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SUMMARY & GENERAL DISCUSSION

Chapter 7

LAND’S END
The aim of this dissertation

The aim of this dissertation was to investigate the neural basis of apathy. Since Marin (1990) described apathy as a separate, classifiable, and clinically relevant condition, apathy has been of increasing interest to researchers from different disciplines. A considerable literature has grown concerning its prevalence, etiology, and clinical relevance in diverse patient populations. Despite this increment in studies, available treatment strategies for apathy are still limited. Increasing knowledge of the neural and neuropsychological underpinnings of apathy may eventually guide or aid treatment strategies.

Existing definitions of apathy acknowledge a multidimensional structure, including emotional, cognitive, and auto-activation/behavioral components (Levy & Dubois, 2006; Marin, 1990; Robert et al., 2009; Stuss, van Reekum, & Murphy, 2000). However, the existing literature on the neural underpinnings of apathy rarely distinguishes these or related components or focuses on their separate neural substrates. This dissertation aimed to complement the literature by investigating auto-activation (i.e. self-initiation) as well as cognitive aspects of apathy (i.e. cognitive flexibility) together with their neural correlates. For this purpose, functional Magnetic Resonance Imaging was used in healthy as well as schizophrenia populations.

Furthermore, currently, neurostimulative treatment is under investigation as a possible additive strategy for alleviation of apathy symptoms. To understand variability in treatment response after neurostimulation, this dissertation aimed to provide insight into associations between morphological factors of the brain and efficacy in reducing schizophrenia-related symptoms.

Summary

In this dissertation, the neural basis of apathy was investigated and discussed in various populations. In order to advance the understanding of potential shared or unique neural underpinnings of apathy within separate patient groups, we performed a systematic review, which was presented in Chapter 2. The purpose of this review was to provide an extensive overview of the available neuroimaging literature on apathy. Therefore, we included studies with patients suffering from neurodegenerative disorders, acquired brain injury, or psychiatric disorders, with apathy as an important dimension in their symptomatology. The included studies used diverse neuroimaging methods. Although we included patients from different diagnostic groups, the definitions of apathy that were provided were often comparable, incorporating reduced motivation and reduced goal-directed behavior. Our findings suggest that, across different pathological conditions, apathy is associated with abnormalities in frontal and striatal brain regions. Furthermore, the anterior cingulate cortex and inferior parietal cortex appeared to be consistently associated with apathy. In particular, the role of the parietal cortex was not emphasized in earlier neuroanatomical models of apathy.

In Chapter 3 and Chapter 4 we studied apathy and its neural basis in a healthy sample with minimal to near-clinically relevant levels of apathy. In Chapter 3, the behavioral and neural correlates of initiation of actions were studied in relation to apathy severity. Auto-activation or self-initiation is a critical component of goal-directed behavior (Levy & Dubois, 2006). By means of functional Magnetic Resonance Imaging (fMRI) during the performance of a task with varying levels of freedom in deciding on timing and selection of actions, we studied activation of involved brain regions along dimensions of self-reported apathy. Increasing levels of freedom during the task performed in
the fMRI scanner were robustly related to stronger recruitment of fronto-parietal brain areas. However, no relation between brain activation and apathy severity was observed. Therefore, our results suggest that neural correlates of auto-activation and self-initiation as operationalized in the task we used, do not explain varying levels of apathy in the normal population.

The cognitive dimension of apathy refers to cognitive functions that are needed to pursue goal-directed behavior, including executive functions such as planning, rule-finding, and flexible shifting between behaviors (set-shifting) (Levy, 2012). In Chapter 4, one of these critical components underlying goal-directed behavior was studied in healthy participants, namely cognitive flexibility, i.e. set-shifting. This was studied by means of an fMRI task that tapped into behavioral shifting, cognitive set-shifting, and sensitivity for salience. Results showed that higher apathy in this population was related to lower activation of medial superior prefrontal and cerebellar regions (crus I/II) during rule switching, i.e. cognitive set-switching. Other aspects of the task, i.e. responding to a different stimulus type or decoupling of salient stimuli, did not yield differences in brain activation. These findings indicate that healthy participants with higher apathy may show an altered neural basis for cognitive control compared to healthy participants with lower apathy.

In Chapter 5 apathy was investigated by evaluating associations between distinct measures for apathy, including clinical, behavioral, and neural measures. To our knowledge, these different measurement types have never been combined in a single study investigating apathy. Clinical measures included interviews and questionnaires, behavioral measures included quantity, variability, and initiation of motor behavior as measured with actigraphy, and lastly, neural measures were obtained using fMRI during self-initiation. The use of actigraphy could provide a more objective and continuous measure of apathy in the home environment of the patient. Results from this study showed that reduced and less variable motor behavior was associated with “negative symptoms” in general, but not with apathy severity specifically (Chapter 5). Negative symptoms are a constellation of symptoms, including apathy but also encompassing alogia, affective flattening, asociality, and anhedonia. In patients with higher levels of negative symptoms, motor behavior was shown to be reduced and less variable. Furthermore, motor behavior parameters as well as negative symptoms were associated with brain activation during the self-initiative task in various brain regions including cingulate and parietal regions. Overall, these results indicate that actigraphy can provide valuable quantitative information about motor activity in a natural setting, which might however be less suitable for detailed characterization of severity of apathy but instead related to the occurrence of negative symptoms in general.

In order to find possible treatment options for apathy, our research group is currently studying the efficacy and working mechanisms of two neurostimulation techniques, namely Transcranial Direct Current Stimulation (TDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) in a multicenter, randomized controlled trial. Both techniques target the dorsolateral prefrontal cortex to relieve apathy symptoms. In order to gain insight into the possible morphological predictors of neurostimulation treatment efficacy, we studied associations between the distance from the scalp to the cortex, the density of the gray matter region that was stimulated, and treatment response in Chapter 6. For this purpose, multiple recently completed clinical treatment trials using rTMS as main intervention (that were executed at our center and at the University Medical Center Utrecht)
were combined. In accordance with earlier findings of another research group (Nathou, Simon, Dollfus, & Etard, 2015), we observed an association between greater scalp-to-cortex distance and lower gray matter density and reduced treatment efficacy, albeit only for treatment of auditory verbal hallucinations with rTMS targeted at the temporo-parietal junction. Within the single included trial that was designed to alleviate negative symptoms, scalp-to-cortex distance and gray matter density of the stimulated region were not associated with treatment efficacy. These results suggest that variability in treatment effects might be caused by variability in morphological characteristics like scalp-to-cortex distance and gray matter density, but further research is necessary.

**Neuroanatomical models for apathy**

Over the past decades, various neuroimaging studies investigated the neural basis of apathy. Reviews on the available literature on apathy in neurodegenerative disorders (e.g. Benoit & Robert, 2011; Stella et al., 2014; Theileritis, Politis, Siarkos, & Lyketsos, 2014), acquired brain damage (Jorge, Starkstein, & Robinson, 2010), neuropsychiatric disorders (Chase, 2011), and HIV (McIntosh, Rosselli, Uddin, & Antoni, 2015) report abnormalities within the fronto-striatal network in relation to apathy. The systematic review presented in Chapter 2 confirms abnormalities in relation to apathy within the fronto-striatal network across diagnostic categories. Moreover, the inferior parietal cortex was also found to be consistently associated with apathy in various patient populations. To our knowledge, this region has not been included in neuroanatomical models of apathy. However, the inferior parietal cortex has previously been related to movement intention, movement awareness, executive functioning, planning actions, regulation of actions, and self-initiated movements (Desmurget & Sirigu, 2009; Desmurget & Sirigu, 2012; Hoffstaedter, Grefkes, Zilles, & Eickhoff, 2013; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Westerholz, Schack, & Koester, 2014). Although we demonstrated consistency in regions related to apathy, there was also variance in involved brain regions across separate patient populations, with more lateral frontal involvement in neurodegenerative disorders and more medial (cortical midline) involvement in psychiatric disorders. This may suggest that different routes towards apathy are possible, or that specific types of lesions might lead to specific types of apathy, a suggestion that is in line with previous hypotheses (Levy & Dubois, 2006). However, these differences may also be caused in part by methodological variations between diagnostic categories.

The definition and classification of apathy that was proposed by Marin in the early 1990’s, as well as successive conceptualizations of apathy, described apathy as a multidimensional construct, including emotional, cognitive, and behavioral/auto-activation subdomains (Levy & Dubois, 2006; Marin, 1990; Robert et al., 2009; Stuss et al., 2000). Levy & Dubois (2006) hypothesized that abnormalities within distinct fronto-striatal circuits could be causal to specific apathetic subtypes. Although the multidimensional definition of apathy is recognized in the current literature, these separate subdomains and possible separate neural correlates of apathy have only been studied to a minimal extent. Within this dissertation, particular aspects of these separate subdomains have been studied, including self-initiation as a component of auto-activation, and set-shifting as a cognitive correlate of apathy.

**Apathy as an auto-activation disorder?**

The most severe form of apathy has been proposed to be caused by deficits in auto-activation, which can result in complete unresponsive patients with ‘empty minds’ after acquired brain injury (Levy
& Dubois, 2006). These symptoms have been reported after focal lesions to one or more regions within the basal ganglia (Adam, Baulac, Hauw, Laplane, & Duyckaerts, 2008; Fukuoka et al., 2012; Laplane, Baulac, Widlocher, & Dubois, 1984) and thalamus (Engelborghs, Marien, Pickut, Verstraeten, & De Deyn, 2000). Similar cases have been described after lesions to the dorso-medial regions of the frontal cortex, premotor medial regions, and dorsal anterior cingulate regions. Although primarily severe cases of apathy have been described in relation to auto-activation deficits, it is still unknown whether difficulties with motor initiation and thought initiation also exist in less severe forms of apathy (i.e. in apathetic but not completely unresponsive patients). In Chapter 3, brain activation during self-initiated actions was measured in healthy individuals with varying levels of apathy, as well as in patients with schizophrenia and clinical apathy in Chapter 5. In the latter chapter, motor behavior was also assessed in daily life using actigraphy. Quantity, variability, and initiation of motor behavior were measured and possible associations with apathy severity were investigated. Results from both studies (with healthy participants and patients with schizophrenia) confirm greater fronto-parietal involvement with higher levels of self-initiation. In contrast, associations with apathy severity in this context were not demonstrated, not in the healthy sample, nor in the sample including schizophrenia patients. Furthermore, quantity, variability, and initiation of motor behavior in patients with schizophrenia (as investigated in Chapter 5), did not correlate with apathy severity. Based on these results, we concluded that self-initiation deficits were unlikely to be the underlying mechanism for apathy in these patients with schizophrenia (despite the presence of apathy at clinical levels). However, caution is needed, because there might be other explanations possible for our findings. It could be, for example, that correlations between motor behavior measures and apathy severity were low because the included sample only reported high levels of apathy. At present, our research group is working on a follow-up study whereby activity levels will be measured in patients with schizophrenia with a wider range in apathy scores (i.e., also low scores). Within this follow-up study, additional healthy participants will be included to evaluate whether reduced motor behavior might be characteristic of the schizophrenia population in general, or specifically to patients with apathy. Overall, based on this dissertation it can be concluded that apathy in the normal population and in the schizophrenia population was not associated with auto-activation deficits as evaluated within our study design, but in order to firmly establish this, further research is necessary.

**Apathy as a disorder of cognitive functioning?**

The cognitive dimension of apathy is hypothesized to be related to impairments in cognitive functions that are needed to execute a plan of action (Levy & Dubois, 2006). According to this notion, apathy may in part result from the inability to plan or execute an action. This might be due to impairments in executive functions, including (amongst others) working memory functions and planning, and impairments in cognitive flexibility, i.e. set-shifting (Levy & Dubois, 2006). In order to perform successful goal-directed actions in a constantly changing environment, flexible shifting between behaviors and mind sets is essential. While at the same time it is important to inhibit inappropriate or competing behaviors and ignore distractions in order to maintain current behavior (Jurado & Rosselli, 2007). Reduced flexibility could result in a state of perseveration, while too flexible shifting might hamper goal-directed behavior due to increased distractibility (Liu & Xu, 2016). A large portion of the lateral regions of the prefrontal cortex, including dorsolateral, ventrolateral and frontopolar regions, are involved in executive functioning (for reviews see Tanji & Hoshi, 2008; Tekin & Cummings, 2002). Areas involving the dorsal prefrontal cortex and dorsal caudate are strongly
interconnected, and these regions particularly contribute to executive functioning as demonstrated in various patient studies and electrophysiological studies (for a short overview see Levy & Dubois, 2006). Lesions in either of these dorsal regions have been associated with deficits in cognitive strategies that can be causal to apathy, i.e. cognitive apathy, due to difficulties in establishing new patterns of behavior (Levy & Dubois, 2006). In Chapter 4, the neural correlates of a critical component of cognitive apathy, i.e. cognitive flexibility, were studied. Within the healthy sample that was included, higher apathy severity was associated with reduced activation in medial superior prefrontal and cerebellar regions (crus I/II). The medial prefrontal regions have previously been implicated in cognitive control functions as well, through their strong interconnections with the lateral prefrontal regions (Coutlee & Huettel, 2012; Taren, Venkatraman, & Huettel, 2011). Furthermore, particularly crus I and II from the cerebellum have been implicated in executive functions (Habas et al., 2009; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015). Another study performed in our research group, investigated higher order cognitive functioning in patients with schizophrenia (Liemburg et al., 2015). Higher levels of apathy were associated with abnormally increased activation in parietal regions (inferior parietal lobe, precuneus, paracentral lobule), middle temporal regions, and the thalamus during planning (Liemburg et al., 2015). Taking these results together, it can be suggested besides previously described dorsolateral and dorsal caudal regions, also medial frontal and selective cerebellar regions are involved in dysfunctional cognitive processes underlying apathy.

Apathy as a disorder in emotional processing?

Emotional components of apathy, which were not systematically studied in this dissertation, can be described as deficits in coupling of emotions to behavior (Levy & Dubois, 2006). Due to these deficits, a person is not motivated to execute behavior and not able to evaluate the pleasurable consequences of their behavior, which could lead to reductions in goal-directed behavior (Levy & Dubois, 2006). In other words, the experience of anticipatory pleasure is critical in pursuing goal-directed behavior, besides the fact that the action is enjoyed and rewarding when it is performed (consummatory pleasure). The ability to experience anticipatory pleasure may be reduced as part of the pathogenesis of apathy, while consummatory pleasure appears to be intact. This has been demonstrated in clinical (Waltz et al., 2009) as well as in healthy samples (Gard, Gard, Kring, & John, 2006), including the healthy sample that was studied in Chapter 3 and Chapter 4.

According to Levy & Dubois (2006), the prefrontal regions are strongly connected to the limbic regions of the basal ganglia, including the ventral striatum and ventral pallidum, and sensory cortices. These regions provide the prefrontal cortex with the necessary emotional information that is needed to guide forthcoming and ongoing behavior (Levy & Dubois, 2006). It has been suggested that lesions in the orbito-medial prefrontal cortex may result in apathy, particularly emotional apathy (Levy & Dubois, 2006). Studies that investigate emotional components of apathy by means of reward and effort related paradigms using fMRI, indeed report fronto-striatal alterations in patients and healthy individuals with higher apathy (e.g. Mucci et al., 2015; Park et al., 2015; Waltz et al., 2009; Waltz et al., 2010; Waltz et al., 2013). These findings were confirmed in the literature review described in Chapter 2. The neural substrates of the emotional subdomain of apathy were however not investigated in this dissertation, although our research group is working on the analyses of an effort-reward paradigm that was included in the studies with healthy participants with varying levels of apathy. Nevertheless, results from the set-shifting task, which was described in Chapter 3, did not indicate
behavioral or neural abnormalities in salience decoupling (which is also related to emotional components of apathy) in a normal population with varying levels of apathy.

**General discussion**

Taken together, the findings presented in this dissertation strengthen the idea that apathy is associated with alterations in fronto-striatal circuits. Apathy severity was however not related to self-initiation or auto-activation deficits: not at a behavioral nor at a neural level, not in the normal population, nor in a population of patients with schizophrenia. However, there were indications for alterations in the neural basis of cognitive control in association with higher apathy levels. The presented findings thus tentatively strengthen the idea that apathy is not a unidimensional concept, though this deserves further investigation.

In order to guide future research and situate current findings, a framework for pathways towards apathy is proposed in Figure 1. This figure is largely based on previous suggestions (Aleman, 2014; Levy & Dubois, 2006; Stuss et al., 2000) and describes the involvement of neuropsychological functions, as well as neuroanatomical correlates of possible underlying processes that underlie apathy, including emotional, cognitive, and auto-activation/behavioral components. The model illustrates that particular neuropsychological functions are more strongly related to specific components of apathy, but it is important to bear in mind that these functions are not exclusively related to that particular subdomain. Furthermore, the included anatomical representations provide a general view of the most important regions involved in the neuropsychological processes that are related to apathy. These include a (ventral) fronto-striatal network in relation to emotional processes, a dorso-medial-striatal network in relation to cognitive processes, and striatal and inferior parietal regions in auto-activation processes.

**Methodological considerations**

**Sample characteristics**

The studies included in this dissertation included participants with varying levels of apathy from the normal population, and participants with high levels of apathy from a population of schizophrenia patients. On the one hand, inclusion of a clinical, high severity sample can be regarded as an accomplishment because people with high levels of apathy are not easy to motivate for participation in research. Furthermore, it stands out from a considerable amount of studies on apathy that did not include participants with clinical levels of apathy. On the other hand, inclusion of a high severity sample compromises the ability to draw general conclusions on the effect of presence of clinical relevant apathy. In Chapter 5, the associations between apathy severity and quantity, variety, and initiation of motor behavior were studied. Because we only included patients with high apathy levels, we can only state that motor behavior measures cannot predict apathy severity in this clinical, high apathy group. These findings may not be generalizable to all patients with schizophrenia, and may underestimate the relationships between data from actigraphy and clinical measures of apathy and negative symptoms in schizophrenia. For this reason, it would be interesting to evaluate if motor behavior in this particular (high severity) group is distinct from other patients with schizophrenia, including those without apathy, or with lower levels of apathy. Furthermore, as becomes apparent from Chapter 2, apathy is a frequently occurring symptom in a wider variety of disorders. Therefore, our conclusions are limited towards the included populations, and further studies are needed to explore the generalizability of our findings. Still the findings from Chapter 2 may be useful in detecting brain areas and networks, involved in the initiation of goal-directed behavior or areas of dysfunction in other disorders.
Figure 1. A schematic representation of possible underlying neuropsychological functions and neuroanatomical correlates of apathy-related processes. This model is based upon previous research supplemented with findings described in this dissertation. The neuropsychological functions mentioned in the orange balloons primarily (but not exclusively), relate to emotional processes that possibly underlie apathy, the pink balloons to cognitive processes, and the green balloons to the auto-activation dimension of apathy. Relationships amongst neuropsychological functions are complex and often reciprocal of nature and in order not to simplify, relationships are not included in this figure.

Measuring apathy with questionnaires and interviews

Based on the systematic review that was described in Chapter 2, we have learned that quantification of apathy in separate patient populations is done using widely varying questionnaires or interviews. Within the studies described in this dissertation, clinical measures were used to quantify apathy, including the Apathy Evaluation Scale (AES), the Lille Apathy Rating Scale (LARS), the Scale for the Assessment of Negative Symptoms (SANS), and the Positive and Negative Syndrome Scale (PANSS). Although the underlying constructs of the majority of the available clinical measures are largely in accordance with the international consensus criteria for a diagnosis of apathy (Robert et al., 2009), there is no generally accepted “Gold standard” apathy instrument. The variance in usage of different questionnaires in different fields of research inevitably compromises the comparability of apathy prevalence and severity amongst patient populations. Moreover, in Chapter 5 multiple measures were used within the same population to quantify apathy, or the related but somewhat broader concept of negative symptoms, and although most of these measures correlated significantly with each other, correlation coefficients were perhaps not as high as one would expect.

There are various possible reasons why the instruments, although all aimed at measuring apathy or negative symptoms, show these moderate correlations amongst each other. First, apathy question-
naries differ in their length and extent to which apathy-related problems are questioned and rated. Sometimes the instrument only includes an apathy subscale (as with the SANS) or a selection of items based upon factor analysis (as with the PANSS). Furthermore, for some questionnaires information from informants is mandatory (PANSS), while for other instruments information coming from informants is optional (AES, SANS).

Moreover, the continuing discussion on the conceptualization and definition of apathy induces variability in the behavioral characteristics that are questioned. For example, more recently developed scales such as the Brief Negative Symptom Scale ([BNSS] Kirkpatrick et al., 2011), the Clinical Assessment Interview for Negative Symptoms ([CAINS] Forbes et al., 2010), and the Self-evaluation of Negative Symptoms ([SNS] Dollfus, Mach, & Morello, 2016) incorporate subjective experiences and desires while other scales such as the Scale for the Assessment of Negative Symptoms ([SANS] Andreasen, 1984) rely more on the clinicians judgement or observed behavior. The vast majority of instruments consider apathy as a unidimensional concept and do not allow for subdivisions into emotional, cognitive, and auto-activation/behavioral subdomains of apathy. Only in a small number of instruments a substructure of apathy is recognized, including the Lille Apathy Rating Scale (LARS), and the Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014). For our research questions, it would have been informative to have included the DAS as well. By means of this scale, specific cognitive or behavioral aspects of apathy could have been investigated in relation to set-shifting and self-initiative, for example. However, this scale was not available yet for the studies that were described in this dissertation.

Because apathy and depression are related concepts with overlapping symptoms, it was important for our studies to include depression scales in addition to scales for the evaluation of apathy and negative symptoms. For the studies on apathy in healthy samples, described in Chapter 3 and Chapter 4, the Beck Depression Inventory ([BDI] Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was used to measure depression severity. Importantly, the BDI allows for the evaluation of ‘core depression symptoms’, excluding mood-motivation items and somatic concerns (Shafer, 2006). For the study that is described in Chapter 5, whereby patients with schizophrenia were included, the Calgary Depression Scale for Schizophrenia patients was used ([CDSS] Addington, Addington, & Schissel, 1990). The CDSS was specifically developed to demarcate depression from negative symptoms and was therefore most suitable to include (Lako et al., 2012). Furthermore, in order to be able to evaluate the neural correlates underlying apathy independently of depression, the analyses in Chapters 3, 4, and 5 were performed with the inclusion of covariates, among which was depression. Thus, we could exclude depression levels as a rival explanation for our apathy-related findings.

Clinical instruments for measuring apathy, negative symptoms, and depression, require a certain insight of the clinician into the patients’ functioning or insight of the patient into its own functioning compared to persons from the normal population. During the treatment trials that are being performed by our group, we so far noticed that some of the clinicians have difficulties with quantification of apathy or negative symptoms, especially in outpatients. Part of the patients that were included with high apathy and high negative symptoms, were initially not qualified as such by their clinicians. Confronted with ratings of the formal rating scales, clinicians often acknowledge their bias. The underestimation of symptom severity by clinicians may be explained by clinician’s judge-
ments that are inevitably biased by the main patient group they work with and the limited information they have on daily functioning. For example, although patients exert less goal-directed behavior in comparison to healthy individuals, their levels of activity might be rather well in comparison to other patients with more severe symptomatology. In order to circumvent problems in reliably rating apathy or negative symptoms, and provide an additional objective measurement of apathy, the use of actigraphy has been introduced. Actigraphy is a promising measurement type that has also been investigated in Chapter 5 of this dissertation.

**Measuring apathy with actigraphy**

By means of actigraphy, motor behavior can be measured in the natural, home environment of a patient, for longer periods of time (hours, days, weeks, or even months). Quantity of motor behavior, as measured with an actigraph, has previously been associated with the presence of apathy in elderly patients with dementia (Valembois et al., 2015), patients with post-stroke apathy (Goldfine et al., 2016), and in patients with schizophrenia (Docx, Sabbe, Provinciael, Merckx, & Morrens, 2013). In Chapter 5 we did not find statistically significant associations between quantity of motor behavior, variability of motor behavior, or initiation of behavior as measured with the actigraph and apathy severity as measured with clinical instruments like the AES. We can speculate on underlying reasons for these low correlations. It might for example be the case that the actigraph does not only measure goal-directed behavior, but also routine and reactive behavior, which might compromise the apathy measurement. In order to evaluate this possibility in future studies, it would be interesting to include experience sampling methods together with actigraphy. Alternatively, it could be possible that the actigraph only measures the quantity of goal-directed behavior, while clinical instruments incorporate broader aspects of behavior, including more cognitive and emotional processes.

**Measuring neural correlates of apathy-related constructs with fMRI**

A possible tool for the evaluation of neural correlates of apathy-related constructs includes fMRI. In Chapter 3, Chapter 4, and Chapter 5 fMRI is used to measure brain activation during a self-initiation task and cognitive set-shifting task. These tasks tap into separate components possibly involved in apathy and thus may further provide insight into its possible multidimensional structure and underlying neural mechanisms. This type of neuroimaging research offers a wide variety of possible task paradigms that can be used in measuring the emotional, cognitive, and behavioral underpinnings of apathy. This is a great advantage, but also inherently compromises comparability amongst studies because a large amount of studies use unique task designs. Moreover, tasks that can be used in an MR-scanner have their own methodological and practical considerations. In general, tasks are limited in their set-up, because only a limited amount of response possibilities can be allowed, persons need to lie very still, assignments need to be clear and concise, and confounding factors need to be minimized (such as noise, sound, and smell). However, in doing this, the task inevitably moves further away from real life performance and experiences. One can also imagine that assigning a person to act freely during the self-initiation task that was used in Chapter 3, might turn out to be paradoxical in such a restricted task and environment. However, the different conditions of the task described in Chapter 3 did allow for more or less freedom in initiation of behavior, although within a limited range. Nevertheless, we acknowledge that the design is not optimal and the development of better research paradigms to evaluate self-initiation of behavior is of importance.
A general limitation of the usage of fMRI, is that a fair number of potential participants decide not to participate as they are anxious to go into an MR-scanner. This might have influenced our results and might have caused a selection bias in our included sample. A final consideration that should be kept in mind when interpreting the results of this dissertation, is that although initiation of behavior and cognitive flexibility are of importance to goal-directed behavior, they are only pieces of the puzzle in the understanding of possible involved mechanisms. To date, neuroimaging but also behavioral studies have not been able to consistently demonstrate unique factors contributing to separate apathy domains. Therefore, before further conclusions can be drawn, our neuroimaging findings regarding apathy-related constructs need to be replicated. Eventually, evidence for the existence of these dimensions will become stronger if specific neural circuits for each of them can be identified.

**Clinical implications and consequences for future studies**

Apathy is a problem that can be easily missed by clinicians. Inherent to the condition, patients suffering from apathy often seem to lack apparent distress, only infrequently seek help, or fail to mention apathy as a problem when meeting with their clinician (Massimo, Evans, & Grossman, 2014). One of the reasons for these challenges in recognizing apathy is that the clinicians’ tools are not always sufficient for these purposes. As was suggested in a previous paragraph; the actigraph may be an alternative and objective measure for quantification of goal-directed behavior. In clinical practice, the actigraph could for example be used to compare patients amongst each other or over a treatment course. However, based upon our study in patients with schizophrenia that wore the actigraph (described in Chapter 5), we can suggest to only use it as an indicator of clinically relevant apathy presence (and negative symptomatology), instead of a measure of apathy severity.

In many cases where apathy is recognized, treatment options fall short and apathy remains undertreated (Chase, 2011). Future studies should determine whether clinicians could benefit from a more detailed exploration of the sub processes that might induce a reduction in goal-directed behavior. Based upon a literature review and a proposed pathophysiological model of goal-directed behavior, Massimo and coworkers (2014) encourage a more detailed exploration of disrupted goal-directed processes in order to implement appropriate and individualized treatment. The authors suggest that in case apathy emerges from planning difficulties, apathy might best be relieved through assistance in restructuring complex activities into simpler components. If apathy is related to emotional deficits, it is suggested to enhance rewarding aspects of behavior or the environment (Massimo et al., 2014). Behavior could be rewarded by means of rewarding nutrition or verbal feedback for example (Merrilees, Klapper, Murphy, Lomen-Hoerth, & Miller, 2010). To enhance the rewarding potential of the environment adequate lighting could be used (onto a specific object or within a room), usage of familiar faces, or orientation interventions (Ishii, Weintraub, & Mervis, 2009).

In patient selection for neurostimulative treatments, variations in symptom severity on the suggested subdimensions of apathy have also not been taken into account. It could be possible that by means of neurostimulation only a selective neural network and selective subdomain of negative symptoms or apathy-related component is targeted. Information on separate apathy domains were however not taken into account at time of development of the rTMS treatment trials that were described in Chapter 6, but it might be of interest to include in future research.
Future perspectives and concluding remarks

Apathy is a common and clinically relevant behavioral abnormality that occurs in a variety of psychiatric and neurological conditions. Across patient populations, apathy has been associated with lower quality of life, lower medication compliance, higher family and caregiver burden, and more problems in daily functioning, which underlines its clinical importance. With this dissertation, we aimed to provide insight into the neural basis of apathy, but also a selection of neurocognitive processes involved in goal-directed behavior. The results of this dissertation can be used to further evaluate apathy, as it is recommended to more extensively explore the putatively underlying dimensions of apathy (possibly through alternative measurement tools). Such research should focus on differential neural networks involved in apathy, in addition to associations (and predictive values) regarding clinical variables such as disease severity and duration. Finally, in order to facilitate research into treatment efficacy, it is imperative to evaluate apathy to a more detailed extent and design interventions specifically targeting the individual needs of a person suffering from apathy. Such efforts will eventually improve patients’ quality of life: a most rewarding outcome for researchers and clinicians alike.