurred in response to a certain negative life event or as part of a disease or disorder for example. Moreover, the majority of the instruments that are available to quantify apathy do not specify which questions can be used for subtyping apathy into emotional, cognitive, and auto-activation subdomains, with the exception of one more recent dimensional apathy scale (DAS, Radakovic & Abrahams, 2014).

**An overview of the most often used assessment tools for apathy**

The first scale, to our knowledge, that was specifically designed to measure apathy is the Apathy Evaluation Scale (AES) and was introduced by Marin (Marin, Biedrzycki, & Firinciogullari, 1991). This instrument includes 18 items and is available as a self-rating scale (AES-S), a clinical interview...
(AES-C), and as a questionnaire for ‘informants’, which means that the questionnaire is completed by someone close to the person suffering from apathy (i.e. a family member or therapist). Together with the neuropsychiatric inventory ([NPI] Cummings et al., 1994; Cummings, 1997) the AES is one of the most frequently used and most psychometrically robust questionnaires to measure apathy in various populations (Clarke et al., 2011). The NPI was developed to assess various neuropsychiatric symptoms particularly in patients with neurodegenerative disorders. The apathy subscale of the NPI consists of eight items, in addition to follow-up questions on its frequency, severity, and possible associations with emotional distress. Overall, the items of these two questionnaires are largely in accordance with the international consensus criteria described by Robert et al. (2009), and partly in accordance with the more behavioral approach as described by Levy & Dubois (2006).

Population-specific apathy questionnaires or questionnaires with an apathy subscale have also been developed, including instruments for patients with neurodegenerative disorders: Apathy Scale ([AS] Starkstein et al., 1992), Apathy Inventory ([AI] P. H. Robert et al., 2002), Irritability Apathy Scale ([IAS] Burns, Folstein, Brandt, & Folstein, 1990), Dementia Apathy Interview and Rating ([DAIR] Strauss & Sperry, 2002), and Lille Apathy Rating Scale ([LARS] Sockeel et al., 2006). In addition to instruments for patients with frontal lobe lesions (i.e. the frontal system behavioral scale ([FrSBe] Grace, Stout, & Malloy, 1999) and patients with psychiatric disorders (i.e. the Scale for the Assessment of Negative Symptoms ([SANS] Andreasen, 1984), and Brief Psychiatric Rating Scale ([BPRS] Overall & Gorham, 1962). Factor-analyses on instruments assessing other or more general symptoms have revealed items specifically loading on apathy (Liemburg et al., 2013), as was demonstrated in (amongst others) the Positive and Negative Syndrome Scale ([PANSS] Kay, Fiszbein, & Opler, 1987), an instrument frequently used in patients with schizophrenia. Furthermore, more recent instruments have also been developed to quantify separate negative symptoms domains in patients with schizophrenia, including an apathy and expressive deficits domain (Daniel, 2013). These are the Brief Negative Symptom Scale ([BNSS] Kirkpatrick et al., 2011) and the Clinical Assessment Interview for Negative Symptoms ([CAINS] Forbes et al., 2010). These instruments have promising psychometric properties and, in contrast to other scales, both allow quantification of subjective experiences and desires, independent of possible behavioral manifestations (Mucci et al., 2015).

**Behavioral measures**

In addition to traditional assessment tools, leaning on clinical observations and interviews (introducing many sources of bias, including recall bias), other more objective strategies have recently been introduced and explored to measure apathy, of which actigraphy is the most promising one. Within actigraphical measurements physical behavior is measured continuously in the natural environment of a person, by means of a small device (called an actimeter, accelerometer, or actigraph) that is attached to the wrist, ankle or hip. This device records the number of steps, frequency, and intensity of behavior (measured in activity counts). The use of actimeters in the assessment of apathy has been applied in patients with Alzheimer’s disease (Valembois et al., 2015), stroke (Goldfine et al., 2016), and schizophrenia (Docx, Sabbe, Provinciael, Merckx, & Morrens, 2013) and results from these studies suggest that actigraphy can be used to objectively and reliably quantify apathy. Instruments like the actigraph might especially be of use in clinical practice, providing more reliable data without leaning on external observations or self-observation, and preventing recall bias. Actigraphical
information can for example be used to quantify apathy severity and evaluate the results of clinical interventions for apathy in a reliable manner. However, it is still unknown if actigraphy can be used for this purpose as it has never been studied in a sample of patients with schizophrenia suffering from severe and clinically relevant apathy.

**Treatment options for apathy**

Dependent on the cause of apathy, different treatment strategies can be implemented. If causes can be attributed to psychosocial or environmental problems, it is probably helpful to intervene in that context. If apathy is secondary to other symptoms or problems, again it is better to implement treatment targeted at causal factors (Marin, 1990). In schizophrenia, apathy may be secondary to psychotic symptoms (e.g. staying indoors due to anxious or paranoid experiences, Kirschner, Aleman, & Kaiser, 2016). Therefore, pharmaceutical treatment aimed at reduction of positive symptoms (including hallucinations) may also alleviate negative symptoms including apathy. In contrast, when apathy (or negative symptoms in general) are primary symptoms, antipsychotic medication might not always be helpful and other treatment strategies should be tried (Aleman et al., 2016).

One possible treatment option that could be considered for treating primary apathy is pharmaceutical intervention, targeting for instance dopaminergic, cholinergic, glutamatergic, or GABAergic systems (Chase, 2011; van Reekum et al., 2005). However, although some studies have reported positive effects of antipsychotics and antidepressants on apathy or negative symptoms in for instance patients with schizophrenia (Barnes et al., 2016; Corcoran, Wong, & O’Keane, 2004; Kantrowitz et al., 2015; Leentjens et al., 2009), such effects may be rather limited (Aleman et al., 2016; Fervaha et al., 2015; Starkstein et al., 2016). Of note, based on a review of the existing literature on pharmaceutical interventions targeting apathetic symptoms in neurodegenerative disorders, Drijgers et al. (2009) concluded that there was insufficient evidence that pharmaceutical treatment can benefit apathy.

Because apathy is difficult to treat with drugs, alternative treatment options have been suggested. Evidence has been provided for the efficacy of interventions tailored at individual needs, including creative activities, cooking, Montessori methods (e.g. breaking up tasks in multiple components, order components according to the level of difficulty, use guided repetition, van der Ploeg et al., 2013), and multisensory stimulation (for review see Lanctot et al., 2016). Another potential treatment option for apathy is neurostimulation, including repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (TDCS). By means of magnetic pulses (used in rTMS) or a weak electrical current (in TDCS) that passes through the skull, neuronal activation can be non-invasively influenced. In schizophrenia research, rTMS and TDCS have been investigated as treatment options for negative symptoms, targeting the dorsolateral prefrontal cortex, with inconclusive, but promising results (Brunelin et al., 2012; Dlabac-de Lange et al., 2015; and for a meta-analyses see Prikryl & Kucerova, 2013; Wobrock et al., 2015). At present, the efficacy and neural correlates of (theta-burst) rTMS and TDCS as treatment options for apathy are studied at our center in an ongoing randomized controlled trial (which is not part of this dissertation, though the study described in Chapter 5 is based on the baseline measurement of this trial). The efficacy of neurostimulative treatment is influenced by numerous parameters that can be adjusted for stimulation, a.o. the frequency of the magnetic pulses, the stimulation intensity, and location of coil place-
ment. Indeed, optimal stimulation parameters for the treatment of negative symptoms or apathy still have to be determined. Furthermore, there are large inter-individual differences in morphological characteristics, e.g. the scalp-to-cortex distance and neural density of the stimulated region, that are likely to influence neurostimulative treatment efficacy. It is still unknown which patients can profit most from these types of treatment or how these treatments could be better individually tailored.

**Aims and outline of this dissertation**

The aim of this dissertation is to provide insight into the neural basis of apathy in non-clinical as well as clinical populations. This first chapter serves as an introduction to apathy, what is already known about the neural correlates, the ways of measuring apathy, and possibilities for treatment. The aim of the remaining part of this dissertation is to further increase knowledge on the behavioral and neural basis of apathy in various populations. Firstly, in **Chapter 2** a systematic review of the existing neuroimaging literature on apathy is presented. This chapter provides a general introduction into apathy and an overview of neural correlates of apathy in different patient populations, including patients with neurodegenerative disorders, acquired brain damage, and psychiatric disorders. Various neuroimaging studies have been performed to investigate the possible underlying neural abnormalities of apathy, and the question is addressed whether apathy in these patient populations shares a common neural basis. Identifying and understanding these neural underpinnings is essential for development and guidance of potential treatments for apathy.

In **Chapters 3 and 4**, we report two studies in which we focused on apathy in a healthy, non-clinical, sample. In these chapters, we focused on two particular aspects of apathy, namely self-initiative and cognitive flexibility. These aspects are pivotal for performing goal-directed behavior. Both aspects have been scarcely studied in normal as well as in patient populations as a function of self-initiated goal-directed behavior. Although the participants in the study described in **Chapters 3 and 4** were well-functioning healthy individuals, levels of apathy were sometimes high and in some within range comparable to those reported in clinical populations. Studying these separate concepts, initiative and cognitive flexibility, in a non-clinical sample provides us with information on which behavioral characteristics could contribute to variations in goal-directed behavior or apathy and if this is already measurable on a neural level, without complicating factors as those that are usually seen in patient studies (i.e. medication use and comorbid disorders).

In **Chapter 5** we describe the association between apathy and motor behavior, as measured with an actigraph. Studying motor behavior in an objective manner in the patients’ natural environment provides us with a unique source of information. In **Chapter 5** we present a study that evaluated motor behavior outcomes in association with traditional assessment tools of apathy, i.e. questionnaires and interviews. Furthermore, in this study motor behavior is investigated in relation to the neural correlates associated with self-initiated motor behavior.

Within various randomized controlled trials in schizophrenia patients, the efficacy of neurostimulation in reducing clinical symptoms, such as negative symptoms including apathy, has been investigated. Within our research group such studies have also been performed with the aim to reduce negative symptoms (Dlabac-de Lange et al., 2015), and we observed large individual differences in response to treatment. In order to predict treatment success and optimize patient selection it is
necessary to evaluate which factors contribute to these inter-individual differences. In Chapter 6 we present a study that aimed to investigate possible predictive morphological biomarkers, including scalp-to-cortex distance and gray matter density of brain regions that are targeted during treatment. Results from this study could possibly help in treatment selection of patients characterized by high levels of apathy.

Lastly, in Chapter 7 the main findings are summarized and discussed in a broader context, including an evaluation of possible contributions to clinical practice. Furthermore, based on the existing literature and our contributions to it, recommendations for future studies are given.