Apathy and depression in mild cognitive impairment and Alzheimer's disease and the role of pre-morbid motivational abilities as a predictor and moderator

Mortby, Moyra Elizabeth

Abstract: Die sozialen und wirtschaftlichen Kosten sowie die persönlichen Folgen der zunehmenden Prävalenz von Demenz und ihrer neuropsychiatrischen Symptomen, unterstreichen die Notwendigkeit für ein besseres Verständnis der Risikofaktoren und die Identifizierung und Entwicklung von effektiveren und langanhaltenden Interventionen. Neuropsychiatrische Symptome, wie Apathie und Depression, sind in mehr als 80% der Mild Cognitive Impairment (MCI) und Alzheimer Demenz (AD) Fällen vorhanden. Forstmeier und Maercker (2008) zeigten, dass hohe motivationale Fähigkeiten im mittleren Lebensalter mit geringeren kognitiven Beeinträchtigungen einhergehen. Diese kumulative Dissertation begutachtet die nosologische Stellung von Apathie in der Demenz (Paper 1); evaluiert in einer Querschnittsstudie ob motivationale Fähigkeiten im mittleren Lebensalter ein Prädiktor von Apathie und Depression in MCI und früher AD sind (Paper 2); und untersucht in einer Längschnittsstudie ob motivationale Fähigkeiten des mittleren Lebensalters den Fortschritt von Apathie und Depression in MCI und AD beeinflussen (Paper 3). Diese Doktorarbeit demonstriert insbesondere die Anwendbarkeit von Forstmeier und Maerckers (2008) Modell der motivationalen Fähigkeiten für Apathie und Depression in der Demenz. Es zeigt, dass Apathie und Depression getrennte Syndrome sind, dass Forstmeier und Maerckers (2008) Modell der motivationalen Fähigkeiten für Apathie und Depression bei MCI und AD angewendet werden kann, und dass motivationale Fähigkeiten ein Prädiktor und schützender Faktor für Apathie und Depression in Fällen von MCI und AD sind. Diese Erkenntnisse sind besonders wichtig, da motivationale Fähigkeiten ein modifizierbares Konstrukt sind, die durch Training und Intervention eine kosteneffektive Prävention und Intervention für kognitive Beeinträchtigung und deren assoziierten neuropsychiatrischen Symptomen bieten. The social and economic costs and personal consequences of the increasing prevalence of dementia and its neuropsychiatric symptoms emphasize the need for better understanding of risk factors and the identification and development of more effective and long-lasting interventions. Neuropsychiatric symptoms of apathy and depression accompany more than 80% of Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) cases. Forstmeier and Maercker (2008) have shown that high midlife motivational abilities predict lower levels of cognitive impairment. This cumulative PhD thesis assesses the nosological position of apathy in dementia in a critical review (Paper 1); evaluates midlife motivational abilities as a predictor of apathy and depression in MCI and early AD in a cross-sectional study (Paper 2); and examines midlife motivational abilities as a predictor of the progression of apathy and depression in MCI and AD in a longitudinal study (Paper 3). Specifically, this PhD thesis establishes the applicability of Forstmeier and Maercker's (2008) motivational abilities model to apathy and depression in dementia. It provides evidence that apathy and depression are two separate syndromes, concludes that Forstmeier and Maercker's (2008) motivational abilities model is applicable to apathy and depression in individuals with MCI and AD and demonstrates midlife motivational abilities to be a predictor and protective factor for apathy and depression in MCI and AD. These findings are important as motivational abilities are modifiable constructs which, with increased training and intervention, may provide an inexpensive and effective prevention and intervention for not only cognitive decline but also the presence of highly disabling neuropsychiatry symptoms.

Apathy and Depression in Mild Cognitive Impairment and Alzheimer's Disease and the Role of Pre-morbid Motivational Abilities as a Predictor and Moderator

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Moyra Elizabeth Mortby

of Zurich / Zurich

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Prof. Dr. Dr. Andreas Maercker and Prof. Dr. Mike Martin

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Abstract

The social and economic costs and personal consequences of the increasing prevalence of dementia and its neuropsychiatric symptoms emphasize the need for better understanding of risk factors and the identification and development of more effective and long-lasting interventions. Neuropsychiatric symptoms of apathy and depression accompany more than 80% of Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) cases. Forstmeier and Maercker (2008) have shown that high midlife motivational abilities predict lower levels of cognitive impairment. This cumulative PhD thesis assesses the nosological position of apathy in dementia in a critical review (Paper 1); evaluates midlife motivational abilities as a predictor of apathy and depression in MCI and early AD in a cross-sectional study (Paper 2); and examines midlife motivational abilities as a predictor of the progression of apathy and depression in MCI and AD in a longitudinal study (Paper 3). Specifically, this PhD thesis establishes the applicability of Forstmeier and Maercker's (2008) motivational abilities model to apathy and depression in dementia. It provides evidence that apathy and depression are two separate syndromes, concludes that Forstmeier and Maercker's (2008) motivational abilities model is applicable to apathy and depression in individuals with MCI and AD and demonstrates midlife motivational abilities to be a predictor and protective factor for apathy and depression in MCI and AD. These findings are important as motivational abilities are modifiable constructs which, with increased training and intervention, may provide an inexpensive and effective prevention and intervention for not only cognitive decline but also the presence of highly disabling neuropsychiatry symptoms.

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Apathy and Depression in Mild Cognitive Impairment and Alzheimer's Disease and the Role of Pre-morbid Motivational Abilities as a Predictor and Moderator

1. Introduction and Aims

In 2010 the worldwide prevalence of dementia was estimated at 35.6 million people and this total is expected to rise to 65.7 million people by 2030 and reach 115.4 million people by 2050 (Wimo & Prince, 2010). Dementia not only impacts those suffering from it but also has far-reaching implications for families and friends, affecting them on personal, emotional, financial and social levels (Wimo & Prince, 2010). Dementia (especially Alzheimer's Disease) is accompanied in more than 80% of cases by prominent neuropsychiatric symptoms such as apathy and depression (Aalten et al., 2007; Assal & Cummings, 2002; Lanctôt et al., 2008; Lyketsos et al., 2002; Mega, Cummings, Fiorello & Gornbein, 1996). These contribute significantly to increased patient and caregiver distress and loss of quality of life (Aalten et al., 2007; Banerjee et al., 2006; Garcia-Alberca et al., 2008; Lanctôt et al., 2008).

These social and economic costs, combined with the personal consequences, emphasize the need for a better understanding of risk factors for dementia and their associated neuropsychiatric symptoms, including apathy and depression. Developing a better understanding of the factors behind the progression of Mild Cognitive Impairment and Alzheimer's Disease and identifying more effective and long-lasting interventions is becoming a pressing challenge to medical professions, psychologists, social workers, caregivers and, especially, patients and their families.

Forstmeier and Maercker (2008) have offered an alternative approach to classical risk factors for Mild Cognitive Impairment and Alzheimer's Disease, proposing a *motivational*

abilities model in which motivational abilities are used to predict cognitive impairment and Alzheimer's Disease. Their model is based within the framework of the brain reserve hypothesis in which the exercising of motivational abilities provides resilience to neuropathological damage by enabling the toleration without clinical manifestation of age- and dementia-related changes (Forstmeier & Maercker, 2008; Fratiglioni & Wang, 2007; Stern, 2006; Valenzuela & Sachdev, 2006). The importance of midlife motivational abilities as a possible modifiable predictor of cognitive impairment was initially suggested by Forstmeier and Rueddel (2007) and supported by Forstmeier and Maercker (2008) who demonstrated that strong pre-morbid motivational ability lowered the risk of cognitive impairment.

The aim of this PhD thesis was to test whether Forstmeier and Maercker's (2008) midlife motivational abilities model could be applied to the presence and progression of the neuropsychiatric symptoms of apathy and depression in Mild Cognitive Impairment and Alzheimer's Disease. The following research questions were addressed:

i) What is the nosological position of apathy in dementia?

ii) Can Forstmeier and Maercker's (2008) midlife motivation model be applied to the neuropsychiatric symptoms of apathy and depression in Mild Cognitive Impairment and Alzheimer's Disease?

iii) Are midlife motivational abilities a predictor for apathy and/or depression in Mild Cognitive Impairment and Alzheimer's Disease?

iv) If midlife motivational abilities predict apathy and/or depression, then how does the level of pre-morbid midlife motivational abilities (low/ high) affect the expression of such neuropsychiatric symptoms?

v) What impact do midlife motivational abilities have on the relationship between cognitive impairment and apathy or depression?

vi) What implications could the identification of midlife motivational abilities as a predictor of apathy and depression in Mild Cognitive Impairment and Alzheimer's Disease have for our understanding of modifiable risk factors and the development of interventions?

This PhD thesis is based on three articles: a critical review which evaluates the nosological position of apathy as a separate syndrome from depression in dementia (Paper 1); a cross-sectional research study investigating the role of midlife motivational abilities as a predictor of apathy and depression in Mild Cognitive Impairment and early Alzheimer's Disease in a Swiss and Austrian sample (Paper 2); and a longitudinal (18 months) research study investigating midlife motivational abilities as a predictor of the progression of apathy and depression in Mild Cognitive Impairment and Alzheimer's Disease in a US-representative sample (Paper 3).

It was hypothesized that i) apathy and depression are two separate syndromes in dementia; ii) that midlife motivational abilities predict apathy and/or depression in dementia; and iii) that midlife motivational abilities moderate the relationship between cognitive impairment and apathy/ depression.

The following section defines the key concepts.

2. Definitions

Alzheimer's Disease (AD) is the most common form of dementia in the elderly and is a progressive neurodegenerative disorder of the central nervous system affecting cognitive functions (Cummings, 2000; 2004; Cummings & Cole, 2002). The American Psychiatric Association (2000) defines dementia of the Alzheimer's type as the development of multiple cognitive deficits manifested in terms of both memory impairments (in the ability to learn or recall information) and at least one cognitive disturbance, including aphasia (language disturbance), apraxia (impaired motor activity), agnosia (recognition/ identification failure of

objects) and executive function disturbance (e.g. planning, judgment). AD is often, but not always, preceded by *Mild Cognitive Impairment* (MCI), with some individuals progressing from MCI to AD or other dementias, while others remain stable or even recover (Winblad et al., 2004). MCI is a preclinical stage between normal aging and dementia, in which individuals are at risk of developing dementia but, so far, do not fulfill the clinical criteria for a diagnosis of dementia or AD (Caselli, Beach, Yaari & Reiman, 2006; Mariani, Monastero & Mecocci, 2007; Monastero, Mangialasche, Camarda, Ercolani & Camarda, 2009; Petersen, 2004; Petersen et al., 2001; Petersen et al., 1999; Salmon & Hodges, 2005; Winblad et al., 2004). Specifically, MCI is defined as a syndrome where 'cognitive decline [is] greater than that expected for an individual's age and education level but that does not interfere notably with activities of daily life', distinguishing it from dementia in which 'cognitive deficits are more severe and widespread and have a substantial effect on daily function' (Gauthier et al., 2006, p. 1262). Notably, conversion rates from MCI to AD range between 10 and 15% per year, with approximately half of all patients with MCI meeting the criteria for dementia (particularly AD) after five years and most having AD or another dementia syndrome after ten years (Caselli et al., 2006). This increases by up to 25% in the presence of depression, sleep disorders, or benzodiazepine or alcohol abuse (Eschweiler, Leyhe, Kloppel & Hull, 2008; Petersen et al., 1999). These high conversion rates and post-mortem results, confirming that approximately 80% of MCI cases have developed an AD pathology, support the notion of MCI as a predictor for dementia (Caselli et al., 2006; Morris et al., 2001). Such an association has been supported by neuroimaging study results, demonstrating those who convert from MCI to AD to have increased hippocampal and entorhinal volume loss, changes to the hippocampal shape and deficits in regional cerebral blood flow and regional cerebral glucose metabolism (Apostolova et al., 2006; Devanand et al., 2007; Karas et al., 2008; Winblad et al., 2004).

Neuropsychiatric symptoms such as apathy and depression accompany at least one third of MCI patients (Apostolova & Cummings, 2008), approximately 90% of early AD patients (Chen, Borson & Scanlan, 2000) and more than 80% of advanced AD cases (Aalten et al., 2007; Assal & Cummings, 2002; Cummings & Cole, 2002; Lanctôt et al., 2008; Lyketsos et al., 2002; Mega et al., 1996). The behavioral and psychological symptoms of apathy and depression are important manifestations of MCI and AD, contributing significantly to patient and caregiver stress and loss of quality of life (Aalten et al., 2007; Banerjee et al., 2006; Garcia-Alberca et al., 2008; Lanctôt et al., 2008). Their presence is associated with severe functional and cognitive deficits, more functional disability, mild extrapyramidal signs, increased conversion from MCI to AD, earlier institutionalization and more caregiver distress (Barnes, Alexopoulos, Lopez, Williamson & Yaffe, 2006; Donaldson, Tarrier & Burns, 1998; Geda et al., 2006; Hollingworth et al., 2006; Jeste, Wragg, Salmon, Harris & Thal, 1992; Monastero et al., 2009; Steele, Rovner, Chase & Folstein, 1990; Stepaniuk, Ritchie & Tuokko, 2008; Stern et al., 1994; Wilson, Gilley, Bennett, Beckett & Evans, 2000). While depression is associated with increased risks of AD (Green et al., 2003), apathy is most frequently observed in patients with dementia and AD, appearing in mild and moderate stages and increasing with cognitive decline (e.g. Caputo et al., 2008; Lyketsos et al., 2000).

Apathy is defined as a loss of motivation, manifested in behaviors of diminished initiation, poor persistence, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight not attributable to decreased consciousness levels, cognitive impairment or emotional distress (Landes, Sperry, Strauss & Geldmacher, 2001; Starkstein, Petracca, Chemerinski & Kremer, 2001). Marin and colleagues (1990; 1991; 1991) originally defined apathy as a lack of motivation (i.e. direction, intensity and persistence of goal-directed behavior) relative to the patient's previous level of functioning or standards of age and culture, as indicated either by subjective accounts or observations by others. Modern

conceptualizations acknowledge apathy to reflect a multitude of dimensions, with Robert and colleagues (2009) providing revised diagnostic criteria defining apathy as a disorder of motivation persistent over time, in which the following criteria need to be meet: i) diminished motivation (the core feature of apathy) is present for a minimum of four weeks; ii) presence of impairments in at least two of the apathetic dimensions (i.e. reduced goal-directed behavior, goal-directed cognitive activity and emotions); iii) functional impairments are attributable to apathy; iv) symptoms and conditions which mimic apathy are excluded (Mulin et al., 2011).

Apathy is an important indicator of early AD, strongly correlated with more impairments of daily living activities than normally associated with cognitive status, increased dependency on caregivers to initiate activities and provide support and management (e.g. initiation of activities for which the patient actually is still capable of performing independently), reduced quality of life, rapid progression of cognitive degeneration and various psychobehavioral disturbances, which contribute to heightened caregiver distress and burden (Boyle et al., 2003; Derouesne, 2003; Devanand et al., 1992; Freels et al., 1992; Lanctôt et al., 2008; Landes, Sperry & Strauss, 2005; Landes et al., 2001; Starkstein et al., 2001; Strauss & Sperry, 2002).

Depression in AD is characteristically expressed by high frequencies of motivational disturbances and symptoms of social isolation, withdrawal, irritability or emotional distress, and vegetative symptoms of diminished interest, psychomotor retardation, fatigue, hypersomnia and lack of insight (Lee & Lyketsos, 2003; Levy et al., 1998; Marin, 1990; Marin, Firinciogullari & Biedrzycki, 1993; Olin, Katz, Meyers, Schneider & Lebowitz, 2002a; Teng et al., 2008). While these vegetative symptoms are also key symptoms of apathy (Lee & Lyketsos, 2003; Marin, 1990; Marin et al., 1993), depression differs from apathy based on key clinical dysphoric symptoms of sadness, feelings of guilt, self-criticism, helplessness and hopelessness (Lee & Lyketsos, 2003). Concurrence in the literature proposes

dysphoria and loss of interest to be the most common symptoms of depression in AD (Ballard, Bannister, Solis, Oyebode & Wilcock, 1996; Olin et al., 2002a).

Depression in AD has been proposed by Olin and colleagues (2002a; 2002b) to be an atypical form in which motivational symptoms and delusions are experienced more frequently by AD patients than those non-cognitively impaired (Janzing, Hooijer, van 't Hof & Zitman, 2002; Vilalta-Franch et al., 2006; Zubenko et al., 2003). Difficulties in assessment have led Olin and colleagues (2002a; 2002b) to develop the National Institute of Mental Health Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (NIMH-dAD), based on the criteria for a major depressive episode (American Psychiatric Association, 2000) but broadened to include those AD patients experiencing 'clinically significant affective disturbances but [who] do not meet the standardized diagnostic criteria for depression' (Vilalta-Franch et al., 2006 p. 590). The NIMH-dAD diagnostic criteria have been modified to be independent of verbal expression (i.e. subjective reporting) and not confounded by cognitive AD symptomology and are aimed to improve understanding of nosology, etiology and treatment (Olin et al. 2002a; 2002b). The NIMH-dAD criteria require i) the presence of three (or more) symptoms of clinically significant depressed mood (e.g. depressed, sad, hopeless, discouraged, tearful); decreased positive affect or pleasure as a response to social contact and usual activities; social isolation or withdrawal; appetite disruption; sleep disruption; psychomotor changes (e.g. agitation, retardation); irritability; fatigue or loss of energy; feelings of worthlessness, hopelessness, or excessive or inappropriate guilt; or recurrent thoughts of death or suicidal ideation (plan or attempt), ii) that all criteria for Dementia of the Alzheimer's Type of the DSM-IV-TR are met, iii) that significant distress or disruption to functioning is caused by the symptoms, iv) that symptoms are not exclusive to the course of delirium, nor that they are the direct result of physiological substance effects (e.g. drug abuse, medication), or that the symptoms may be better accounted for by other conditions (e.g. major depressive disorder, bipolar disorder, bereavement, schizophrenia,

schizoaffective disorder, psychosis of AD, anxiety disorder or substance-related disorder) (Olin et al., 2002b). The NIMH-dAD proposes that AD related depression has a heterogeneous etiology which is characterized into one of four subtypes: i) emotional reaction to cognitive deficits in AD; ii) recurrence of early and midlife major and minor depressive disorders; iii) vascular diseases associated with AD; or iv) the neurodegenerative process of AD (Lee & Lyketsos, 2003, p. 357-358). Notably, depressive AD patients demonstrate significant impairments in quality of life, activities of daily living and executive function, while no difference is observed for attention, language, memory and visuospatial functions when compared to patients with no change in mood (Cummings, 2000; Fitz & Teri, 1994; Forsell & Winblad, 1998; Lyketsos et al., 1997a; Lyketsos et al., 1997b; Royall, Mahurin & Cornell, 1995). Depression in AD has far-reaching consequences. For AD patients, depression is associated with increased likelihood of physical aggression, being discharged from an assisted living facility and earlier entry into a nursing home, and higher mortality and suicide, while for caregivers it is associated with higher personal depression and burden (Gonzalez-Salvador, Arango, Lyketsos & Barba, 1999; Gonzalez-Salvador et al., 2000; Kopetz et al., 2000; Lee & Lyketsos, 2003; Lyketsos & Olin, 2002; Lyketsos et al., 1997b; Lyketsos et al., 1999; Starkstein, Mizrahi & Power, 2008; Steele et al., 1990).

Midlife motivational abilities have been proposed by Forstmeier and Maercker (2008) to predict cognitive impairment and AD, by providing resilience to neuropathological damage by enabling the toleration without clinical manifestation of age- and dementia-related changes (Fratiglioni & Wang, 2007; Stern, 2006; Valenzuela & Sachdev, 2006). Forstmeier and Maercker (2008) based their motivational abilities model on Heckhausen and Heckhausen's (2006) action phase model which differentiates between a pre-intentional (choosing between alternative goals) and a post-intentional (implementation of a chosen goal) phase. Specifically, Forstmeier and Maercker's (2008) model focuses on the motivational processes involved in the regulation of motivation in the post-intentional phase (Kuhl, 2000). These

core motivational abilities are: decision regulation (a skill used to arrive at a self-congruent decision quickly), activation regulation (a skill used to bring oneself to readiness to act), motivation regulation (a skill used to motivate oneself to persevere when faced with difficulties) and self-efficacy (a belief to be able to master difficult environmental demands) (Gollwitzer & Bargh, 1996; Kehr, 2004; Kuhl, 2000; Kuhl & Fuhrmann, 1998). These processes reflect the skills required for the implementation of personal goals and comprise the motivational processes required to shield an intention from competing ones by allowing the implementation of an intention in a self-regulated way (Bandura, 1997; Gollwitzer & Bargh, 1996; Kehr, 2004; Kuhl, 2000; Kuhl & Fuhrmann, 1998).

Forstmeier and Maercker (2008) have demonstrated these motivational abilities to combine to reflect the skills of action planning and goal orientation, demonstrating them to correlate significantly with self-reported motivational abilities and not with cognitive abilities. Notably, Forstmeier and Maercker (2009a) have proposed that increased use and training of these motivational abilities throughout the life-course contribute to brain plasticity in later life (Kempermann, Gast & Gage, 2002). This is indicated by the enlargement of synapses and the development and stimulation of new neurons, more efficient use of relevant neuronal networks and the compensation of disrupted networks (Forstmeier & Maercker, 2009a). This has led Forstmeier and Maercker (2009a) to propose that such neuroplastic advantages are the result of higher pre-morbid motivational abilities and lead to an increased tolerance of the AD-pathology. Research has provided evidence for the importance of the individual motivational abilities processes involved in Forstmeier and Maercker's (2008) motivational abilities model as predictors of emotional health (e.g. Forstmeier & Rueddel, 2007; Kruglanski et al., 2000; Kuhl & Fuhrmann, 1998; Rholes, Michas & Shroff, 1989).

The following section will consider the importance of modifiable risk factors for dementia.

3. Importance of Modifiable Risk Factors

With an increasingly aging population it is important to identify possibly modifiable risk factors and develop interventions which will delay the onset of dementia, slow progression rates and alleviate patient and caregiver burden. Research has started to focus on modifiable risk factors of dementia. So far, the main focus has been placed on cognitive abilities (e.g. education level, pre-morbid intelligence, cognitive activity, occupational attainment), emotional health (e.g. apathy, depression), physical activity, social activity and networks, vascular factors (e.g. diabetes, hypertension, hypercholesterol, obesity) and nutrition (e.g. vitamins, fat intake, dietary pattern) (Forstmeier & Maercker, 2009b; Teng, Lu & Cummings, 2007).

Interestingly, pre-morbid motivational abilities, which previously have been found to predict depression and wellbeing in cognitively healthy people, so far have not been investigated as a predictor of depression and apathy in MCI and dementia. The identification of a protective association of high midlife motivational abilities for apathy and depression in dementia may have far-reaching implications, as the presence of such neuropsychiatric symptoms in early stages has been associated with increased risk of conversion to AD (Barnes et al., 2006; Geda et al., 2006; Lopez et al., 2003; Stepaniuk et al., 2008) and contributes significantly to higher levels of patient and caregiver distress and reduced quality of life (Aalten et al., 2007; Banerjee et al., 2006; Garcia-Alberca et al., 2008; Lanctôt et al., 2008).

Forstmeier and Rueddel (2007) highlighted the role of midlife motivational abilities for a range of health outcomes. This notion has been supported by Forstmeier and Maercker's (2008) findings in which strong pre-morbid motivational ability lowered the risk of cognitive impairment. These findings that motivational abilities are modifiable constructs are fundamental as this may provide an inexpensive and effective prevention of or intervention for not only cognitive impairment but also the presence of highly disabling neuropsychiatry symptoms such as apathy and depression.

4. Linking Motivational Abilities with Apathy and Depression in Mild Cognitive Impairment and Alzheimer's Disease

Midlife motivational abilities as a predictor of apathy and depression in MCI and AD can be expected for the following four considerations. First, diminished motivation, according to Robert et al.'s (2009) revised diagnostic criteria, is the core feature of apathy, and motivational dysfunction – besides depressive mood – is one of the core symptoms of depression. High pre-morbid motivational abilities may therefore function as a buffer against motivational dysfunction in the cognitively impaired because motivational abilities seem to be relatively stable across adulthood (Johnson & Barer, 1993; Staudinger, Freund, Linden & Maas, 1999). Secondly, motivational abilities have been found to be predictive of depression in cognitively unimpaired individuals (Bandura, 1997; Kruglanski et al., 2000; Rholes et al., 1989; Tangney, Baumeister & Boone, 2004), and this may be similar in the cognitively impaired. Thirdly, as depressive symptoms have been associated with increased conversion rates from MCI to dementia (Gabryelewicz et al., 2007; Modrego & Ferrandez, 2004), and in particular motivation-related symptoms of depression have been found to be more predictive of conversion rates than affect-related symptoms (Bartolini, Coccia, Luzzi, Provinciali & Ceravolo, 2005; Berger, Fratiglioni, Forsell, Winblad & Backman, 1999), it can be expected that motivational abilities may play a significant role in the presence of depression in dementia. Fourthly, Robert et al.'s (2009) revised diagnostic criteria define apathy as a disorder of motivation persistent over time. As the presence of apathy has also been associated with higher conversion from MCI to dementia (Robert et al., 2006; 2008; Teng et al., 2007), and its core symptom is diminished motivation (Robert et al., 2009), pre-morbid motivational abilities, which have been associated with goal-directed behaviors (Brown & Pluck, 2000), may have an influential role both for the presence of apathy in dementia and consequently the progression from MCI to dementia. Therefore, it is plausible to assume that

higher mid-life motivational abilities may predict a lower rate of apathy and depression and may play an important role in their involvement within the progression from MCI to AD.

The following sections will outline the findings of the three papers of this PhD thesis.

5. Findings of the PhD Thesis

Paper 1 was a critical review evaluating the nosological position of apathy as a separate syndrome from depression in dementia. Paper 2 assessed midlife motivational abilities as a predictor of apathy and depression in a cross-sectional design in MCI and early AD (early cognitive decline). Paper 3 assessed midlife motivational abilities as a predictor of the presence and progression of apathy and depression in MCI and AD across 18 months in a US-representative sample. This PhD thesis concludes that i) apathy is a separate syndrome from depression in dementia; ii) midlife motivational abilities are an independent predictor of apathy and depression in MCI and AD; and iii) midlife motivational abilities moderate the relationship between cognitive impairment and depression in early stages and between cognitive impairment and apathy in late stages of cognitive decline. The following sections briefly describe each paper's findings.

5.1. Paper 1 - Apathy: A Separate Syndrome from Depression in Dementia? A Critical Review

Paper 1 provided an in-depth review of the literature both in support of apathy as a separate syndrome from depression and apathy as a symptom of depression. Specific focus was placed on the areas of clinical manifestation, symptomology, assessment, prevalence and neuropathology. The review found that i) although apathy and depression demonstrate an overlap in key symptoms and their diagnostic criteria often include the assessment of these joint key symptoms, the presence of separate symptoms of apathy and depression suggest that they are distinct; ii) apathy and depression differ based on prevalence and progression rates.

While apathy occurs in early and mild stages of cognitive impairment and increases in prevalence to become universal amongst severely cognitively impaired, depression is an initial symptom apparent already in the pre-clinical stage of MCI and mild to moderate stages of impairment. In contrast to apathy, depression becomes less prevalent with increasing cognitive decline, maybe as a consequence of methodological limitations (e.g. AD pathology, cognitive decline and unwillingness or inability to disclose the presence of such neuropsychiatric symptoms); iii) in AD, apathy is associated with bilateral hypoperfusion within the basal ganglia and dorsolateral prefrontal cortex (Lopez et al., 2001), a reduction in perfusion of anterior temporal, orbito-frontal, anterior cingulate and dorsolateral prefrontal regions (Benoit et al., 2002; Migneco et al., 2001), hypometabolism in the left orbitofrontal areas (Holthoff et al., 2005) and left anterior cingulate neurofibrillary tangle burden (Tekin et al., 2001). Conversely, AD related depression is associated with hypometabolism in the left prefrontal cortex and superior frontal cortex (Holthoff et al., 2005), white matter lesions (Lopez et al., 1997a), reduced glucose metabolism in the bilateral anterior cingulate and superior temporal cortex (Lopez et al., 2001) and bilateral superior frontal and left anterior cingulate cortex (Hirono et al., 1998) or parietal lobes (Sultzer et al., 1995). Paper 1 concluded that although no consensus on the nosological position of apathy in dementia has been reached, apathy, despite some symptomatic overlap with depression, may be viewed as a separate syndrome from depression in dementia and the arguments in support of apathy as a separate syndrome from depression in dementia are persuasive. There is a need for a clear definition and differentiation between apathy and depression in order to provide treatment, develop and implement more suitable diagnostic measures and criteria, more effective research and clinical practice and better understanding of associated neuropsychiatric disorders in dementia.

5.2. Paper 2 - Midlife Motivation: A Predictor of Apathy and Depression in Mild Cognitive Impairment and Early Alzheimer's Disease

Paper 2 investigated midlife motivational abilities as a predictor of apathy and depression in early stages of cognitive impairment, specifically MCI and early AD. It examined whether: i) midlife motivational abilities and severity of cognitive impairment are independent predictors of symptoms of depression or apathy in individuals with MCI or early AD; and ii) midlife motivational abilities moderate the relationship between the severity of cognitive impairment and depressive and apathetic symptoms. Midlife motivational abilities were hypothesized i) to be a separate predictor of depressive and apathetic symptoms to cognitive impairment; ii) that individuals with high pre-morbid motivational abilities would have lower levels of apathetic and depressive symptoms than those with low pre-morbid motivational abilities; and iii) that midlife motivational abilities would moderate the relationship between the level of cognitive impairment and apathetic and depressive symptoms, resulting in lower prevalence rates of these neuropsychiatric symptoms.

Midlife motivational abilities as a predictor of apathy and depression in early stages of cognitive impairment, specifically MCI and early AD, were investigated using a cross-sectional design. Participants (N = 56) were recruited in cooperation with local memory clinics in Switzerland and Austria. Inclusion was based on a clinical diagnosis of MCI (N = 29) or early AD (N = 27) and participants were above the age of 60. The findings of Paper 2 demonstrated that: i) midlife motivational abilities are an independent predictor of symptoms of apathy and depression in MCI and early AD. Specifically, individuals with high pre-morbid midlife motivational abilities had fewer symptoms of apathy and depression than those with low midlife motivational abilities; and ii) midlife motivational abilities moderate the relationship between cognitive impairment and depression but not apathy in individuals with MCI and early AD. This study provided evidence for the need to consolidate the view that midlife motivational abilities are a protective factor for both cognitive impairment and

neuropsychiatric symptoms in MCI and AD and that apathy and depression are separate syndromes in dementia.

5.3. Paper 3 - Midlife Motivational Abilities predict apathy and depression in Alzheimer's disease: The Aging, Demographics and Memory Study

Paper 3 explored midlife motivational abilities as a predictor of the progression of apathetic and depressive symptoms in a longitudinal design. As severity of cognitive impairment has been found to be associated with apathy (Zuidema, de Jonghe, Verhey & Koopmans, 2009), the study explored motivational abilities as a possible moderator of the relationship between cognitive impairment (normal cognition; MCI; AD), time (baseline; 18-month follow-up) and apathy/depression. It was hypothesized that i) high motivational abilities are associated with fewer symptoms of apathy/depression; ii) severity of cognitive impairment is positively associated with symptoms of apathy/depression; iii) apathetic symptoms increase and depressive symptoms remain stable over time (i.e. during the progression of the disease); and iv) the association of motivational abilities with apathy/depression is stronger in the more severely impaired and increases with progression.

Paper 3 demonstrated that high motivational abilities - contrary to the hypotheses – were associated with more symptoms of apathy and depression over time. This positive association was particularly strong in patients with AD compared to MCI and normal cognition. The hypotheses were based on the assumption that high motivational abilities operated as a protective factor reducing the risk of motivational dysfunction in the cognitively impaired. The findings that apathy and depression were higher in AD patients compared to MCI and cognitive healthy individuals support previous research in which the presence of apathy increases with increasing cognitive impairment (Zuidema et al., 2009). Furthermore, while depression levels stayed relatively constant over time, apathy was found to increase during the course of the 18-month interval, but only in those with AD and high motivational

abilities. Thus, midlife motivational abilities were found to moderate the relationship between cognitive impairment and the presence and progression of apathy. Our finding that depression remained stable over time, regardless of severity of impairment, but apathy increased over time in AD patients, can be interpreted as additional support that apathy and depression are two separate syndromes (Landes et al., 2001).

6. Implication of PhD Findings and Discussion

This PhD thesis provides not only a theoretical framework for the psychopathological position of apathy in dementia (Paper 1) but also additional indirect empirical evidence for the conclusion that apathy is a separate syndrome from depression, demonstrating midlife motivational abilities to exert a different effect on apathy and depression depending on the level of cognitive decline. The findings of Paper 1 that apathy and depression are two separate syndromes in dementia have far-reaching implication for more efficient identification of the presence of such neuropsychiatric symptoms, the development and implementation of more efficient interventions early in the course of cognitive decline, more adequate treatment of symptoms, more efficient dissemination to those affected by apathy and depression (i.e. patients, caregivers, family members, medical staff) and less financial burden. A consensus on the nosological position of apathy will therefore allow for more efficient identification, more adequate intervention and better treatment tailored to the characteristics of each of these individual neuropsychatric syndromes of apathy and depression. Fundamentally this differentiation between the syndromes of apathy and depression in dementia is supported by empirical evidence of prevalence rates. This was further supported, in an indirect way, by the findings of Paper 2 and Paper 3.

The findings of Paper 2 were that midlife motivational abilities are an independent predictor of symptoms of apathy and depression in MCI and early AD. Individuals with high pre-morbid midlife motivational abilities had fewer symptoms of apathy and depression than

those with low midlife motivational abilities. Midlife motivational abilities were found to moderate the relationship between cognitive impairment and depression but not apathy in individuals with MCI and early AD. These findings are important as they may possibly indicate differing effects of midlife motivational abilities on apathy and depression depending on the levels of cognitive impairment. Specifically, they reflect a similar process to those in the current findings on prevalence of apathy and depression in MCI and AD. While apathy is present in early stages of cognitive decline and increases in prevalence with the progression of dementia to become universal in the severely cognitively impaired (e.g. Cummings, 2000; Geda et al., 2004; Landes et al., 2001; Lerner, Strauss & Sami, 2007; Mega et al., 1996; Ready, Ott, Grace & Cahn-Weiner, 2003; Robert et al., 2006; Strauss & Sperry, 2002), depression is more frequent in MCI and early AD (Forsell, Jorm & Winblad, 1993a; Lyketsos & Olin, 2002; Lyketsos et al., 2000; Olin et al., 2002a). Thus, this PhD study concludes that midlife motivational abilities act as a protective factor for the neuropsychiatric symptoms of apathy and depression in early stages of cognitive decline (i.e. MCI and early AD).

Paper 3 provides further evidence for the predictive nature of midlife motivational abilities for the presence and progression of apathy and depression in MCI and AD. The findings that high motivational abilities were associated with *more* symptoms of apathy and depression over time, especially in patients with AD compared to MCI and normal cognition, were somewhat surprising. One explanation for these findings could be that there are circumstances when high motivational abilities may have a negative outcome, particularly when coping with irreversible losses and constraints (Thompson, Cheek & Graham, 1988). Such circumstances become more likely as individuals age and are confronted with chronic disease. For example, Wolk (1976) found motivational beliefs of control to have a negative effect on wellbeing in settings which are not responsive to the individual's initiatives or demands. Being confronted with severe cognitive loss, as in the case of AD, may be such a situation where holding on to unattainable goals with strong motivational efforts leads to

unproductive persistence, depressive reaction and more apathetic behavior. Therefore, holding on to unattainable goals in the face of a degenerative disease such as AD can to lead to a depressive state, as working memory is occupied with cognitions about the unattained goal, ultimately blocking the processing of new and realistic goals (Kuhl & Helle, 1986). The model of assimilative and accommodative processes (Brandtstädter & Rothermund, 2002) offers an explanation for the findings of Paper 3. It integrates (assimilative) persisting goal pursuit and (accommodative) flexible goal adjustment. In the assimilative mode, motivational strategies are applied to stick to a goal and modify the environment to attain a closer fit with personal goals. In the accommodative mode, strategies are applied to adjust personal goals to available resources. While, generally speaking, the adaptive application of both assimilative persistence and accommodative flexibility shows positive correlations with wellbeing, accommodative processes gain particular importance for coping with age- and disease-related challenges (see Brandtstädter & Rothermund, 2002 for a review of empirical data). AD patients, especially those with high motivational abilities, realize the current and impending limitations of their condition and therefore exhibit more symptoms of apathy and depression over time. The results of Paper 3 therefore indicate that once an individual has reached the advanced stages of cognitive decline of AD, these compensatory mechanisms can no-longer protect against the cognitive and neuropsychiatric symptoms as pathological decline has advanced to a high level. The findings that apathy and depression were higher in AD patients compared to MCI and cognitive healthy individuals support previous research in which the presence of apathy increases with increasing cognitive impairment (Zuidema et al., 2009).

The findings of Paper 2 that midlife motivational abilities moderated depression but not apathy in early stages of MCI and early AD, while Paper 3 found midlife motivational abilities to moderate the relationship between cognitive impairment and apathy, but not depression, in more advanced AD, proposes that midlife motivational abilities may have a different effect on the presence and progression of apathy and depression depending on the

level of cognitive impairment (i.e. early stages – MCI or early AD vs. later stages of AD). Therefore midlife motivational abilities may be viewed as multifaceted in terms of their protective features for apathy and depression throughout the progression of cognitive decline.

An alternative explanation may be that, in accordance with Forstmeier and Maercker's (2008) motivational abilities model, the proposed protective and compensatory capacity is effective in early stages of MCI or early AD but that in more advanced stages of AD this capacity has been used up and no longer can compensate for the neuropathological damage, resulting in even higher levels of apathy being observed in those with advanced AD and high pre-morbid motivational abilities. Therefore, it could be proposed that neuropathological deficits are compensated for by pre-morbid motivational abilities for a certain period (until the capacity can no longer counterbalance the neuropathology) and that once this capacity is depleted more severe impairments (i.e. cognitive or neuropsychiatric symptoms) become evident. The identification of such a protective association of high midlife motivational abilities for apathy and depression in MCI and early AD may have far-reaching implications. For one, intervention and training on how to increase motivational abilities may result in a lower prevalence of neuropsychiatric symptoms of apathy and depression in MCI and early AD, and consequently reduce patient and caregiver distress and caregiver burden, increase quality of life for patients and caregivers and reduce costs. The identification of motivational abilities as a modifiable risk factor for apathy and depression, and the association of high pre-morbid motivational abilities with reduced levels of apathy and depression in MCI and early AD, may also contribute to reducing the risk of conversion from MCI to AD.

The findings of Study 2 and Study 3 are fundamental as they provide the first empirical evidence in support of midlife motivational abilities as a predictor and moderator of apathy and depression in dementia and the applicability of Forstmeier and Maercker's (2008) midlife motivation model to the neuropsychiatric symptoms of apathy and depression in MCI and AD. These findings have far-reaching implications as this may facilitate the identification

and treatment of such neuropsychiatric symptoms. They are especially important as motivational abilities are easily modifiable constructs, which, through training and intervention at early stages (e.g. in school or at work), and potentially also during the course of the illness, may be highly effective in reducing patient and caregiver distress and improving quality of life without being tied to additional costs.

7. Limitations

While this PhD thesis has met its aims, several *limitations* must be considered. As a result of the respective study designs both Paper 2 and Paper 3 suffered from small sample sizes (N = 56 and N = 137 respectively) and Paper 3 had unequal sizes of cognitive impairment groups. This specifically limits the generalizability of the findings to the wider population. However, the results of both studies are particularly strong and indicate the importance of the concept of midlife motivational abilities as a predictor for the presence of apathy and depression in MCI and AD. Future studies are required with a broader sample, ranging from MCI to more advanced and severe dementia, to determine the more subtle effects of midlife motivational abilities and their specific impact on apathy and depression.

While the cross-sectional design of Paper 2 may be viewed as a further limitation as this does not allow for a conclusion regarding causality and directionality of effects, Paper 3 provides insight into causality and directionality due to its longitudinal design. With consideration to both studies, the current findings are important as they provide additional insight into and understanding of the differing role and level of importance of midlife motivational abilities on apathy and depression at different stages of cognitive decline and dementia.

A further limiting factor is the reliance in both studies on informant and self-report measures to assess apathy and depression. However, personality assessments in psychiatric settings readily use informant reports, despite the discrepancies between self- and informant

reporting, suggesting this not to be a major limitation (Ready, Watson & Clark, 2002). Future studies should implement more objective measures, including clinician assessments, in order to avoid possible patient or caregiver reporting bias.

The very low rates of apathy and depression (under the cut-off level for clinically significant symptoms in Paper 3) also must be noted. Possible explanations for these low levels may be, despite its good psychometric properties (Cummings et al., 1994; Okura et al. 2010), measurement error in the Neuropsychiatric Inventory as it is dependent on caregiver assessment and not a clinician interview, inter-rater variability in administration, caregiver willingness to report such neuropsychiatric symptoms or caregiver misinterpretation of such neuropsychiatric symptoms as symptoms of cognitive decline.

A further limitation may be the reliance on informant based retrospective assessments which may suffer from hindsight bias induced by the current cognitive state of a participant (MCI, early AD or AD). Specifically, this applies to the implementation of retrospective informant-based measures of midlife motivational abilities and informant ratings of apathy and depression.

The implementation of an occupation based estimate of pre-morbid motivational abilities also deserves particular attention. Estimates of pre-morbid characteristics based on educational and occupational data have a long tradition in dementia research, usually serving to estimate pre-morbid cognitive abilities. Paper 3 was the first to apply the O*NET database on worker skills and characteristics to predict apathy and depression in MCI and AD. Although this estimate of midlife motivational abilities is not a direct measure, its validity in estimating motivational as opposed to cognitive abilities has previously been demonstrated (Forstmeier & Maercker, 2008). Further studies should implement additional measures of motivational abilities which do not rely on retrospective assessments of midlife motivational abilities. Preferably, these should be assessed in a longitudinal design during midlife and also

on an every day basis to determine how and if they fluctuate and what impact they may have longitudinally and also short-term.

Despite such limitations, these current studies demonstrate the importance of midlife motivational abilities as a predictor for apathy and depression throughout the course of cognitive decline and dementia (MCI, early AD and AD). They extend previous findings (Forstmeier & Maercker, 2008), provide a new perspective on the importance of midlife motivational abilities as a predictor and possible modifiable risk factor for apathy and depression in MCI and AD, and are of fundamental importance to the development of interventions, early detection and adequate and successful treatment of apathy and depression in dementia. This PhD thesis represents an important step in research on predictors of neuropsychiatric symptoms in MCI and AD by investigating motivational abilities as predictors of depression and apathy in dementia. Further studies are needed to elucidate under which circumstances strong motivational abilities are helpful or debilitating. Insights into the mechanisms linking motivational abilities to risk of apathy and depression in MCI and AD may lead to new strategies for reducing the frequency of these symptoms.

8. Conclusion

In conclusion, this PhD thesis provides further evidence that apathy and depression are two separate syndromes in dementia, that Forstmeier and Maercker's (2008) motivational abilities model is specifically applicable to apathy and depression in individuals with MCI and AD and that midlife motivational abilities are a predictor and protective factor for apathy and depression in MCI and AD. These findings are important as motivational abilities are modifiable constructs which, with increased training and intervention (see Forstmeier & Rueddel, 2007), may provide an inexpensive and effective prevention and intervention for not only cognitive decline but also the presence of highly disabling neuropsychiatry symptoms.

The following section provides suggestions for future research.

9. Future Research

This PhD thesis provides a significant contribution to our current understanding of apathy and depression in dementia. Its unique contribution to research on dementia is the identification of midlife motivational abilities as a predictor for apathy and depression in MCI and AD. There are six issues which should be addressed in the future to advance understanding of this topic.

First, reaching a consensus on the psychopathological position of apathy within dementia is vital. Once it is accepted that apathy and depression are two separate syndromes in dementia, research can focus on the important aspects of each syndrome, in particular their risk factors. This will lead to better development and implementation of diagnostic measures and criteria, more effective research and clinical practice, better understanding of associated neuropsychiatric disorders in dementia and a better support system for patients, caregivers and families.

Secondly, in contrast with AD, little research has focused on risk factors for apathy and depression in dementia. This PhD thesis shows the importance of retrospectively assessed midlife motivational abilities as an independent predictor of apathy and depression in dementia. However, broader assessment of motivational abilities, including those which are not based on retrospective assessment and which predominantly rely on informant reports, must be developed. This is necessary to provide an assessment of motivational abilities which is not subject to hindsight bias induced by the current cognitive state of the patients. Further research is also needed to investigate whether different measures of motivational abilities might relate differently to apathy or depression and their accompanying symptoms (e.g. dysphoria in depression, poor persistence in apathy). Despite midlife motivational abilities having been reported to be a stable construct, future research should investigate the importance of short-term fluctuations of motivational abilities and how these affect or predict neuropsychiatric symptoms in dementia. Motivational abilities should be assessed

continuously, both during midlife and following diagnosis, to determine the effects that smaller fluctuations in motivational abilities have on the presence and progression of dementia related apathy and depression. This may provide an alternative method for early detection and successful treatment of apathy and depression in dementia.

Thirdly, future research should investigate a possible relationship between training of motivational abilities following diagnosis to determine whether such an intervention provides short-term difference in personal wellbeing, decreases patient and caregiver distress, reduces the presence of neuropsychiatric symptoms and increases quality of life for patients and caregivers. This should also be extended to investigate whether and how such intervention based training leads to long-term changes and the durability these effects.

Fourthly, although the model of assimilative and accommodative processes may provide a good explanation for the current findings, future research should consider alternative explanations. For example, consideration should be given to the goal-directed behavior and motivational model in which negative symptoms (e.g. apathy and depression) may be useful in modeling cognitive and motivational processes which underlie intentionality, volition and will (Brown & Pluck, 2000). Brown and Pluck (2000) summarize goal-directed behavior as a set of related processes in which action translates internal states into goal attainment. Such a model can be described to be at the core of the current proposed role of midlife motivational ability. In particular, this model may be linked to apathy, as its core element is reduced goal-directed behavior due to impaired motivation (Marin, 1991). As the goal-directed behavior model puts functional integration of motivational, emotional, cognitive and motor processes at its centre, this may possibly be a further model worth investigating in the context of midlife motivational abilities as a protective factor for cognitive impairment and associated neuropsychiatric symptoms, such as apathy in particular.

Fifthly, the applicability of the motivational abilities model as a protective factor for apathy and depression needs to be tested against other neurodegenerative diseases in which

apathy and depression are also common occurrences such as, for example, Parkinson's disease. The role that midlife motivational abilities play for other neuropsychiatric symptoms associated with dementia (e.g. agitation/aggression, dysphoria, anxiety, irritability/ lability) should also be investigated.

Sixthly, future research should consider using neuroimmaging procedures to identify what brain structures specifically underlie these motivational abilities, how interventions and training affect these areas and the impact of motivation-based interventions and training on the neuropathology of apathy and depression. The neuropathological overlap and interaction between the areas involved in motivational abilities, cognitive decline (MCI and AD) and neuropsychiatric symptoms (apathy and depression) need to be examined.

The following sections provide the studies of this PhD thesis.

10. Paper 1: Apathy: A Separate Syndrome from Depression in Dementia? A Critical Review

Mortby, M. E., Maercker, A. and Forstmeier, S. (first published 16.11.2011)

Aging, Clinical and Experimental Research**.**

10.1. Abstract

Apathy and depression are the most prevalent neuropsychiatric symptoms in Alzheimer's disease and Mild Cognitive Impairment. Despite much research on apathy and depression in dementia, the nosological position of apathy as a separate syndrome from depression remains debated. This literature review provides a critical analysis of the areas of clinical manifestation, symptomology, assessment, prevalence and neuropathology. Evidence does not provide a clear view of the nosological position of apathy in dementia for symptoms and neuropathology. However, the ambiguity of the evidence can be attributed in large part to a lack of clarity in definition and etiology, clinical criteria and assessment overlap. Given the evidence, it is concluded that the argument in favour of apathy as a separate syndrome from depression in dementia is persuasive. Reaching a consensus on the definition and nosological position of apathy within dementia is vital to provide patients and caregivers with the support they require, increase understanding of risk factors and enable comparisons across research and practice.

10.2. Introduction

Apathy and depression are prevalent neuropsychiatric symptoms in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) (Lyketsos et al., 2002). While closely clinically related, demonstrating co-morbidities and key symptom overlap (e.g. loss of interest and motivation, reduced activity or hedonism, and lack of insight) (Marin et al., 1993; Starkstein, Ingram, Garau & Mizrahi, 2005a), they are also pathophysiologically distinct (Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Bradshaw & White, 2006), with several studies suggesting two separate syndromes due to differential prevalence rates, neuropsychiatric symptoms and cognitive function (Benoit et al., 2008; Ishii, Weintraub & Mervis, 2009; Landes et al., 2005; Marin et al., 1993; Winograd-Gurvich et al., 2006). The nosological position of apathy as a separate syndrome from depression remains debated (Aalten et al., 2007; Starkstein et al., 2005a; Tagariello, Girardi & Amore, 2009) despite extensive research. Review and research papers mostly address this issue only briefly, not providing in-depth understanding of how and why apathy and depression differ in dementia. For example, Ishii et al. (2009) provided a detailed review on apathy as a common psychiatric syndrome in the elderly, but offered only a subsection on the differentiation analysis both in support of apathy as a separate syndrome from depression and apathy as a symptom of depression. To our knowledge, only Tagariello et al. (2009) provide a literature review on this specific subject. Due to its brevity it only provides a summary of the main issues and does not provide a comprehensive evaluation. The current paper provides an in-depth analysis considering the research both in support of apathy as a separate syndrome from depression and apathy as a symptom of depression.

10.3. Apathy in Dementia

Apathy is a behavioral and personality change prominently observed in AD and is generally defined as a loss of motivation, manifested in behaviors of diminished initiation, poor persistence, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight, not attributable to decreased consciousness levels, cognitive impairment or emotional distress (Landes et al., 2001; Starkstein et al., 2001). Marin and colleagues (1990; 1991; 1991) originally defined apathy as a lack of motivation (i.e. direction, intensity and persistence of goal-directed behavior) relative to the patient's previous level of functioning or standards of age and culture, as indicated either by subjective accounts or observations by others. While Marin's (1990; 1991) concept of apathy centers on reduced goal-directed behavior, cognition or emotion (Levy & Dubois, 2006), modern conceptualizations acknowledge apathy to reflect a multitude of dimensions (Robert et al., 2009). These see apathy as a disorder of motivation with cognitive, sensory, motor and affective subtypes (Marin et al., 1991); a disorder of interest or motivation, including lack of emotion, lack of initiation and lack of enthusiasm (Cummings et al., 1994); a disorder of initiative, manifested in a lack of self-initiated action (affective, behavioral or cognitive) and include 'social apathy' (a disorder of sense of self and of social awareness) (Stuss, Van Reekum & Murphy, 2000); a disorder of motivation with emotional blunting, lack of initiative and lack of interest (Robert et al., 2002); a disorder of intellectual curiosity, action initiation, emotion and self-awareness (Sockeel et al., 2006); a disorder of voluntary and goal-directed behaviors with three subtypes of disrupted "signal" processing: emotional-affective, cognitive and auto-activation (Levy & Dubois, 2006); and a disorder of motivation with diminished goal-directed behavior and cognition (Starkstein & Leentjens, 2008). Despite these differing views on the core features of apathy, namely whether the central feature of apathy is disturbance of motivation (Marin et al., 1991) or initiative and self-generated voluntary and purposeful behavior (Levy & Dubois, 2006; Stuss et al., 2000), the consensus is that

motivation, interest, action, initiation and emotional reactivity are dimensions of apathy and lack of motivation is central to the disorder (Robert et al., 2009). A correlation has been found between apathy and increased cognitive impairment, as well as lower cognitive test performance (Onyike et al., 2007; Turro-Garriga et al., 2009), higher conversion rates from MCI to AD (Robert et al., 2006), depression (Lavretsky, Lesser, Wohl, Miller & Mehringer, 1999; Starkstein, Jorge, Mizrahi & Robinson, 2006), and increased impairment to functional activities (Freels et al., 1992; Starkstein et al., 2001). Apathy is an important indicator of early AD diagnosis, strongly correlated with more impairments of daily living activities than normally associated with cognitive status, increased dependency on caregivers to initiate activities and provide support and management (e.g. initiation of activities for which the patient actually is still capable of performing independently), reduced quality of life, rapid progression of cognitive degeneration and various psychobehavioral disturbances, which contribute to heightened caregiver distress and burden (Boyle et al., 2003; Derouesne, 2003; Devanand et al., 1992; Freels et al., 1992; Lanctôt et al., 2008; Landes et al., 2005; Landes et al., 2001; Starkstein et al., 2001; Strauss & Sperry, 2002).

Assessing apathy in AD is complicated, as loss of motivation must be differentiated from loss of ability (Landes et al., 2001). This is particularly difficult in the cognitively impaired, as apathy is generally defined as a reduction in behavior in comparison to the patient's pre-morbid state (Landes et al., 2001). Cognitive function decline complicates such an assessment as patients face increased difficulty in the organization and conduct of complex behaviors, reduced behavior resulting from impaired motivational abilities, less task initiation, and increased frustration and confusion with hobbies (Gilley, 1993; Landes et al., 2001; Marin, 1990). Although apathy is a behavioral sign of cognitive dysfunction where impairments negatively affect the initiation, planning, and problem solving of successful task performance (Duffy & Campbell, 1994; Fogel, 1994; Landes et al., 2001; Royall, 1994), Marin and Wilkosz (2005) observed apathetic individuals generally to be 'able to initiate and

sustain behavior, describe their plans, goals and interests, and react emotionally to significant events and experiences' despite diminished motivation associated with apathy (Starkstein & Leentjens, 2008, p. 1088-1089). Apathy must therefore be distinguished from cognitive decline, as the dynamic interaction between apathy and cognitive impairment may result in AD patients demonstrating less interest in regular activities as they lose the ability to engage in cognitively complex behaviors and become less likely to initiate regular activities where they are unsure of the steps required (Landes et al., 2001). Consequently, apathetic symptoms must be considered when increased functional impairments and reliance on caregiver initiation become more evident than expected for a given level of cognitive impairment (Landes et al., 2001).

The need for applicable diagnostic criteria for apathy in dementia was originally addressed by Starkstein and colleagues (2001; 2008) and recently revised by Robert and colleagues (2009). Starkstein and colleagues (2001; 2008) operationalized Marin et al.'s (1991) definition of apathy into applicable diagnostic criteria which require: (i) the presence during most of the day for a minimum of 4 weeks of at least one symptom of diminished goal-directed behavior (e.g. lack of effort and initiative, or energy to perform everyday activities; dependency on prompts from others to structure everyday activities); diminished goal-directed cognition (e.g. lack of interest in learning new things or in new experiences; lack of plans and goals, lack of concern about one's own health, functional status or personal problems) or diminished concomitants of goal-directed behavior (e.g. unchanging or flat affect; lack of emotional responsiveness to positive or negative events and restricted responses to important life events); (ii) clinically significant distress or impairments in social, occupational or other important areas of functioning caused by the apathetic symptoms; and (iii) the symptoms are not due to a diminished level of consciousness or direct physiological substance effects (e.g. drug abuse, medication) (Starkstein & Leentjens, 2008; Starkstein et al., 2001). Thus diminished motivation, initiative and interest, and emotional blunting are at

the core of Starkstein et al.'s (2001) definition of apathy (Robert et al., 2009). These criteria have recently been revised into semi-operationalized criteria by Robert and colleagues (2009) based on the synthesis of current concepts of apathy applicable to both research and practice. The revised criteria follow Starkstein and colleagues' (2001; 2008) structure and require:
i) loss of or diminished motivation compared to previous functioning levels, not consistent with age or culture, and reported either by the patient or observers; ii) the presence of impairments (minimum of one symptom) in at least two of the apathetic dimensions of reduced goal-directed behavior, goal-directed cognitive activity, and emotions; iii) functional impairments attributable to apathy; and iv) the exclusion of symptoms and conditions mimicking apathy (Mulin et al., 2011). However, future research is required to assess the reliability and validity of these criteria.

10.4. Depression in Dementia

Depression in AD is characteristically expressed by high frequencies of motivational disturbances (e.g. fatigue, psychomotor slowing and apathy), symptoms of social isolation, withdrawal, irritability or emotional distress, and vegetative symptoms of diminished interest, psychomotor retardation, fatigue, hypersomnia and lack of insight (Lee & Lyketsos, 2003; Levy et al., 1998; Marin, 1990; Marin et al., 1993; Olin et al., 2002a; Teng et al., 2008). While these vegetative symptoms are also key symptoms of apathy (Lee & Lyketsos, 2003; Marin, 1990; Marin et al., 1993), depression differs from apathy based on key clinical dysphoric symptoms of sadness, feelings of guilt, self-criticism, helplessness and hopelessness (Lee & Lyketsos, 2003) and concurrence in the literature proposes dysphoria and loss of interest to be the most common symptoms of depression in AD (Ballard et al., 1996; Olin et al., 2002a). However, these findings may be tautological due to assessment requirements (Ballard et al., 1996; Olin et al., 2002a). Notably, depressive AD patients demonstrate significant impairments in quality of life, activities of daily living and executive

function, while no difference is observed for attention, language, memory and visuospatial functions when compared to patients with no change in mood (Cummings, 2000; Fitz & Teri, 1994; Forsell & Winblad, 1998; Lyketsos et al., 1997a; Lyketsos et al., 1997b; Royall et al., 1995). Depression in AD has far-reaching consequences. For AD patients, depression is associated with increased likelihood of physical aggression, being discharged from an assisted living facility and earlier entry into a nursing home, and higher mortality and suicide, while for caregivers it is associated with higher personal depression and burden (Gonzalez-Salvador et al., 1999; Gonzalez-Salvador et al., 2000; Kopetz et al., 2000; Lee & Lyketsos, 2003; Lyketsos & Olin, 2002; Lyketsos et al., 1997b; Lyketsos et al., 1999; Starkstein et al., 2008; Steele et al., 1990). Risk factors for depression in AD include a family history of mood disorders (affective disorders) in first degree relatives, prior personal depressive history, female gender and younger age at AD onset (Cummings, 2000; Harwood, Barker, Ownby & Duara, 1999; Lawlor, Ryan, Schmeidler, Mohs & Davis, 1994; Lyketsos & Olin, 2002; Migliorelli et al., 1995; Pearlson et al., 1990; Strauss & Ogrocki, 1996).

Assessing depression in AD is complicated as symptoms of psychomotor slowing, emotional lability, crying spells, insomnia, weight loss, inability to verbalize affective state and pessimism are prevalent in both depressed and non-depressed AD patients (Lee & Lyketsos, 2003; McGuire & Rabins, 1994). Standardized diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorder (DSM) or the International Classification of Diseases (ICD) (Vilalta-Franch et al., 2006) have been implemented to assess depression in AD. For example, in the DSM-IV criteria for depression, a principal symptom is loss of interest or pleasure in activities as opposed to depressed mood itself (American Psychiatric Association, 1994). However, in the demented, such a loss of interest or pleasure may reflect more a loss of motivation or ability than a change in affect or depression (Landes et al., 2005). Such symptom overlap (e.g. lack of interest, anxiety, lack of energy, concentration difficulty, agitation or psychomotor retardation, sleep and eating

disorders) has not only resulted in blurring between AD and depressive symptomology (Olin et al., 2002a; Vilalta-Franch et al., 2006), but also resulted in apathetic individuals meeting the diagnostic criteria for major depression even in the absence of dysphoric symptoms (Landes et al., 2005; Lerner et al., 2007; Mega et al., 1996). Symptom overlap has not only resulted in blurring between AD and depressive symptomology due to a lack of sensitivity to accurately differentiate between symptoms of cognitive decline and depression (Ballard et al., 1996; Olin et al., 2002a; 2002b; Starkstein et al., 2008; Vilalta-Franch et al., 2006), but has also resulted in apathetic individuals meeting the diagnostic criteria for major depression even in the absence of dysphoric symptoms (Landes et al., 2005; Lerner et al., 2007; Mega et al., 1996).

A further limitation of the use of non-dementia specific assessments is their reliance on ability to verbally report subjective depressive symptoms (e.g. mood changes, loss of interest, hopelessness), a process commonly impaired in AD patients (Olin et al., 2002b). Non-dementia specific diagnostic criteria for depression (e.g. DSM, ICD), developed for use in younger, cognitively unimpaired individuals, lack sensitivity to accurately differentiate between symptoms of cognitive decline and depression and have decreased validity in AD samples (Ballard et al., 1996; Olin et al., 2002a; 2002b; Rosenberg et al., 2005; Starkstein et al., 2008; Vilalta-Franch et al., 2006). This may be explained by differences in clinical manifestations of late life mood disturbance compared to younger life and the denial by depressive elderly of sad mood, rather reporting lack of feeling or emotion and acknowledging a loss of interest and pleasure in activities (i.e. depressive elderly report fewer affective symptoms – known as 'depression without sadness') (Alexopoulos et al., 1996; Ballard et al., 1996; Gallo & Rabins, 1999; Olin et al., 2002a; 2002b; Rosenberg et al., 2005; Starkstein et al., 2008; Vilalta-Franch et al., 2006).

Pertinently, depression and dementia overlap in the underreporting of depressive symptoms by dementia sufferers and increased reliance on caregiver and observational reports

(Lee & Lyketsos, 2003; Teri & Wagner, 1991). Due to aphasia, many dementia patients lack the ability to express their distress coherently - a further complication when diagnosing depression in AD (Lee & Lyketsos, 2003). Furthermore, the tendency of depressive AD patients to deny the presence of depressed moods and instead report a lack of feeling or emotion, or loss of interest and pleasure in activities, hampers the diagnosis with non-dementia specific assessments of depression in elderly with and without cognitive impairment (Lee & Lyketsos, 2003). This, and the observed difference in depressive symptoms between elderly with and without dementia, have lead Olin and colleagues (2002a; 2002b) to propose depression in AD to be an atypical form in which motivational symptoms and delusions are experienced more frequently by AD patients than those non-cognitively impaired (Janzing et al., 2002; Vilalta-Franch et al., 2006; Zubenko et al., 2003).

Such difficulties in assessment have led Olin and colleagues (2002a; 2002b) to develop the National Institute of Mental Health Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (NIMH-dAD), based on the criteria for a major depressive episode (American Psychiatric Association, 2000), but broadened to include those AD patients experiencing 'clinically significant affective disturbances but do not meet the standardized diagnostic criteria for depression' (Vilalta-Franch et al., 2006 p. 590). The NIMH-dAD diagnostic criteria have been modified to be independent of verbal expression (i.e. subjective reporting) and not confounded by cognitive AD symptomology and are aimed to improve understanding of nosology, etiology and treatment of AD related depression (Olin et al., 2002a; 2002b). The NIMH-dAD criteria require i) the presence of three (or more) symptoms of clinically significant depressed mood (e.g. depressed, sad, hopeless, discouraged, tearful); decreased positive affect or pleasure as a response to social contact and usual activities; social isolation or withdrawal; appetite disruption; sleep disruption; psychomotor changes (e.g. agitation, retardation); irritability; fatigue or loss of energy; feelings of worthlessness, hopelessness, or excessive or inappropriate guilt; or recurrent

thoughts of death or suicidal ideation (plan or attempt), ii) that all criteria for Dementia of the Alzheimer's Type of the DSM-IV-TR are met, iii) that significant distress or disruption to functioning is caused by the symptoms, iv) that symptoms are not exclusive to the course of delirium, nor that they are the direct result of physiological substance effects (e.g. drug abuse, medication), or that the symptoms may be better accounted for by other conditions (e.g. major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer's disease, anxiety disorder or substance-related disorder) (Olin et al., 2002b).

The NIMH-dAD proposes that AD related depression has a heterogeneous etiology characterized into one of four subtypes: i) emotional reaction to cognitive deficits in AD (e.g. adjustment disorder with depressed mood), where the depressive state may be a reaction to the diagnosis of AD and/ or associated with the awareness of loss and disability, or a reaction of certain personality types vulnerable to depressive symptomology in response to negative life events; ii) recurrence of early and midlife major and minor depressive disorders is a risk factor for later life dementia, and may share its etiology with early or midlife depression; iii) vascular diseases associated with AD causing depressive symptoms (so-called vascular depression), where occurrence of subcortical lesions in depressed elderly patients with vascular disease suggest vascular depression may result from 'critical lesions or an accumulation of lesions leading to disruption of frontostriatal pathways or their modulating systems'; iv) the neurodegenerative process of AD causes depressive symptoms (e.g. mood disorder due to general medical condition), with pathophysiological overlap between AD and the depressive syndrome in AD, where the 'neurodegenerative process may directly contribute to the development of depressive symptoms' (Lee & Lyketsos, 2003, p. 357-358). This set of criteria has been shown to be particularly sensitive, with higher rates of depression reported in both retrospective (27.4%) (Vilalta-Franch et al., 2006) and prospective (44%) (Teng et al., 2008) implementations of the NIMH-dAD in compared with other sets of criteria

(e.g. DSM-IV, CAMDEX and ICD-10). In support of Olin et al.'s (2002a) proposition, Teng et al. (2008) demonstrated that an interview using NIMH-dAD criteria more effectively distinguishes significant depressive symptoms in AD patients. These criteria have face validity (Vilalta-Franch et al., 2006) and Rosenberg et al. (2005) have demonstrated their clinical application.

10.5. Symptomatic Overlap or Assessment Overlap?

Apathy and depression are frequently associated in AD due to joint key symptoms of diminished motivation and interest, vegetative symptoms of psychomotor retardation, fatigue and hypersomnia, lack of insight and pessimism, diminished ability to concentrate, and weight loss (Landes et al., 2001; Starkstein et al., 2008; Tagariello et al., 2009). Such symptomatic overlap often results in the misinterpretation of apathy as depression even in the absence of depressed mood or signs of dysphoria according to the DSM criteria (American Psychiatric Association, 1994; Landes et al., 2005; Landes et al., 2001; Lerner et al., 2007; Starkstein et al., 2008). According to the DSM-IV criteria for depression, a principal symptom is the loss of interest or pleasure in activities as opposed to depressed mood itself (American Psychiatric Association, 1994). However, in demented, such a loss of interest or pleasure may reflect more a loss of motivation or ability than a change in affect or depression (Landes et al., 2005). This both complicates its assessment (Ballard et al., 1996; Lee & Lyketsos, 2003; Starkstein et al., 2008) and results in apathetic individuals meeting the diagnostic criteria for major depression even in the absence of dysphoric symptoms (Landes et al., 2005; Landes et al., 2001; Lerner et al., 2007; Mega et al., 1996).

The observed overlap may be explained by methodological variations of assessments relating to symptoms common to both syndromes (e.g. closely related subset of items such as diminished interest, psychomotor retardation, lack of energy, loss of insight; or dysphoric items such as depressed mood, guilt, hopelessness and vegetative symptoms) (Hamilton,

1960; Landes et al., 2001; Marin et al., 1993; Mega et al., 1996). Research has demonstrated high correlations between apathy and depression scores for items corresponding to symptoms commonly observed in the syndrome of apathy (Marin et al., 1991; Marin et al., 1993; Ready et al., 2003; Starkstein et al., 2006) as well as the categorization of patients into cohorts of "pure apathy", "pure depression" or "apathy and depression" (Levy et al., 1998; Starkstein, Fedoroff, Price, Leiguarda & Robinson, 1993; Starkstein et al., 2001; Starkstein et al., 2005a). This has led to the conclusion that apathy and depression have divergent natural histories and can be differentiated (Ishii et al., 2009; Starkstein, Mizrahi & Garau, 2005b).

Forsell and colleagues (1993b; 1994) described depressive symptoms in the elderly to fall into two categories: mood problems (symptoms of dysphoria, feelings of guilt and suicidal ideation) and motivational problems (symptoms of lack of interest, low energy and psychomotor slowing). Depression can be distinguished from apathy (characterized by lack of emotional responsiveness) on the basis of dysphoric symptoms of sadness, feelings of guilt, self-criticism, helplessness and hopelessness (Landes et al., 2001; Marin, 1996; 1997; Royall, 1997). The observed loss of interest in depression may rather reflect feelings of despair, pessimism and hopelessness, which combined with dysphoria in depression, differentiates depression from apathy (Landes et al., 2001; Marin, 1997). Apathy, conversely, is distinguishable from depression based on lack of emotional responsiveness, emotional indifference, 'lack or lessening of ability to initiate in multiple domains (motor, gait, cognitive)' and a lack of concern – not all of which are exclusively observed in depressive individuals (Landes et al., 2001; Lerner et al., 2007, p.16; Marin, 1990; 1996; Royall, 1997).

Differences are also observed for neuropsychiatric symptoms, with apathy associated with disinhibition and aberrant motor behavior, and depression with anxiety, agitation, irritability and hallucinations (Levy et al., 1998; Tagariello et al., 2009). Presence of negative mood and dysphoric symptoms in depression, but not apathy, provides a further difference (Landes et al., 2005). Various studies have demonstrated differences between apathy and

depression in AD for associated cognitive deficits (Kuzis, Sabe, Tiberti, Dorrego & Starkstein, 1999; Landes et al., 2001; Paulsen et al., 1996). Research by Kuzis et al. (1999) compared only apathetic, only depressive, and co-morbid apathetic and depressive early AD patients. In contrast with only depressive patients, only apathetic patients showed specific cognitive deficits in naming performance, word list learning, verbal fluency and set-shifting (Kuzis et al., 1999). The co-morbid apathetic and depressive group had worse impairments to abstract reasoning ability than those with only apathy, while no association with cognitive dysfunction was found for the depression only group (Kuzis et al., 1999; Landes et al., 2001).

Although the notion of apathy as a separate syndrome from depression has received much valid support, there are opposing arguments to be countered. Firstly, for Marin (1990) the diagnosis of apathy should not be made in the context of diminished levels of consciousness, moderate or severe cognitive deficits, or marked emotional distress as apathy may be an intrinsic symptom of dementia (Starkstein & Leentjens, 2008). Although Marin's (1990) point is useful in identifying a 'pure' apathy syndrome 'uncontaminated by changes in cognitive or affective domains', conceptual and empirical evidence argues against such an approach (Starkstein & Leentjens, 2008, p. 1089). One conceptual issue is that a syndrome is defined as a constellation of symptoms without reference to a specific etiology and it is therefore not clear why apathy should be 'considered a syndrome in some contexts (e.g. stroke), but not in others (e.g. dementia)' (Starkstein & Leentjens, 2008, p. 1089). A second opposing argument is that some psychopathological syndromes (e.g. apathy and depression) co-occur in some neurodegenerative diseases (Starkstein et al., 2006; Starkstein & Leentjens, 2008). In response, while the apathetic syndrome is observed most frequently in 'individuals with neurological disorders and some degree of cognitive impairment and depression' (e.g. AD, stroke or Parkinson's disease) (Starkstein et al., 1992; 1993; Starkstein & Leentjens, 2008, p. 1089;), this may be due instead to an inability of assessments to differentiate between symptoms of apathy, cognitive impairment and depression. A third opposing argument is that

both DSM-IV and ICD-10 allow for the diagnosis of mild or moderate depression in the absence of depressed mood, while requiring loss of interest or anhedonia ('inability to experience pleasure, as manifested in facial expression, speech, behaviour, lifestyle and the individual's account of personal experience'), or a decrease in energy (Sims, 2003; Starkstein & Leentjens, 2008, p. 1090). Starkstein and Leentjens (2008, p. 1089) rightly question whether: i) such a definition adequately explains high co-occurrence of apathy and depression, ii) such a reliable separation of non-dysphoric depression from apathy can occur, and iii) 'lack of interest and/or anhedonia are core symptoms of diminished motivation' as Starkstein and colleagues' (2001; 2008) apathy diagnostic criteria, require diminished goal directed behaviour for apathy (assessed by 'lack of interest'). Accordingly, the above stated argument for apathy as a symptom of depression must be questioned. In summary, although apathy and depression demonstrate an overlap in key symptoms and their diagnostic criteria often include the assessment of these joint key symptoms, the presence of separate symptoms of apathy and depression suggest that they are distinct. On balance, the weight of literary evidence points towards apathy as a separate and distinct syndrome from depression and this view is further supported by findings on prevalence of apathy and depression in dementia.

10.6. Does prevalence indicate similarity or difference?

Prevalence and progression rates further support apathy as a separate syndrome from depression. While apathy is a prominent feature of AD related behavioral and personality change (Bozzola, Gorelick & Freels, 1992; Devanand et al., 1992; Freels et al., 1992; Landes et al., 2001; Marin et al., 1994; Mega et al., 1996; Starkstein et al., 2006), appearing early in the course of the disease (reports ranging between 11 and 39% of individuals with MCI) and increasing in prevalence with illness progression until it is universal amongst severely cognitively impaired (up to 92% of AD patients) (Cummings, 2000; Geda et al., 2004; Hwang, Masterman, Ortiz, Fairbanks & Cummings, 2004; Landes et al., 2001; Lerner et al.,

2007; Mega et al., 1996; Ready et al., 2003; Robert et al., 2006; Strauss & Sperry, 2002), depression, conversely, precedes the onset of AD (Burns, Jacoby & Levy, 1990; Cummings, 2000; Landes et al., 2005; Mega et al., 1996; Merriam, Aronson, Gaston, Wey & Katz, 1988; Starkstein et al., 2001) and is often an initial symptom in AD, appearing in mild to moderate stages (including MCI) and becoming less prevalent in more severe stages (Forsell et al., 1993a; Lyketsos & Olin, 2002; Lyketsos et al., 2000; Olin et al., 2002a). Prevalence rates of depression (major and minor) in AD reportedly range between 30% and 50% (with more extreme studies reporting rates between 1% and 90%) (Lee & Lyketsos, 2003; Olin et al., 2002a). Such inconsistencies may be explained by the large variability in definition, assessment and clinical manifestation in research (Lee & Lyketsos, 2003; Olin et al., 2002a). Notably, with the progression of AD the expression of depressive syndromes change, resulting in an under-recognition of late-life depression due to clinical and nosological ambiguities (Forsell et al., 1993; Mulsant & Ganguli, 1999). However, the declining prevalence of depression in more advanced AD stages may be the consequence of assessment difficulties due to the advanced cognitive decline (Lee & Lyketsos, 2003; Olin et al., 2002a).

Apathy also occurs without depression in AD, suggesting that apathy may be a distinct and distinguishable syndrome from depression (Landes et al., 2001; Levy et al., 1998; Starkstein et al., 2005; Starkstein & Leentjens, 2008). Marin, Firinciougullari and Biedrzycki (1994) demonstrated that 55% of AD patients had high levels of apathy and low levels of depression, while 47% of older adults with major depression had low levels of apathy (Landes et al., 2001). This suggests differential patterns of apathy and depression in AD patients and patients with major depression 'despite a positive correlation between apathy and depression scores in both groups' (Landes et al., 2001, p. 1704). Such findings of no concomitant depression in AD patients supports apathy as a separate neuropsychiatric syndrome from depression (Tagariello et al., 2009).

Other research demonstrates co-occurrence of apathy and depression varying across neurological conditions, suggesting them to be two neuroanatomically distinct entities (Levy et al., 1998; Marin et al., 1993). Starkstein et al. (2006) supported this notion in their longitudinal examination of the association between apathy and depression. Their findings that 25% of non-depressed patients had apathy and that 50% of depressed patients had apathy, led them to conclude that depression is not a requisite for the presence of apathy in AD (Starkstein et al., 2006). Additionally, they found a significant increase in apathy over time, that baseline subsyndromal depression was not associated with follow-up apathy levels, and that baseline apathy levels were a significant predictor of increased follow-up depression (Starkstein et al., 2006). This last finding led them to suggest that apathy may be either an early indicator for depression or a prodromal stage of depression (Starkstein et al., 2006). However, if a prodromal stage of depression, then the prevalence rates of apathy should reflect higher levels of apathy prior to depression. This is not found. While depression is most common in early stages and decreases in prevalence with cognitive decline, apathy increases with increasing cognitive impairment. Therefore, although apathy may be a possible risk factor for the development of later life depression, Starkstein et al's (2006) proposal of apathy as a prodromal stage of depression requires further investigation. Accordingly, on the basis of current understanding of the prevalence and progression rates of apathy and depression, it is plausible to postulate that apathy and depression are separate syndromes in dementia.

In summary, apathy and depression differ based on prevalence and progression rates. While apathy occurs in early and mild stages of cognitive impairment and increases in prevalence to become universal amongst severely cognitively impaired, depression is an initial symptom apparent already in the pre-clinical stage of MCI and mild to moderate stages of impairment. In contrast to apathy, depression becomes less prevalent with increasing cognitive decline, maybe as a consequence of methodological limitations (e.g. AD pathology, cognitive decline and unwillingness or inability to disclose the presence of such

neuropsychiatric symptoms). The development of more accurate and effective ways to assess the presence of such neuropsychiatric symptoms is required where diagnosis is not predominantly dependent on caregiver report or clinician interpretation.

10.7. A Neuropathological explanation?

Similarities and differences of apathy and depression have not only been found for symptomatic overlap, but also on a neuropathological level (Landes et al., 2001). Apathy has most commonly been observed with damage to the frontal lobes or subcortical structures connecting them (e.g. frontal lobe lesion) and impairments in these areas are associated particularly with executive dysfunction and cognitive and behavioral changes (Fogel, 1994; Landes et al., 2001; Lerner et al., 2007; Mattson & Levin, 1990; Mega & Cummings, 1994). Apathy is 'correlated with neuronal loss, higher tangle counts and white-matter hyperintensities in areas that are thought to be essential component' of frontal subcortical circuits (Burns & Forstl, 1996; Forstl et al., 1993; Landes et al., 2001, p. 1701; Starkstein et al., 1997; Tekin et al., 2001). Significantly reduced blood flow in the anterior temporal, orbito-frontal, anterior cingulate and dorsolateral prefrontal regions has been observed more frequently in patients with moderate or severe apathy than those with no or mild apathy (Craig et al., 1996; Cummings, 2000). The involvement of frontal-subcortical circuits originating from frontal cortical regions, which mediate executive function and motivation, occurs in apathetic patients (Cummings, 1993; McPherson & Cummings, 1998). Apathy in AD is therefore strongly associated with neuropathological impairments in components of the anterior cingulate frontal-subcortical circuit (e.g. anterior cingulate, nucleus basalis of Meynert, hippocampus and medial frontal region) (Burns & Forstl, 1996; Forstl et al., 1993; Landes et al., 2005; Starkstein et al., 1997; Tekin et al., 2001).

Conversely, the neuropathology of depression in AD is primarily associated with frontal-striatal and subcortical limbic structures (locus ceruleus, substantia nigra,

hippocampus and hypothalamus) (Cummings, 2000; Ebmeier et al., 1997; Landes et al., 2005; Mayberg, 1994; Tagariello et al., 2009). Post-mortem evidence has demonstrated a reduction in the locus ceruleus cell population, the number of substantia nigra cells, and neurochemical changes, i.e., marked reduction of norepinephrine levels in the middle frontal and temporal cortex cortical regions, increased entorhinal cortex dopamine levels and normal frontal and temporal cortex serotonin levels – even with significant reductions of serotonin uptake sites in the temporal regions (Chan-Palay, 1989; Chen et al., 1996; Forstl et al., 1992; Zubenko & Moossy, 1988; Zubenko, Moossy & Kopp, 1990). Post-mortem evidence also suggests a selective noradrenergic cell loss in the locus ceruleus and dorsal raphe serotonergic nuclei loss (Forstl et al., 1992; Lyketsos & Olin, 2002; Zubenko, 1992; Zubenko et al., 1991; Zweig et al., 1988; 1989). Apoptotic processes occurring as a function of AD may also contribute to the loss of aminergic nuclei, in turn affecting mood (Olin et al., 2002a; Zubenko, 2000). The presence of depression correlates with elevated global scores of deep white matter lesions, particularly lesions to frontal lobe white matter (Lopez et al., 1997a; 1997b). However, although findings of functional neuroimaging studies are inconsistent, AD related depression has been associated with reduced parietal lobes metabolism, cerebral hypoprofusion in temporal-parietal regions and hemispheric hypoperfusions in the dorsolateral, frontal, temporal and parietal regions (Cummings, 2000).

Apathy and depression are neuropathologically similar due to hypoperfusion or hypoactivity in frontal, parietal and temporal regions (Benoit et al., 1999; Craig et al., 1996; Ebmeier et al., 1997; Hirono et al., 1998; Landes et al., 2001; 2005; Lopez et al., 2001; Mayberg, 1994; Ott, Noto & Fogel, 1996; Starkstein et al., 1997; Tagariello et al., 2009). Landes et al. (2001, p. 1704) suggested the ‘co-occurrence of apathy and depression may relate to involvement of frontal subcortical circuits in both syndromes’. Other research proposed a mixed behavioral presentation of apathy and depression due to impairment of the frontal circuitry in major depression resulting from the proximity of such subcortical circuits

(i.e. a subcortical lesion simultaneously affects multiple circuits) (Duffy & Campbell, 1994; Joseph, 1999; Landes et al., 2001; Levy et al., 1998; Mega & Cummings, 1994; Royall, 1999). Conversely, neuropathological differences are observed as 'AD patients with isolated motivational or mood disturbances reveal differing cortical dysfunction during early disease, confirming a different neuroanatomical basis for the emergence of apathy and depression in AD' (Holthoff et al., 2005, p. 418). Holthoff et al.'s (2005) positron emission tomography study showed that apathetic early AD patients had significant glucose metabolism decreases in the left orbitofrontal regions, while hypometabolism in the dorsolateral prefrontal regions was associated with depression.

Other research suggests apathy and depression to differ on a neurochemical basis, with apathy associated with cholinergic deficits and depression with serotoninergic deficits or a dopamine and norepinepherine imbalance (Cummings, 2000; Cummings & Back, 1998; Landes et al., 2005; Meltzer et al., 1999; Zubenko et al., 1999). Symptoms of apathy in early AD are related to cholinergic input loss to the prefrontal and subcortical structures of the nucleus basalis of Meynert, while deepening apathy in later illness stages results from severe cholinergic denervation, the involvement of the prefrontal cortex and the anterior and medial temporal structures supplying adherent input to this circuit (Landes et al., 2001; Tagariello et al., 2009). Thus, an interaction between the neuropathological frontal brain changes and the cholinergic deficiency is reflected in AD related apathy (Tagariello et al., 2009).

The identification of more pronounced apathetic symptoms in AD patients exhibiting extra-pyramidal symptoms and empirical results on modulated dopaminergic neurotransmission treatment further suggest that dopamine plays a mediating role in apathetic AD patients (Gilley, Wilson, Bennett, Bernard & Fox, 1991; Landes et al., 2001; Lerner et al., 2007). Conversely, serotoninergic agents (e.g. selective serotonin reuptake inhibitors) worsen apathetic symptoms but relieve depression (Hoehn-Saric, Lipsey & McLeod, 1990; Levy et al., 1998; Marin, 1996; Marin, Fogel, Hawkins, Duffy & Krupp, 1995; Settle, 1998;

Wongpakaran, van Reekum, Wongpakaran & Clarke, 2007). While apathy treatment may be supported by increasing dopaminergic function, serotonergic activity increase is detrimental (Lanctôt et al., 2008). Thus, as cholinomimetic agents reduce apathy and do not affect mood, only apath, and not depression is relieved by dopaminergic agents (Kaufer, Cummings & Christine, 1996; Levy et al., 1998). A possible explanation is that depression results from an imbalance in paralimbic neurotransmitter function, while apathy may be traced to a functional disconnection of the cortex from relevant paralimbic input (Tagariello et al., 2009). While the treatment of apathy with cholinesterase inhibitors (e.g. tacrine) have demonstrated significant reductions in apathetic symptoms in AD, suggesting a 'cholinergic contribution to the pathophysiology of apathy in AD' (Cummings, 2000, p. 852; Kaufer, Cummings & Christine, 1998), between 38% (Cummings, McRae & Zhang, 2006) and 60% (Mega, Masterman, O'Connor, Barclay & Cummings, 1999) do not respond to such treatment (Lanctôt et al., 2008). Such involvement of differing neurochemical pathways and, to some extent, of neuropathological structures can therefore be a further indication that apathy and depression are two separate syndromes in dementia.

In summary, apathy in AD is associated with bilateral hypoperfusion within the basal ganglia and dorsolateral prefrontal cortex (Lopez et al., 2001), a reduction in perfusion of anterior temporal, orbito-frontal, anterior cingulate and dorsolateral prefrontal regions (Benoit et al., 2002; Migneco et al., 2001), hypometabolism in the left orbitofrontal areas (Holthoff et al., 2005) and left anterior cingulate neurofibrillary tangle burden (Tekin et al., 2001). Conversely, AD related depression is associated with hypometabolism in the left prefrontal cortex and superior frontal cortex (Holthoff et al., 2005), white matter lesions (Lopez et al., 1997), reduced glucose metabolism in the bilateral anterior cingulate and superior temporal cortex (Lopez et al., 2001) and bilateral superior frontal and left anterior cingulate cortex (Hirono et al., 1998) or parietal lobes (Sultzer et al., 1995).

10.8. Conclusion and future directions

Although no consensus on the nosological position of apathy in dementia has been reached, apathy, despite some symptomatic overlap with depression, may be viewed as a separate syndrome from depression in dementia. This review provided an overview of the literature focusing on the areas of clinical manifestation, symptomology, assessment, prevalence and neuropathology. We conclude that given the evidence, the arguments in support of apathy as a separate syndrome from depression in dementia are persuasive. The fact that the definitions of apathy and depression overlap in terms of key symptoms, resulting in a high mis-diagnosis of apathy as depression however raises some concerns. These concerns regard treatment, as medical treatment of depression does not alleviate the negative impact of apathy. To provide sufficient support to individuals suffering from dementia and their caregivers, it is vital that apathy as a syndrome is recognized and treated. Reaching a consensus on the definition of apathy within dementia is vital for patients suffering from such neuropsychiatric symptoms to receive deserved support and attention. A consensus on the definition of apathy and its nosological position will lead to better development and implementation of diagnostic measures and criteria, more effective research and clinical practice, and better understanding of associated neuropsychiatric disorders in dementia. The identification of apathy as a separate syndrome and its management (whether pharmacologically or non-pharmacologically) requires a better understanding of potential risk factors for both apathy and depression in dementia. This is important when considering the direction of future research, specifically on potentially modifiable risk factors for the development of apathy and depression in dementia. While there is ample research on risk factors of AD (Forstmeier & Maercker, 2009b), little research has focused on risk factors for apathy and depression in dementia. Research by Mortby, Maercker and Forstmeier (2011) is the first to consider midlife motivational abilities as a predictor for apathy and depression in

dementia, demonstrating midlife motivational abilities to moderate the causal relationship between cognitive impairment and apathy, but not depression.

11. Paper 2: Midlife Motivation: A Predictor of Apathy and Depression in Mild Cognitive Impairment and Early Alzheimer's Disease

Mortby, M. E., Maercker, A., Drobetz, R., Fankhauser, S. and Forstmeier, S.

(Submitted)

11.1. Abstract

Apathy and depression in Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) is associated with increased risk of conversion. Midlife motivational abilities as a predictor of apathy and depression in MCI and early AD is little researched. In a sample of 56, an informant-rated retrospective measure of midlife motivational abilities predicted symptoms of apathy (β = -0.313, $p < 0.05$) and depression (β = -0.396, $p < 0.01$) and moderated the relationship between severity of cognitive impairment and depression (β = -0.253, $p < 0.05$) but not apathy. Midlife motivational abilities as a modifiable risk factor for apathy and depression is fundamental to the development and implementation of preventative measures to reduce such neuropsychiatric symptoms and risk of conversion.

Key words: Alzheimer's Disease, Mild Cognitive Impairment, Dementia, Midlife Motivational Abilities, Depression, Apathy.

11.2. Introduction

Mild Cognitive Impairment (MCI) is a preclinical stage between normal aging and dementia, in which individuals are at risk of developing dementia but, so far, do not fulfill the clinical criteria for a diagnosis of dementia or Alzheimer's Disease (AD) (Caselli et al, 2006; Monastero et al., 2009; Petersen, 2004; Petersen et al., 1999; Winblad et al., 2004). Research only recently focused on neuropsychiatric features in MCI and early stages of AD (eAD) in which the level of care and assistance required is still low (see Apostolova & Cummings, 2008; Brookmeyer, Johnson, Ziegler-Graham and Arrighi, 2007). The consideration of neuropsychiatric symptoms in pre-clinical and early stages of dementia is vital as at least one third of MCI patients (Apostolova & Cummings, 2008) and approximately 90% of eAD patients display neuropsychiatric symptoms (Chen et al., 2000). These symptoms are associated with poorer cognitive performance, more functional disability and mild extrapyramidal signs (Monastero et al., 2009) and have been associated with increased conversion from MCI to AD (Barnes et al., 2006; Geda et al., 2006; Lopez et al., 2003; Stepaniuk et al., 2008). Approximately 10-15% of MCI cases progress to AD within one year and this increases by up to 25% in the presence of depression, sleep disorders, or benzodiazepine or alcohol abuse (Eschweiler et al., 2008; Petersen et al., 1999). The prevalence of eAD is estimated by Brookmeyer et al. (2007) at 56% of all AD cases.

Apathy and depression are two of the most prevalent neuropsychiatric symptoms associated with MCI and AD (Aalten et al., 2007; Assal & Cummings, 2002; Lanctôt et al., 2008; Lyketsos et al., 2002; Mega et al., 1996) contributing significantly to increased patient and caregiver distress and loss of quality of life (Aalten et al., 2007; Banerjee et al., 2006; Garcia-Alberca et al., 2008; Lanctôt et al., 2008). While depression has been associated with increased risks of AD (Green et al., 2003), apathy is most frequently observed in patients with dementia and AD, appearing in mild and moderate stages and increasing with cognitive

decline (e.g. Caputo et al., 2008; Lyketsos et al., 2000). Population-based studies on MCI have stressed the importance of apathy and depression in MCI. While Solfrizzi et al. (2007) demonstrated 63% of their MCI population to display depressive symptoms, apathy is the second most prevalent behavioral symptom in MCI, with the Swedish Kungsholmen Project reporting 36% of MCI cases to demonstrate motivation-related symptoms (Lyketsos et al., 2002; Monastero et al., 2009; Palmer et al., 2007).

The presence of apathy and depression in MCI is also a risk factor for AD (Teng et al., 2007). Forstmeier and Maercker (2009b) have provided a literature review on modifiable risk factors, demonstrating the focus up to now to have been placed on cognitive abilities (e.g. education level, pre-morbid intelligence, cognitive activity, occupational attainment), emotional health (e.g. depression), physical activity; social activity and networks, vascular factors (e.g. diabetes, hypertension, hypercholesterol, obesity) and nutrition (e.g. vitamins, fat intake, dietary pattern). However, little research has focused on midlife motivational abilities as a risk factor for MCI and AD (Forstmeier & Maercker, 2008) and the neuropsychiatric symptoms of apathy and depression in dementia (Mortby, Maercker & Forstmeier, 2011). Midlife motivational abilities as a potentially modifiable risk factor for dementia was originally proposed by Forstmeier and Maercker (2008) who demonstrated that strong pre-morbid motivational ability lowered the risk of cognitive impairment while Mortby et al. (2011) were the first to apply this model to the progression of apathy and depression in individuals with MCI and AD.

Forstmeier and Maercker's (2008) motivational abilities model is rooted within the brain reserve hypothesis framework in which the exercising of motivational abilities provides resilience to neuropathological damage by enabling the toleration without clinical manifestation of age- and dementia-related changes (Fratiglioni & Wang, 2007; Valenzuela & Sachdev, 2006). Core motivational abilities are decision regulation (a skill used to arrive at a self-congruent decision quickly), activation regulation (a skill used to bring oneself to

readiness to act), motivation regulation (a skill used to motivate oneself to persevere when faced with difficulties) and self-efficacy (a belief to be able to master difficult environmental demands) (Gollwitzer & Bargh, 1996; Kehr, 2004; Kuhl, 2000; Kuhl & Fuhrmann, 1998). These processes reflect the skills required for the implementation of personal goals and comprise the motivational processes required to shield an intention from competing ones by allowing the implementation of an intention in a self-regulated way (Bandura, 1997; Gollwitzer & Bargh, 1996; Kehr, 2004; Kuhl, 2000; Kuhl & Fuhrmann, 1998).

Research has provided evidence for the importance of these individual processes as predictors of emotional health (e.g. Forstmeier & Rueddel, 2007; Kruglanski et al., 2000; Kuhl & Fuhrmann, 1998; Rholes et al., 1989). Specifically, self-efficacy and action control have been shown to be negatively associated with depression (Kuhl & Fuhrmann, 1998; Luszczynska, Gutiérrez & Schwarzer, 2005; Rholes et al., 1989) and Bandura (1997) demonstrated a positive association between self-efficacy and well-being. Forstmeier and Maercker (2008) supported such an association, demonstrating an occupation based estimate of midlife motivational abilities to be negatively associated with depressive symptoms and positively with wellbeing. Importantly, research has shown that motivation-related symptoms of depression have a more predictive value for conversion than affect-related symptoms (Bartolini et al., 2005; Berger et al., 1999). While these studies used cognitively unimpaired, Mortby et al. (2011) were the first to investigate midlife motivational abilities as a predictor for the progression of apathy and depression in MCI and AD. Using the same retrospective estimate of motivational abilities as Forstmeier and Maercker (2008), Mortby et al. (2011) demonstrated midlife motivational abilities to be associated with the progression of apathy and depression in MCI and AD.

This study aimed to expand on Forstmeier and Maercker's (2008) and Mortby et al.'s (2011) findings by implementing a different methodology to assess midlife motivational abilities (i.e. the processes of decision regulation, activation regulation, motivation regulation

and self-efficacy) to determine the predictive nature of midlife motivational abilities for apathy and depression in early stages of cognitive impairment, specifically MCI and eAD. Based on these previous findings, and the associated increased risk of conversion from MCI to AD through the presence of apathy and depression, the following questions arise: Are midlife motivational abilities a predictor for presence of apathy and depression in MCI and early AD? If midlife motivational abilities predict apathy and depression in individuals with MCI and early AD, then how do differing levels (low/ high) of pre-morbid motivational abilities affect the expression of neuropsychiatric symptoms? Does Forstmeier and Maercker's (2008) model of a protective function of high midlife motivational abilities for cognitive impairment also apply to the neuropsychiatric symptoms of apathy and depression? What impact can the identification of midlife motivational abilities as a predictor of apathy and depression in MCI and AD have for our understanding of modifiable risk factors and the development of interventions?

Based on these questions, this study aimed to investigate whether: i) midlife motivational abilities and severity of cognitive impairment are independent predictors of symptoms of depression or apathy in individuals with MCI or eAD and ii) midlife motivational abilities moderate the relationship between the severity of cognitive impairment and depressive and apathetic symptoms? Midlife motivational abilities were predicted to be a separate predictor of depressive and apathetic symptoms to cognitive impairment. Specifically, individuals with high pre-morbid motivational abilities were expected to have lower levels of apathetic and depressive symptoms than those with low pre-morbid motivational abilities and that midlife motivational abilities would moderate the relationship between level of cognitive impairment and apathetic and depressive symptoms, resulting in lower prevalence rates of these neuropsychiatric symptoms.

11.3. Method

Participants (N=56) were recruited in cooperation with local memory clinics mainly in Switzerland but also in Austria. Inclusion was based on a clinical diagnosis of MCI (N=29) or eAD (N=27) and participants were above the age of 60. Individuals with a history of malignant disease, severe organ failure, metabolic or hematologic disorders, neurosurgery or other neurological conditions (e.g. Pick's disease, Creutzfeld-Jakob's disease, Parkinson's disease, HIV, epilepsy, post-encephalitic and post-concussional syndromes, traumatic brain injuries, alcohol or drug abuse, Schizophrenia or severe depression) and or a diagnosis of pure vascular dementia were excluded from participation.

Table 1 shows the sample characteristics. Ages ranged between 62 and 94 years (M=76.8 years; SD=7.78). 29 participants (51.8%) were female. At the time of assessment, 55% of the participants were married and 57% lived with their partner. For 61% the informant was their partner, for 27% the child, and for 7% another relative. Informants had known the participant between 11 and 71 years, with a mean length of 47.5 (14.1) years.

Diagnosis and Assessment of Severity of Cognitive Impairment

Memory clinics in Switzerland are outpatient based medical centers to which individuals are referred by general practitioners. Neuropsychological, internistic, geriatric, neurological and psychopathological assessments are conducted by an interdisciplinary team (Monsch et al., 2008). Placing the neuropsychological assessment at the center of the assessment, a differentiated profile of cognitive function abilities are provided which include the assessment of attention, working memory, executive function, memory, language and speech, praxis, behavior (e.g. emotional wellbeing) and personality. Neurological imagery assessment may include MRI or CT (exclusion of secondary dementia types). Geriatric assessments include activities of daily living, mobility, function of sensory organs (e.g. sight, hearing), nutrition, mood, social network and social support (Monsch et al., 2008).

Clinical and neuropsychological assessments conducted in accordance with this study included, amongst others, the *Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Assessment (CERAD-NP)* (Morris et al., 1989). The *Mini Mental State Examination (MMSE)* (Folstein, Folstein & McHugh, 1975) screened for and assessed **cognitive function**. **Memory** was assessed using the *CERAD Word List Memory* (Atkinson & Shiffrin, 1971) and the logical memory subtest and visual reproduction subtest of the *Wechsler Memory Scale Revised (WMS-R)* (Wechsler, 1987). **Language** was assessed using the *CERAD Animal Naming Task* (Isaacs & Kennie, 1973), the *Modified Boston Naming Test (BNT)* (Kaplan, Goodglass & Weintraub, 1978) and the *Controlled Oral Word Association Test* (Benton & Hamsher, 1989). **Praxis** was assessed using the *CERAD Constructional Praxis* (Rosen, Mohs & Davis, 1984) test and the *Picture Completion subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III)* (Wechsler, 1997). The **executive function** of task switching was assessed using the *Trail Making Test - Part B* (Reitan, 1985). The executive function of inhibition of prepotent responses was assessed using the *Stroop Color-Word Test* (Stroop, 1935) and the executive function of updating working memory was assessed using the *Digit Span Backward test* of the WAIS-III (Wechsler, 1997). **Attention** was assessed using the *Trail Making Test – Part A* (Reitan, 1985) and the *Digit Symbol Substitution Test* of the WAIS-III (Wechsler, 1997). **Functional abilities** were assessed through *activities of daily living (ADL),* specifically the *Barthel Index* (Mahoney & Barthel, 1965) as this is the standard measure of ADL in German speaking areas (see Lübke, Grassl, Kundy, Meier-Baumgartner & Wilk, 2001). The *Bayer ADL* (Hindmarch, Lehfeld, de Jongh & Erzigkeit, 1998) was used to assess instrumental activities of daily living (IADL) using a 25-item informant-rated questionnaire which is internationally used and has been validated and is reliable.

Global clinical assessments of **severity** included the *Clinical Dementia Rating* (CDR) scale (Morris, 1993), a global scale to clinically identify the presence and severity of dementia of the Alzheimer's type. This semi-structured patient and caregiver interview is used to

determine cognitive performance in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) (Morris, 1997). It is a five-point scale (0 = no cognitive impairment; 0.5 = very mild dementia; 1 = mild; 2 = moderate; 3 = severe cognitive impairment).

Based on the assessments, an interdisciplinary team assigned a diagnosis of MCI or eAD. *MCI* was defined on the basis of the *International Consensus Criteria* (Winblad et al., 2004) which require the absence of dementia as diagnosed by DSM-IV criteria; a MMSE score of ≥ 24 and a CDR score of ≤ 0.5; self and/or informant reported cognitive decline; preserved activities of daily living; and at least mild impairment (minimum of 1 SD under the norm) in one cognitive domain of either memory, language, praxis, executive function and attention. A diagnosis of *eAD* (probable or possible AD) was assigned based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for AD and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) criteria. For this cohort, the severity of dementia had to be mild and was determined by an MMSE score of > 18 or a CDR score of 0.5 or 1.

Neuropsychiatric Symptoms

Depression was assessed using the *Short form of the Geriatric Depression Scale* (GDS) (Yesavage et al., 1982), a 15-item patient and informant rating using yes/no responses. The GDS is a valid and reliable assessment of depression in the elderly and is effective in detecting depression in pre-clinical and mild dementia (Yesavage et al., 1982). Severity of depression is differentiated with scores between 5-10 suggesting light to moderate depression while scores of 11-15 indicate severe depression (Yesavage et al., 1982). The German version of the GDS by Gauggel and Birkner (1999) was implemented.

Apathy was assessed using the *Apathy Evaluation Scale* (AES) (Marin et al., 1991), an 18-item patient, informant and clinician rated scale (4-point Likert-scale ranging from 'not at

all' to 'a lot'). The AES is a validated and reliable assessment of apathy for middle aged and elderly patients with AD and other forms of dementia (Marin et al., 1991). The assessment of apathy by the AES reflects patients' current levels of function and is based on the four weeks preceding testing. It consists of items reflecting overt goal-directed behavior, goal-related cognitions and goal-related emotional responses (in accordance with Marin et al.'s (1991) definition of apathy). This study implemented the validated German version by Lueken et al. (2006). Increased severity of apathy was indicated by higher scores on each AES version (i.e. self, informant, clinician). While the self version of the AES is administered as a paper and pencil test, the informant version is a semi-structured interview and the clinician version is based on the clinician's assessment of the patient's and informant's report. Despite the clinician version being reported to have better validity than the informant and self-report versions, the current study did not use the clinician version due to procedural inconsistencies. Instead, the informant version was used as it has better validity than the self-report measure. Primary caregivers have been shown to be reliable sources in the reporting of apathy demonstrating themselves to be particularly sensitive and reliable (Marin et al., 1991). In accordance with Lueken et al.'s (2006) proposition to use a scale ranging from 0 to 3 rather than 1 to 4, the current total AES scores range from 0 to 54.

Pre-morbid Motivation

Midlife motivational abilities (i.e. motivation regulation, decision regulation, activation regulation and self-efficacy) were retrospectively estimated by the informant using the following four scales:

- From the *Volitional Components Questionnaire (VCQ)* (Kuhl & Fuhrmann, 1998) the sub-scales assessing motivation regulation (example item: "He/she could usually motivate him/herself quite well if his/her determination to persevere weakened") and decision regulation (example item: "When he/she thought about doing or not doing something, he/she usually arrived at a decision quickly") were used. These two sub-scales consisted

of five statements each and the degree of agreement with the statement was rated on a 4-point Likert-scale. Cronbach's alpha (an estimate of internal consistency) for motivation regulation was .86 and for decision regulation .67.

- The *Locomotion and Assessment Questionnaire (LAQ)* (Kruglanski et al., 2000) provided the locomotion scale to assess activation regulation (example item: "When he/she decided to do something, he/she could not wait to get started"). This scale consisted of 10 items relating to 'self-activation' or 'commencing an action' and the degree of agreement with the statement was rated on a 6-point Likert-scale. Cronbach's alpha for activation regulation was .75.
- The *General Self-Efficacy scale (GSE) (*Scholz, Gutierrez, Sud & Schwarzer, 2002, p. 243) was used to assess self-efficacy. Specifically it assessed the 'broad and stable sense of personal competence to deal effectively with a variety of stressful situations'. This scale consisted of 10 items (example item: "He/she was confident that he/she could deal efficiently with unexpected events") and was rated on a 4-point Likert-scale. Cronbach's alpha for self-efficacy was .91.

This questionnaire is a modification of established self-report measures, which have been rephrased to assess the same aspects as the original versions, however from an informant perspective and retrospectively (e.g. "I energetically pursue my goals" was rephrased into "He/she energetically pursued his/her goals"). Informants were instructed to provide answers to each question by focusing on the time in which the participant was between the age of 30 and 50. The cut-off of 30 years was implemented as considerable personality changes still occur during the third decade of life (the 20s).

To reduce the number of variables and to minimize floor and ceiling artifacts and other forms of measurement error, a composite score was calculated by converting the four component tests to z-scores using the baseline mean and standard deviation of all study

participants and averaging the z-scores. In a principal components analysis, all four scales loaded on one factor.

Procedure

Participants were recruited in cooperation with memory clinics (specialized facilities for the diagnosis of cognitive impairment and dementia) in Switzerland and Austria and the research protocol was approved by the ethics committees of each regional medical authority. Following assessment at the memory clinic and diagnosis of MCI or eAD, participants who satisfied the inclusion criteria were informed of the study. Participants and their caregiver/informant were provided with an information pack on the objectives and procedures of the study. Contact details of those prepared to partake in the study were forwarded by the memory clinics to the research team who arranged the assessments. Assessment comprised of two consecutive appointments, usually one week apart, in which both the participant and the primary caregiver/informant were simultaneously interviewed by two separate interviewers. Participant and informant interviews were conducted to provide a comprehensive picture of both perspectives and to provide more accurate information about the participant's personality before the age of 50.

At the initial assessment questions outstanding from the information pack were addressed and written informed consent obtained from both the participant and informant. Assessments (neuropsychological, clinical interviews and midlife motivational abilities) were assessed during two sessions, approximately one week apart. All clinical and neuropsychological data, and the clinical diagnosis were obtained from the referring memory clinic. A full debrief was provided and participants were reimbursed for their participation (50 CHF).

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 18.0. The relationship between the variables was examined using bivariate correlations. A multiple regression was used (all variables entered together) to determine whether cognitive impairment and midlife motivational abilities independently predict depression or apathy and to assess whether midlife motivational abilities moderates the relationship between cognitive impairment and depression or apathy. Age was included as a control variable in the multiple regression analyses as age differed significantly between the cohorts of MCI and eAD. Gender and education were not included as these did not differ significantly between the cohorts. By entering all variables together their effects were controlled for to determine the individual predictive value of each predictor variable on the outcome. The continuous variable of midlife motivational abilities was transformed into a categorical variable (low and high motivation) using a mean split to allow for the comparison between low and high motivational abilities.

11.4. Results

Table 1 demonstrates the sample characteristics. The sample (N=56; 29 women; 27 men) had an average age of 77 (7.78) years. MCI and eAD differed for age (t = -2.09, p < 0.05), indicating cognitive impairment to increase with higher age. Although no significant difference was observed between the cohorts for self-reported depression (t = -0.357, p = 0.722) and informant-reported apathy (t = 0.937, p = 0.353), participants with eAD demonstrated higher levels of depression and lower levels of apathy compared to the MCI cohort. This suggests higher levels of depression to be associated with increased cognitive impairment, while apathy is more common in the pre-clinical stage of MCI in the current sample. As evident from Table 2, severity of cognitive impairment (CDR) correlated with

depression (r = 0.283, p < 0.05) but not with apathy (r = 0.127, p = 0.336). Table 2 demonstrates the correlates of depression and apathy.

Midlife motivational abilities scores (t = -1.00, p = 0.322) did not differ between the cohorts. Overall 29 participants had high midlife motivational abilities and 25 participants had low midlife motivational abilities. In the MCI cohort, 15 participants were classified as having low midlife motivational abilities while in the eAD cohort 16 participants had high midlife motivational abilities. Midlife motivational abilities correlated with depression (r = -0.33, p < 0.05, see Table 2) and apathy (r = -0.286, p < 0.05) but not with severity of cognitive impairment (r = 0.147, p = 0.266).

Table 3 summarizes the multiple regression analyses for depression and apathy. The potential predictors entered simultaneously into the analysis were: age, severity of cognitive impairment (CDR), retrospective estimate of midlife motivational abilities and the interaction of cognitive impairment with midlife motivational abilities. Overall 36% of the variance of depression was explained by these four variables (R^2 = 0.36; F(4, 56) = 7.32; p < .001). A negative relationship was observed for the predictors of age (β = -0.318, p < 0.01), and midlife motivational abilities (β = -0.396, p < 0.01) and a positive relationship was observed for severity of cognitive impairment (β = 0.554, p < 0.01) with the outcome variable of depression. The significant interaction term of cognitive impairment with midlife motivational abilities explained a significant proportion of the variance in the model (β = -0.253, p < 0.05), where individuals with low midlife motivational abilities demonstrated significantly more depression with increasing cognitive impairment (Figure 1). Thus, midlife motivational abilities were a significant moderator for the relationship between cognitive impairment and depression.

Overall 13% of the variance of apathy was explained by these four variables (R^2 = 0.13; F(4, 57) = 1.98; p = 0.111). The only significant predictor of apathy was midlife motivational abilities (β = -0.313, p < 0.05). Neither severity of cognitive impairment nor the

interaction of cognitive impairment with midlife motivational abilities explained a significant proportion of the variance in the model.

11.5. Discussion

This study is part of a series of research investigating midlife motivational abilities (assessed by a retrospective occupation based measure of motivational abilities) as a predictor of i) affective well-being in cognitively unimpaired individuals (Forstmeier and Maercker, 2008) and ii) the progression of apathy and depression in more advanced cognitive decline (Mortby et al., in press). This study complements these previous studies, by implementing a different methodology to assess midlife motivational abilities (i.e. the processes of decision regulation, activation regulation, motivation regulation and self-efficacy) to determine the predictive nature of midlife motivational abilities for apathy and depression in early stages of cognitive impairment, specifically MCI and eAD. These motivational processes, which reflect the regulation of motivation, have so far only been considered as predictors of emotional health in the cognitively unimpaired (e.g. Bandura, 1997; Forstmeier & Rueddel, 2007; Kruglanski et al., 2000; Kuhl & Fuhrmann, 1998; Luszczynska et al., 2005; Rholes et al., 1989) and not within dementia.

With regard to its aims, this study demonstrated: i) that midlife motivational abilities are an independent predictor of symptoms of apathy and depression in MCI and eAD. Individuals with high pre-morbid midlife motivational abilities have fewer symptoms of apathy and depression than those with low midlife motivational abilities; and ii) that midlife motivational abilities moderate the relationship between cognitive impairment and depression but not apathy in individuals with MCI and eAD.

These findings may possibly indicate differing effects of midlife motivational abilities on apathy and depression depending on the levels of cognitive impairment. Specifically, they reflect a similar process to those in the current findings on prevalence of apathy and

depression in MCI and AD. While apathy is present in early stages of cognitive decline and increases in prevalence with the progression of dementia to become universal in the severely cognitively impaired (e.g. Cummings, 2000; Geda et al., 2004; Landes et al., 2001; Lerner et al., 2007; Mega et al., 1996; Ready et al., 2003; Robert et al., 2006; Strauss & Sperry, 2002), depression is more frequent in the MCI and early AD (Forsell et al., 1993; Lyketsos & Olin, 2002; Lyketsos et al., 2000; Olin et al., 2002a). This may explain the different observations between this study (midlife motivational abilities as a moderator of depression but not apathy) and the previous study by Mortby et al. (2011) in which midlife motivational abilities moderated the relationship between cognitive impairment and apathy, but not depression, in more advanced AD. This study thus expands on Mortby et al.'s (2011) previous research, suggesting midlife motivational abilities to be multifaceted in terms of its protective features for apathy and depression throughout the progression of cognitive decline. Additionally, these findings may provide further evidence to support apathy and depression as separate syndromes in dementia (Mortby, Maercker & Forstmeier, submitted).

This study provided further evidence for the need to consolidate the view that midlife motivational abilities are a further possible protective factor for both cognitive impairment and neuropsychiatric symptoms in MCI and AD. Specifically, this study expands on Mortby et al.'s (2011) findings to provide additional support for the applicability of Forstmeier and Maercker's (2008) motivational abilities model in individuals with cognitive impairment and for apathy and depression.

The identification of such a protective association of high midlife motivational abilities for apathy and depression has far-reaching implications, as the presence of such neuropsychiatric symptoms in early stages is associated with increased risk of conversion to AD (Barnes et al., 2006; Geda et al., 2006; Lopez et al., 2003; Stepaniuk et al., 2008) and contributes significantly to higher levels of patient and caregiver distress and reduced quality of life (Aalten et al., 2007; Banerjee et al., 2006; Garcia-Alberca et al., 2008; Lanctôt et al.,

2008). These findings are important as motivational abilities are modifiable constructs which, with increased training and intervention (see Forstmeier & Rueddel, 2007), may provide an inexpensive and effective prevention or intervention for not only cognitive decline but also the presence of highly disabling neuropsychiatry symptoms. Future research is required in which interventions are implemented to determine how midlife motivational abilities can be enhanced to reduce the presence or severity of such debilitating neuropsychiatric symptoms associated with dementia.

This study suffered several limitations. Primarily, the small sample size (N=56) and the recruitment of participants from memory clinics limits the generalizability of these findings to the wider population. Despite the small sample size, the results are particularly strong and indicate the importance of the currently proposed concept of midlife motivational abilities as a predictor and possible modifiable risk factor for apathy and depression in MCI and AD. Future studies are required in which a more diverse sample is included ranging from MCI to more advanced and severe dementia to determine the more subtle and specific role that midlife motivational abilities plays for the presence of apathy and depression. The cross-sectional design provides a further limitation as this does not allow for a conclusion regarding causality and directionality of effects. However, this cross-sectional design reflects the preliminary results of the baseline assessment of a longitudinal study and longitudinal results will follow. Despite this, and in consideration of the findings by Mortby et al. (2011), who implemented a longitudinal design, these findings are important as they provide additional insight into and understanding of the differing role and level of importance of midlife motivational abilities in apathy and depression at different stages of cognitive decline and dementia. Future studies should also implement other measures which do not rely on retrospective assessments of midlife motivational abilities (Forstmeier & Maercker, 2008; Mortby et al., 2011). Specifically the reliance on informant based retrospective assessments may suffer from hindsight bias induced by the current cognitive state of the participant (MCI

or eAD). Preferably, these should be assessed in a longitudinal design during midlife to determine how and if these fluctuate and what impact they may have. Also the current study relied on informant and self-report measures to assess apathy and depression. However, personality assessments in psychiatric settings readily use informant reports, despite the discrepancies between self- and informant report, suggesting this not to be a major limitation (Ready et al., 2002). Future studies should implement more objective measures including clinician assessments to avoid possible patient or caregiver reporting bias.

Despite these limitations, this study demonstrates the importance of midlife motivational abilities as a predictor for apathy and depression in early stages of cognitive decline (i.e. MCI and eAD). It extends previous findings (Forstmeier & Maercker, 2008; Mortby et al., 2011), provides a new perspective on the importance of midlife motivational abilities as a predictor and possible modifiable risk factor for apathy and depression in MCI and AD, and is of fundamental importance to the development of interventions, early detection and adequate and successful treatment of apathy and depression in dementia.

11.6. Funding

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11.7. Tables and Figures

11.7.1. **Table 1.** Sample Characteristics

Variables	Total (N = 56)	MCI (n = 29)	eAD (n = 27)	t / χ^2	P (t / χ^2)
Age (years), M (SD)	76.9 (7.78)	74.9 (6.31)	79.1 (8.6)	-2.09	< 0.05*
Sex				2.61	0.106
Female, n (%)	29 (51.8)	12 (41.4)	17 (62.9)		
Education (years), M (SD)	12.1 (2.88)	12.3 (2.39)	11.9 (3.42)	.349	0.728
Marital status				9.24	0.026*
Single, n (%)	6 (10.7)	3 (10.4)	3 (11.1)		
Married, n (%)	31 (55.4)	21 (72.4)	10 (37.0)		
Divorced/ Separated, n (%)	4 (7.14)	2 (6.89)	2 (7.41)		
Widow, n (%)	15 (26.8)	3 (10.4)	12 (44.4)		
Living Situation				13.4	.01**
Alone, n (%)	14 (25.0)	7 (24.1)	7 (25.9)		
With partner, n (%)	32 (57.1)	22 (75.9)	10 (37.0)		
With family member, n (%)	1 (1.79)	0 (0)	1 (3.7)		
Care home, n (%)	6 (10.7)	0 (0)	6 (22.2)		
With other person, n (%)	2 (3.57)	0 (0)	2 (7.41)		
Informant relationship to participant				13.5	.009**
Partner, n (%)	34 (60.7)	23 (79.3)	11 (40.7)		
Child, n (%)	15 (26.8)	4 (13.9)	11 (4.07)		
Relative, n (%)	4 (7.14)	0 (0)	4 (14.8)		
Work colleague, n (%)	1 (1.79)	0 (0)	1 (3.7)		
Other, n (%)	1 (1.79)	1 (3.45)	0 (0)		
Years of knowing participant, M (SD)	47.5 (14.1)	46.5 (13.2)	48.5 (15.1)	-.519	0.606
MMSE score, M (SD)	24.8 (3.48)	26.8 (2.22)	22.4 (3.16)	6.02	< 0.001***
CDR	0.83 (0.408)	0.621 (0.218)	1.06 (0.446)	-4.69	< 0.001***
Depression					
GDS-S, M (SD)	2.98 (2.62)	2.86 (2.82)	3.12 (2.42)	-.357	0.722
Apathy					
AES-S, M (SD)	14.3 (6.62)	14.8 (7.66)	13.8 (5.38)	.530	0.599
AES-I, M (SD)	21.7 (10.4)	22.9 (10.8)	20.3 (10.0)	.937	0.353
AES-C, M (SD)	18.4 (7.04)	18.6 (8.09)	18.2 (5.82)	0.205	0.838
Midlife Motivation				1.24	0.266
High, n (%)	29 (51.8)	13 (44.8)	16 (59.3)		
Low, n (%)	25 (44.6)	15 (51.7)	10 (37.0)		
Midlife Motivation Total Score	0.0162 (0.784)	-0.0866 (0.679)	0.127 (0.884)	-1.00	0.322

Note: MCI = Mild cognitive impairment; eAD = early Alzheimer's disease; M = mean; SD = standard deviation; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating Scale; GDS-S = Geriatric Depression Scale – Self Report; AES-S = Apathy Evaluation Scale – Self Report; AES-I = Apathy Evaluation Scale – Informant Report; AES-C = Apathy Evaluation Scale – Clinician Report
* p < .05; ** p < .01; *** p < .001

11.7.2. Table 2. Means, Standard Deviation, and Correlations between Depression and Apathy and other variables

			Measure	
Variable	M	SD	Depression	Apathy
Age	77.2	7.76	-0.183	-0.07
Education	12.5	3.09	0.097	-0.019
CDR	0.852	4.22	0.283*	0.127
MMSE	24.8	3.48	0.002	-0.01
Midlife Motivation Total Score	-.0002	0.769	-0.33*	-0.286*

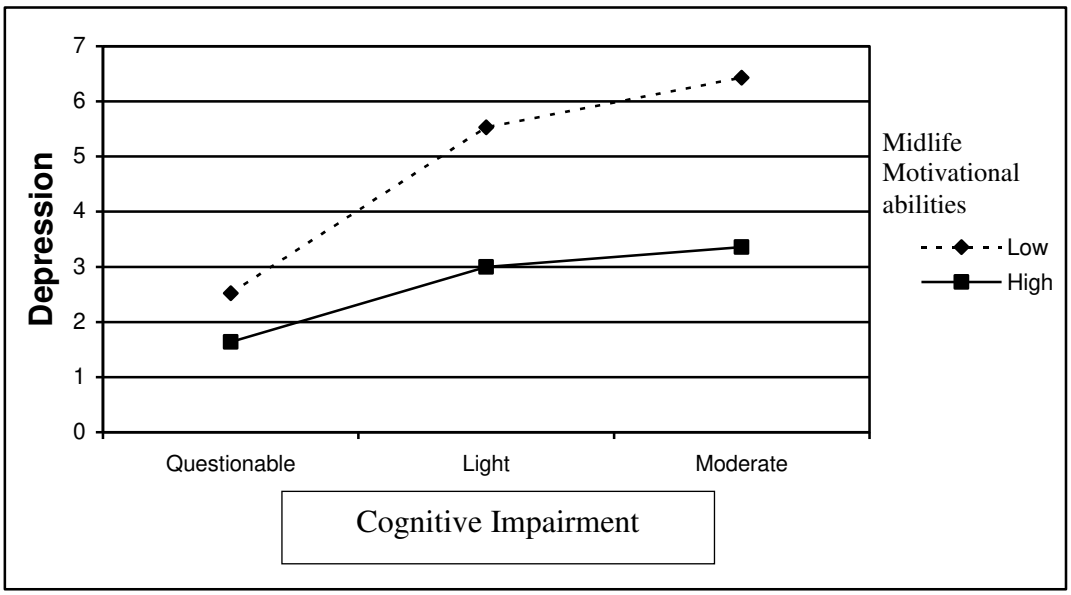
Note. Depression assessed by the Geriatric Depression Scale – Self Report.
Apathy assessed by the Apathy Evaluation Scale – Informant Report.
Midlife Motivational Abilities assessed by the Informant.
Education assessed as total years of education completed.
CDR = Clinical Dementia Rating Scale; MMSE = Minimental State Exam.
* p< .05. ** p < .01

11.7.3. Table 3. Predictors of Self-reported Depression in Mild Cognitive Impairment and early Alzheimer's Disease

	Depression (GDS-S)				Apathy (AES-I)			
Variable	*B*	*SE B*	*β*	95% CI	*B*	*SE B*	*β*	95% CI
Constant	12.1	3.19		[5.65, 18.5]	33.2	14.2		[4.82, 61.6]
Age	-0.112	0.041	-0.318**	[-0.195, -0.029]	-0.14	0.182	-0.104	[-0.506, 0.226]
Midlife Motivation	-1.45	0.409	-0.396**	[-2.27, -0.627]	-4.33	1.79	-0.313*	[-7.93, -0.739]
Cognitive Impairment	1.51	0.367	0.554**	[0.778, 2.25]	1.64	1.63	0.157	[-1.62, 4.91]
Interaction Motivation x Cognitive Impariment	-0.108	0.543	-0.253*	[-0.27, 0.12]	01.35	2.41	0.082	[-3.49, 6.18]
R^2	0.36				0.13			
F	7.32**				1.98			

Note. N = 57. CI = confidence interval. Motivation = Informant rated retrospective motivational abilities. Cognitive Impairment = assessed using the Clinical Dementia Rating Scale. GDS-S = Geriatric Depression Scale Self Report. AES-I = Apathy Evaluation Scale Informant Report.
* p< .05. ** p < .01

11.7.4. Figure 1. Midlife Motivation as a Moderator of the relationship between Cognitive Impairment and Depression



12. Paper 3: Midlife Motivational Abilities predict apathy and depression in Alzheimer's disease: The Aging, Demographics and Memory Study.

Mortby, M. E., Maercker, A. and Forstmeier, S. (2011).

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12.1. Abstract

Apathy and depression are the most common neuropsychiatric symptoms in mild cognitive impairment (MCI) and Alzheimer's disease (AD). This study was the first to explore midlife motivational abilities as a predictor of the progression of apathy and depression in MCI and AD. It used a sub-sample of the Aging, Demographics, and Memory Study (N=137). Participants, aged over 70, were categorized according to baseline clinical diagnosis (normal cognition, MCI or AD). Assessments were conducted at an 18-month interval. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory. Midlife motivational abilities were estimated on the basis of the main occupation using the Occupational Information Network (O*NET) database, which provides detailed information on worker abilities. Repeated measures analysis of covariance was used. Apathy and depression were found to be particularly high in participants with AD and high motivational abilities. Apathy, but not depression, increased over time in those with AD and high motivational abilities. It would appear that holding on to unattainable goals with strong motivational efforts when faced with severe cognitive loss might lead to unproductive persistence, depressive reaction and more apathetic behavior.

12.2. Introduction

Neuropsychiatric symptoms are common in people with mild cognitive impairment (MCI) and dementia (Lyketsos et al., 2002). The current study focused solely on the presence of the neuropsychiatric symptoms of apathy and depression as they are the two most frequent symptoms in MCI (15% and 20% respectively) and dementia (36% and 32% respectively) (Lyketsos et al., 2002) and are associated with faster functional decline and psychotropic prescription (Benoit et al., 2008). Furthermore, apathy has been found to be one of the most important predictors of conversion from MCI to dementia (Palmer et al., 2010). Thus, identifying predictors of these symptoms could have a positive effect on affected individuals and society because prevention and early treatment strategies could be initiated sooner and better geared to the progression of the illness.

Research has only recently started to focus on predictors of apathy and depression in MCI and dementia. Studies have reported associations of the severity of cognitive impairment with apathy but not depression (Zuidema et al., 2009); with cerebrovascular factors such as stroke (Treiber et al., 2008); with environmental factors such as a caring environment (Zuidema, de Jonghe, Verhey & Koopmans, 2010) and living with a spouse (Clarke et al., 2008); and with sociodemographic variables such as older age (Gilley, Wilson, Bienias, Bennett & Evans, 2004) and female gender in depression and male gender in apathy (Zuidema et al., 2009). Psychological variables as predictors of apathy and depression in dementia have focused on pre-morbid personality, mainly neuroticism (i.e. the tendency to experience negative emotions). While some studies found higher neuroticism to be associated with higher depression (Gilley et al., 2004), other studies have shown no such association (Archer et al., 2007).

Interestingly, pre-morbid motivational abilities, which previously have been found to predict depression and wellbeing in cognitively healthy people, so far have not been

investigated as a predictor of depression and apathy in MCI and dementia. Such an association may be expected for the following four considerations. First, diminished motivation as defined in Robert et al.'s (2009) revised diagnostic criteria, is the core feature of apathy, and motivational dysfunction is – besides depressive mood – one of the core symptoms of depression. High pre-morbid motivational abilities may therefore function as a buffer against motivational dysfunction in the cognitively impaired because motivational abilities seem to be relatively stable across adulthood (Johnson & Barer, 1993; Staudinger et al., 1999). Second, motivational abilities have been found to be predictive of depression in cognitively unimpaired individuals (Bandura, 1997; Kruglanski et al., 2000; Rholes et al., 1989; Tangney et al., 2004), and this may be similar in the cognitively impaired. Third, as depressive symptoms have been associated with increased conversion rates from MCI to dementia (Gabryelewicz et al., 2007; Modrego & Ferrandez, 2004), and in particular motivation-related symptoms of depression have been found to be more predictive of conversion rates than affect-related symptoms (Bartolini et al., 2005; Berger et al., 1999), it can be expected that motivational abilities may play a significant role in the presence of depression in dementia. Fourth, Robert et al.'s (2009) revised diagnostic criteria define apathy as a disorder of motivation persistent over time in which the following criteria must be meet: i) diminished motivation (the core feature of apathy) is present for a minimum of four weeks; ii) presence of impairments in at least two of the apathetic dimensions (i.e. reduced goal-directed behavior, goal-directed cognitive activity and emotions); iii) functional impairments are attributable to apathy; iv) symptoms and conditions which mimic apathy are excluded (Mulin et al., 2011). As the presence of apathy has also been associated with higher conversion from MCI to dementia (Robert et al., 2006; 2008; Teng et al., 2007), and its core symptom is diminished motivation (Robert et al., 2009), pre-morbid motivational abilities, which have been associated with goal-directed behaviors (Brown & Pluck, 2000), may have an influential role both for the presence of apathy in dementia and consequently the

progression from MCI to dementia. Therefore, it is plausible to assume that higher mid-life motivational abilities may predict a lower rate of apathy and depression and may play an important role in their involvement within the progression of cognitive impairment.

The present study implemented an occupation-based estimate of midlife motivational abilities. The same estimate has previously been found to predict depressive symptoms and wellbeing in cognitively healthy individuals (Forstmeier & Maercker, 2008). Occupation-based estimates - such as years of education or complexity of work as estimates of pre-morbid cognitive abilities - have a longstanding tradition in dementia research (Andel et al., 2005). All occupations require motivational abilities to a certain extent. The occupational context, in comparison to other areas of life such as relationships, child rearing, or spirituality, can be regarded as one of the areas in which motivational abilities play a crucial role in reaching one's goals. Against this background, this study implemented a procedure to estimate midlife motivational abilities on the basis of an individual's main occupation. This procedure was validated by Forstmeier and Maercker (2008) and included the two motivational variables of goal orientation and action planning which have been shown to correlate with self-reported motivational abilities.

The aim of the present study was to explore midlife motivational abilities as a predictor of apathy and depression in cognitively impaired, and their progression was explored in a longitudinal research design. As severity of cognitive impairment has been found to be associated with apathy (Zuidema et al., 2009), motivational abilities as a possible moderator of the relationship between cognitive impairment (normal cognition; MCI; AD), time (baseline; 18-month follow-up) and apathy/depression was explored. The sample consisted of 137 individuals from a United States representative population-based sample of older adults. It was hypothesized that (1) high motivational abilities are associated with fewer symptoms of apathy/depression; (2) severity of cognitive impairment is positively associated with symptoms of apathy/depression; (3) apathetic symptoms increase and depressive

symptoms remain stable over time (i.e. during the progression of the disease); and (4) the association of motivational abilities with apathy/depression is stronger in the more severely impaired and increases with progression.

12.3. Method

Sample

A sub-sample of the Aging, Demographics and Memory Study (ADAMS) was used. ADAMS is a sub-study of the Health and Retirement Study (HRS) - a longitudinal survey of a US-representative cohort of more than 200,000 adults over the age of 50 (Juster & Suzman, 1995). HRS participants lived either in the community or in nursing homes and were recruited throughout the United States. ADAMS is a stratified random sample (N = 1,770) of the HRS, aiming at identifying the prevalence and consequences of cognitive impairment and dementia (Langa et al., 2005). Individuals over the age of 70 years were selected and stratified according to cognitive function (five cognitive strata based on scores on the HRS cognitive scale), age (70-79 vs. ≥ 80; only the three highest cognitive strata were stratified for age), and sex, to ensure similar numbers in each subgroup (Langa et al., 2005).

Baseline assessments of ADAMS (N=856) were completed between 2001 and 2003 and 18-month follow-up assessments (N=252) were completed between 2002 and 2005 (Plassman et al., 2008). ADAMS diagnoses were made according to three general categories of 'normal cognitive function', 'cognitive impairment, not demented (CIND)' and 'dementia'. These comprised several subcategories denoting the etiology of cognitive impairment (Table 1) (Langa et al., 2005). The present analyses follow the three ADAMS general categories, but were adapted to solely include the subcategories (total of N = 137) of normal/ non-case (cohort of normal cognition; N = 48), MCI or mild-ambiguous – see cognitive impairment section for criteria of mild-ambiguous – (combined to form the cohort MCI; N = 70) and probable or possible Alzheimer's (combined to form the cohort AD; N = 19). Due to their

etiology, those with an ADAMS subsample category diagnosis of vascular dementia, subcortical dementias, other dementias, cognitive impairment secondary to vascular disease, depression, psychiatric disorders, mental retardation, alcohol abuse, stroke, other neurological or medical conditions and CIND non-specified were excluded from the current cohort comparison study (N=115). Further information on sampling frame, eligible participants and respondents is provided in Figure 1.

The ADAMS dataset is publicly available from the HRS website (http://hrsonline.isr.umich.edu). The protocol was approved by the ethics committees of the Duke University Medical Center and the University of Michigan. Informed consent was provided by either the study participant or their caregiver/informant.

Cognitive assessment

Participants and primary caregivers/informants were interviewed by a trained nurse and a PhD-level clinical neuropsychologist using a wide variety of structured assessments both at baseline and at follow-up (see Langa et al., 2005 for full details; Plassman et al., 2008). Assessments were conducted in-home and were reviewed by a geropsychiatrist, a neurologist, a neuropsychologist and a cognitive neuroscientist. Langa et al. (2005) provide full details on assessment and diagnostic procedures. Informant-obtained information included: i) chronological history of cognitive and functional symptoms; ii) medical history; iii) current medications; iv) current neuropsychiatric symptoms; v) measures of severity of cognitive and functional impairment; and vi) family history of memory impairments (Langa et al., 2005; Plassman et al., 2008). Respondents completed a battery of neuropsychological assessments (including assessments of orientation, verbal and visual immediate and delayed memory, language, attention, executive function, praxis, reading ability and general intellect) (Plassman et al., 2008), self-report depression measures, standardized neurological examination, blood pressure measurement, buccal DNA sampling for apolipoprotein E (APOE) genotyping and a 7 minute videotaped segment of the cognitive and neurological

examination (Langa et al., 2005). When available, neuro-imaging and lab reports were acquired and considered by the consensus panel in reaching a diagnosis (Langa et al., 2005). Clinical diagnoses were assigned by the consensus panel in two stages: firstly without medical records and secondly with medical records (Plassman et al., 2008).

Diagnosis of dementia was rooted in published criteria of DSM-III-R and DSM-IV (American Psychiatric Association, 2000). MCI and mild-ambiguous were diagnosed according to the following criteria on the ADAMS dementia checklist. MCI was based on Petersen et al.'s (1999) criteria and assigned when i) memory complaints were verified by the informant (a memory score of > 2 on the Dementia Severity Rating Scale), ii) objective measurement of memory impairment was found (> 1.5 SD below appropriate mean on Wechsler Memory Scale Revised Logical Memory II or Delayed Recall on CERAD Word LIST or Delayed Recall), iii) a Mini-Mental Status Exam (MMSE) score of > 24 was found, iv) a memory score of 0.5 and an overall score of < 1.0 on the Clinical Dementia Rating (CDR), v) major depression as determined by the Neuropsychiatric Inventory and the clinical history did not explain the impairment, and vi) the criteria for CIND are met (functional impairment reported by participants or informants, does not meet criteria for dementia or neuropsychological measure performance below expectation and ≥1.5 SD below published norms for any cognitive domain test, e.g. memory, orientation, language, executive function, praxis).

A diagnosis of mild-ambiguous was assigned when subjects evidenced MCI or borderline impairment where insipient AD was evidenced, however the threshold criteria for specific dementia has not been met (Bigler et al., 2000; Petersen et al., 1999). In ADAMS this required the following criteria to be met: i) impairment is not better explained by another etiology (listed under CIND), it is typically the primary memory impairment (however, memory is not always the only impairment), ii) there is a gradual symptom onset and history suggesting symptom progression, and iii) criteria for CIND (listed above) are met. Even though individuals classified as mild-ambiguous had an MMSE score of < 24, suggesting

dementia, the consensus panel could determine after a review of the individuals' performance on a variety of assessments, caregiver reports and clinician assessments, that these individuals belonged in the CIND category (sub-category of mild-ambiguous) rather than in the dementia category.

Assessment of neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) both at baseline and follow-up. This caregiver-rated measure is widely used to assess affective and behavioral disturbances in dementia by detecting, quantifying and tracking psychiatric symptom changes. It has good psychometric properties (Connor, Sabbagh & Cummings, 2008). It collects information on the presence, frequency and severity of twelve neuropsychiatric domains (hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior change, and appetite/eating change). Each domain is scored by multiplying the domain frequency (5-point Likert-scale, ranging from 0 = 'not at all' to 4 = 'very frequently') by the domain severity (3-point Likert-scale, ranging from 1 = 'mild' to 3 = 'severe'), resulting in scores ranging from 0 to 12. If a symptom is not present, a domain score of 0 is applied. The NPI was used in this study to assess the presence and severity of apathy and depression.

Estimate of midlife motivational abilities

The main predictor in this study was midlife motivational abilities, estimated by reference to a sample of Occupational Information Network (O*NET) variables on the basis of each participant's main occupation. Midlife cognitive abilities, estimated by the same procedure, were used as a covariate in the analyses.

The O*NET is the official occupational classification system of the US Department of Labor (Peterson, Mumford, Borman, Jeanneret & Fleishman, 1999). It consists of a

hierarchically structured lexicon of about 1,100 occupations and a large database of associated work and worker characteristics - the result of an ongoing large-scale research project conducted over recent decades. The database includes empirically collected data on the abilities and skills needed in each occupation. Questionnaires were used in the O*NET data collection program to assess samples of workers in each job. Each new version of the O*NET represents an update of these data. Version 12.0, which was used in the current study, is based on samples of n = 20 to 70 individuals allocated to each occupation. Most O*NET variables relating to skills, abilities and work activities have been shown to have high inter-rater reliability and to be valid (high correlations with expert ratings) (Peterson et al., 1999).

A three-step procedure was used to estimate participants' midlife motivational and cognitive abilities. First, the main (i.e. longest held) occupation of each participant was identified. The main occupation was selected in a rigorous procedure in which the entire HRS or Asset and Health Dynamics among the Oldest Old (AHEAD) occupational history of a participant was reviewed. These variables included, for example, information on employment history, length of employment (including starting and ending years), number of jobs held, type of industry and business worked for and job title and type of work done. Each occupation was coded using either a 3-digit 1980 Standard Occupational Classification (SOC) code (used in HRS), or a 2-digit occupational code (used in the AHEAD study) (Nolte & Servais, 2008). Both the 2- and 3-digit codes were masked for public release to guarantee anonymity and unidentifiability of participants (Nolte & Servais, 2008). HRS maintained the individual occupational codes of participants in a restricted file.

Secondly, HRS/AHEAD codes of the main occupation were transformed into O*NET occupational codes. The occupational title was looked up in the HRS Occupation and Industry Coding user guide (Nolte & Servais, 2008). The occupational title was then entered into the O*NET online system which provided a list of matching O*NET titles, ranked according to relevance. For each participant, each possible match was considered and selected according to

the occupational requirements and characteristics provided by the HRS database. The best matched HRS code was then applied to each participant. For each HRS occupation one matching O*NET code was assigned, e.g. the HRS code "085" (dentist) best matched the O*NET code "29-1021.00" ("dentists, general"). This recoding procedure was carried out independently by two coders; any coding differences were discussed and the most suitable O*NET code was assigned. Initial inter-rater agreement was 78% at the lowest level of the detailed O*NET occupations (8 digits). Participants who had been housewives for the longest period were coded as "personal and home care aides".

Thirdly, two motivational and four cognitive O*NET variable values belonging to this O*NET occupation were assigned to the participant. The selection of these variables is detailed elsewhere (Forstmeier & Maercker, 2008). In short, variables were selected in a sample of non-demented elderly people on the basis of (a) their content validity and (b) their correlations with self-reported motivational abilities and a measure of crystallized (verbal) intelligence. Two variables were highly significantly associated with self-reported motivational abilities but not with intelligence: goal orientation (item 4.A.2.b.6; "developing specific goals and plans to prioritize, organize, and accomplish your work") and action planning (4.A.1.b.3; "determining time, costs, resources, or materials needed to perform a work activity"). Four variables were highly significantly correlated with intelligence but not with self-reported motivational abilities: selective attention (1.A.1.g.1; "ability to concentrate on a task over a period of time without being distracted"), recognizing problems (1.A.1.b.3; "ability to tell when something is wrong or is likely to go wrong"), assessing performance (2.A.2.d; "assessing performance of yourself, other individuals or organizations to make improvements") and social perceptiveness (2.B.1.a; "being aware of others' reactions and understanding why they react as they do").

A composite for midlife motivational abilities was constructed based on the *z*-standardized scores of goal orientation and action planning. Likewise, a composite for midlife

cognitive abilities was constructed based on the *z*-standardized scores of the four cognitive variables. Internal consistency (alpha) was 0.78 for the O*NET motivational abilities total score and 0.81 for the O*NET cognitive abilities total score in the present study. The two total scores were used in the following analyses.

Other variables

Demographic variables included gender, ethnicity and marital status. Education was reported in terms of completed years of formal education. The Mini Mental State Examination (Folstein et al., 1975) was used by the ADAMS study to screen for cognitive impairment and is reported here to describe the study sample. The MMSE consists of 22 items and is scored out of 30.

Statistical analysis

Statistical analysis was conducted using SPSS 18. Repeated measures analysis of covariance (ANCOVA) was conducted to assess the impact on apathy and depression of midlife motivational abilities, cognitive group and time. Midlife cognitive abilities were covaried in order to control for any variance in the results which could be attributed to cognitive abilities. The continuous variable of motivational abilities was transformed into a categorical variable (low, medium, high) using the tertiles of the distribution. The factor "cognitive group" refers to normal cognition, mild cognitive impairment or Alzheimer's disease groups. "Time" captured two test points, baseline and 18-month follow-up. Age, gender, education and midlife cognitive abilities were controlled for in all analyses.

12.4. Results

Table 2 shows the baseline characteristics of study participants. Male and female participants were similarly frequent (51.7% female). On average, participants were 82 years old at inclusion into the study. The three cognitive groups differed significantly with regard to age ($F = 13.92$, < 0.001), indicating that cognitive impairment increased with age. Mean

apathy and depression scores at baseline and follow-up were very low (under the cut-off score for clinically significant symptoms), with apathetic scores of 0.12 (0.64) at baseline and rising to 0.59 (1.95) at follow-up and depressive scores of 0.38 (1.32) rising to 0.41 (1.61) on a scale from 0 to 12. The group of AD patients exhibited more apathy ($F = 4.72$, $p = 0.01$) and depression ($F = 5.27$, $p = 0.006$) than individuals with MCI or no impairment. Although midlife motivational abilities were lower the more cognitively impaired the participants were, this difference was not significant (composite motivational score: $F = 1.11$, $p = 0.334$; goal orientation: $F = 1.09$, $p = 0.338$; action planning: $F = 1.38$, $p = 0.255$). Cognitive impairment did not correlate with goal orientation ($r = -0.11$, $p = 0.198$) or action planning ($r = -0.12$, $p = 0.163$). However, these findings do describe a trend, which with a larger sample, in particular a larger AD sample, may become significant.

Two analyses of covariance were carried out with the factors time, cognitive group and midlife motivational abilities explaining NPI apathy and depression scores. Figure 2 illustrates the results for apathy. The results demonstrated significant main effects of cognitive group and midlife motivational abilities on apathy (see Table 3). Apathy was found to be higher in AD patients compared to MCI and normal cognition ($F = 11.11$, $p < 0.001$) and in individuals with high motivational abilities compared to those with low or medium motivational abilities ($F = 12.21$, $p < 0.001$). All interaction effects were statistically significant. The cognitive group x motivational abilities interaction showed that apathy is particularly high in participants with AD and high motivational abilities ($F = 5.05$, $p = 0.001$). The significant triple interaction indicated that midlife motivational abilities moderate the relationship between cognitive impairment and apathy ($F = 6.95$, $p < 0.001$). However, it should be noted that the moderation observed demonstrated that apathy increases over time, but only in those with AD and high motivational abilities. The lack of visible moderation in the MCI and normal cohorts may be the consequence of minimal levels of apathy.

With regard to depression, significant main effects were found for cognitive group and midlife motivational abilities (see Table 4), indicating depression to be higher in AD patients compared to MCI and normal cognition ($F = 7.77$, $p = 0.001$) and in individuals with high motivational abilities compared to those with low or medium motivational abilities ($F = 6.39$, $p = 0.002$). Only the cognitive group x motivational abilities interaction was significant, showing depression to be particularly high in participants with AD and high motivational abilities ($F = 2.67$, $p = 0.035$). The missing triple interaction suggests that depression levels stay relatively constant over time, even in patients with AD and high motivational abilities.

12.5. Discussion

In this study, high motivational abilities were - contrary to our hypothesis - associated with *more* symptoms of apathy and depression over time. This positive association was particularly strong in patients with AD compared to MCI and normal cognition.

Our hypotheses were based on the assumption that high motivational abilities operated as a protective factor reducing the risk of motivational dysfunction in the cognitively impaired. This assumption rested upon empirical findings with cognitively healthy individuals. For example, the same measure of midlife motivational abilities that was used in this study had been found to be negatively associated with depressive symptoms and positively with wellbeing (Forstmeier & Maercker, 2008). Other measures, such as self-reported self-efficacy and action control, were also negatively associated with depression (Kuhl & Fuhrmann, 1998; Luszczynska et al., 2005; Rholes et al., 1989).

However, there are circumstances when high motivational abilities might have a negative outcome, particularly when coping with irreversible losses and constraints (Thompson et al., 1988). Such circumstances become more likely as individuals age and are confronted with chronic disease. For example, Wolk (1976) found motivational beliefs of control to have a negative effect on wellbeing in settings which are not responsive to the

individual's initiatives or demands. Being confronted with severe cognitive loss, as in the case of AD, might be such a situation where holding on to unattainable goals with strong motivational efforts leads to unproductive persistence, depressive reaction and more apathetic behavior.

Wellbeing therefore depends not only on efficient goal orientation and action planning (the two motivational abilities captured in our occupation-based measure), but also on the ability to adjust personal goals to changing internal and external demands. Holding on to unattainable goals in the face of a degenerative disease such as AD has been found to lead to a depressive state, as working memory is occupied with cognitions about the unattained goal, ultimately blocking the processing of new and realistic goals (Kuhl & Helle, 1986). The model of assimilative and accommodative processes (Brandtstädter & Rothermund, 2002) therefore integrates (assimilative) persisting goal pursuit and (accommodative) flexible goal adjustment. In the assimilative mode, motivational strategies are applied to stick to a goal and modify the environment to attain a closer fit with personal goals. In the accommodative mode, strategies are applied to adjust personal goals to available resources. While, generally speaking, the adaptive application of both assimilative persistence and accommodative flexibility shows positive correlations with wellbeing, accommodative processes gain particular importance for coping with age- and disease-related challenges (see Brandtstädter & Rothermund, 2002 for a review of empirical data). This model therefore offers an explanation for the current findings where AD patients, especially those with high motivational abilities, realize the current and impending limitations of their condition and therefore exhibit more symptoms of apathy and depression over time.

Our findings that apathy and depression were higher in AD patients compared to MCI and cognitive healthy individuals support previous research in which the presence of apathy increases with increasing cognitive impairment (Zuidema et al., 2009). Furthermore, while depression levels stay relatively constant over time, apathy increases during the course of the

18-month interval, but only in those with AD and high motivational abilities. Thus, midlife motivational abilities were found to moderate the relationship between cognitive impairment and the presence and progression of apathy.

Our finding that depression remains stable over time, regardless of severity of impairment, but apathy increases over time in AD patients, can be interpreted as additional support that apathy and depression are two separate syndromes (Landes et al., 2001). Further research is needed to investigate whether different measures of motivational abilities might be differentially related to the two syndromes and its accompanying symptoms (dysphoria in depression, poor persistence in apathy). Also, future research is required in which other psycho-behavioral symptoms associated with dementia (e.g. hallucinations, delusions, anxiety, agitation) are also considered within such a framework of assimilative and accommodative processes. Although this model of assimilative and accommodative processes may provide a good explanation for the current findings, future research is required in which this model is also investigated in, for example, other neurodegenerative diseases in which apathy and depression are also common occurrences such as, for example, Parkinson's disease.

Future research should also consider alternative explanations, such as the goal-directed behavior and motivational model in which negative symptoms (e.g. apathy and depression) may be useful in modeling cognitive and motivational processes which underlie intentionality, volition and will (Brown & Pluck, 2000). Brown and Pluck (2000) summarize goal-directed behavior as a set of related processes in which action translates internal states into goal attainment. Such a model can be described to be at the core of the current proposed role of midlife motivational ability. In particular, this model of goal-directed behavior may be linked to apathy, as its core element is reduced goal-directed behavior due to impaired motivation (Marin, 1991). As the goal-directed behavior model puts functional integration of motivational, emotional, cognitive and motor processes at its centre, this may possibly be a

further model worth investigating in the context of midlife motivational abilities as a protective factor for cognitive impairment and associated neuropsychiatric symptoms, such as apathy in particular.

Several limitations of this study must be considered. First, the sample size of n = 137 is rather small, a consequence of longitudinal data analysis of the ADAMS. However, despite this small sample, the results were statistically significant and can therefore be interpreted. Secondly, the unequal sizes of cognitive impairment groups should be mentioned. Thirdly, the O*NET-based estimate of midlife motivational abilities deserves particular attention. Estimates of pre-morbid characteristics based on educational and occupational data have a long tradition in dementia research, usually serving to estimate pre-morbid cognitive abilities. The present study was the first to apply the O*NET database on worker skills and characteristics to predict apathy and depression in MCI and AD. Although our estimate of midlife motivational abilities is not a direct measure, its validity in estimating motivational as opposed to cognitive abilities has previously been demonstrated (Forstmeier & Maercker, 2008). Further studies should implement additional measures of motivational abilities. Finally, a major limitation is the very low rates of apathy and depression in the current sample which are under the cut-off level for clinically significant symptoms. Research on apathy as a predictor of MCI to AD conversion (Palmer et al., 2010) has always implemented clinically significant symptoms. Possible explanations may be measurement error in the NPI, despite its good psychometric properties (Cummings et al., 1994; Okura et al., 2010) (being dependent on caregiver assessment and not a clinician interview), inter-rater variability in the administration, caregiver willingness to report such neuropsychiatric symptoms or caregiver misinterpretation of such neuropsychiatric symptoms as symptoms of the cognitive decline. Nonetheless, these extremely low levels were unexpected and could have influenced the current results. Also, the low rates of apathy and depression may have reduced the ability to detect a relationship between motivational abilities and apathy or depression in these cohorts.

Future research is required in which higher apathy and depression scores are used to replicate the current findings.

Despite these limitations, this study represents an important step in research on predictors of neuropsychiatric symptoms in MCI and AD. For the first time it has investigated motivational abilities as predictors of depression and apathy in AD. Further studies are needed to elucidate under which circumstances strong motivational abilities are helpful or debilitating. Insights into the mechanisms linking motivational abilities to risk of apathy and depression in MCI and AD may lead to new strategies for reducing the frequency of these symptoms.

12.6. Funding

Data collection was carried out by the Aging, Demographics and Memory Study in the USA. The National Institute on Aging (NIA) provided funding for the HRS and the ADAMS (U01 AG09740). Data analysis of this publicly available dataset was conducted at the Department of Psychology at the University of Zurich, Switzerland. This study was funded by a short mentoring grant (University of Zurich) and a University of Michigan – International Max Planck Research School on the Life Course (LIFE) grant to M. E. Mortby.

12.7. Tables and Figures

12.7.1. Table 1. Diagnoses categories and subcategories according to Aging, Demographics and Memory Study

Demented	Cognitive Impairment, Note demented	Normal Cognitive Function
Alzheimer's Disease (AD)	Mild-ambiguous	Normal/ Non-case
Probable AD	Mild Cognitive Impairment	
Possible AD	Cognitive Impairment secondary to vascular disease	
Vascular Dementia (VD)	Stroke	
Probable VD	Other Neurological conditions	
Possible VD	Other Medical conditions	
Subcortical Dementias	Depression	
Parkinson's Disease	Psychiatric Disorder	
Huntington's Disease	Low Baseline Intellect/ Mental Retardation	
Progressive Supranuclear Palsy	Alcohol Abuse (present)	
Normal Pressure Hydrocephalus	Alcohol Abuse (current)	
Other Dementias	CIND, non-specified	
Dementia of undetermined etiology		
Frontal lobe dementia		
Severe head trauma		
Alcoholic dementia		
ALS with dementia		
Hypoperfusion dementia		
Lewy Body dementia		
Post-encephalitic dementia		

Note: Table adapted from Health and Retirement Study Aging Demographics, and Memory Study (ADAMS) Supplement Early Data Release (v. 3. 0.) November 2008.

12.7.2. Table 2. Sociodemographic and medical characteristics of study participants at baseline by cognitive group (N = 137).

	Total (N = 137)	Normal (n = 48)	MCI (n = 70)	AD (n = 19)	F / χ^2	P (F / χ^2)
Age at baseline (years), M (SD)	81.3 (6.8)	77.7 (4.3)	82.7 (7.4)	85.4 (5.9)	13.92	< 0.001***
Sex						
Female, n (%)	74 (51.7)	24 (50.0)	38 (50.7)	12 (60.0)	0.64	0.726
Education (years), M (SD)	10.0 (4.6)	11.0 (4.2)	9.5 (4.8)	9.4 (4.8)	1.59	0.208
Marital status						
Single	3 (2.2)	0 (0)	2 (2.9)	1 (5.3)		
Married	55 (40.1)	27 (56.3)	24 (34.3)	4 (21.1)		
Divorced	3 (2.2)	2 (4.2)	1 (1.4)	0 (0)	14.53	0.069
Separated	2 (1.5)	0 (0)	1 (1.4)	1 (5.3)		
Widow	74 (54)	19 (39.6)	42 (60)	13 (68.4)		
Ethnicity						
White/Caucasian, n (%)	97 (70.8)	34 (70.8)	49 (70.0)	14 (73.7)		
African-American, n (%)	35 (25.5)	13 (27.1)	18 (25.7)	4 (21.1)	0.76	0.944
Other, n (%)	5 (3.6)	1 (2.1)	3 (4.3)	1 (5.3)		
MMSE score, M (SD)	23.2 (4.6)	25.9 (2.8)	22.4 (4.4)	19.0 (5.2)	21.99	< 0.001***
NPI scores at baseline						
Apathy, M (SD)	0.12 (0.64)	0.08 (0.58)	0.04 (0.27)	0.53 (1.31)	4.72	0.010**
Depression, M (SD)	0.38 (1.32)	0.25 (1.04)	0.23 (0.71)	1.26 (2.73)	5.27	0.006**
NPI scores at follow-up						
Apathy, M (SD)	0.59 (1.95)	0.21 (0.97)	0.50 (1.77)	1.89 (3.49)	5.58	0.005**
Depression, M (SD)	0.41 (1.61)	0.08 (0.35)	0.37 (1.57)	1.37 (2.93)	4.59	0.012*
Midlife motivational abilities						
Total score[a], M (SD)	-0.11 (0.90)	0.02 (0.97)	-0.14 (0.85)	-0.34 (0.89)	1.11	0.334
Low, n (%)	54 (32.8)	15 (31.3)	22 (31.4)	8 (42.1)		
Medium, n (%)	47 (34.3)	16 (33.3)	24 (34.3)	7 (36.8)	1.57	0.814
High, n (%)	45 (32.8)	17 (35.4)	24 (34.3)	4 (21.1)		
Goal Orientation	2.02 (0.82)	2.17 (0.89)	1.95 (0.76)	1.95 (0.87)	1.09	0.338
Action Planning	3.44 (1.16)	3.54 (1.19)	3.48 (1.17)	3.04 (0.96)	1.38	0.255
Midlife cognitive abilities						
Total score[a], M (SD)	0.04 (0.83)	-0.005 (0.81)	0.04 (0.86)	0.19 (0.79)	0.38	0.686

Note: [a] Composite score of z-transformed variables.
MCI = Mild cognitive impairment; AD = Alzheimer's disease; M = mean; SD = standard deviation; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory
* p < .05; ** p < .01; *** p < .001

12.7.3. Table 3. Analysis of covariance for midlife motivational abilities, cognitive group, and time explaining apathy (N = 137).

Source	*df*	F	η	p
Between subjects				
Time	1	0.37	0.003	0.543
Time x cognitive group	2	8.07	0.12	0.001***
Time x motivational abilities	2	14.61	0.19	< 0.001***
Time x cognitive group x motivational abilities	4	6.95	0.18	< 0.001***
Error (Time)	124	(1.14)		
Within subjects				
Cognitive group	2	11.11	0.15	< 0.001***
Motivational abilities	2	12.21	0.17	< 0.001***
Cognitive group x motivational abilities	4	5.05	0.14	0.001***
Error	124	(2.24)		

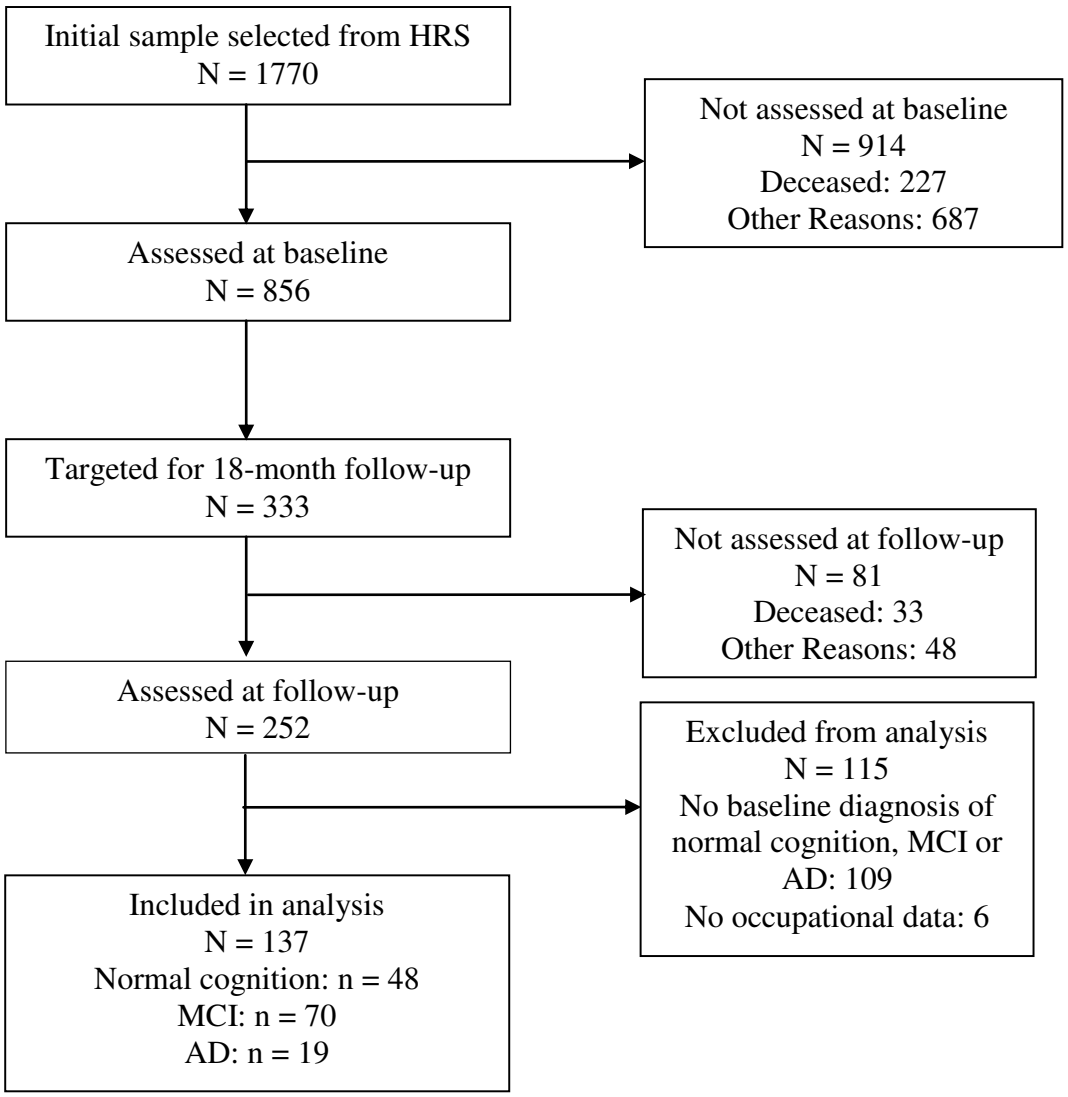
Note: Age, gender, education, and midlife cognitive abilities were controlled.
Values enclosed in parentheses represent mean square errors.
*** p < .001

12.7.4. Table 4. Analysis of covariance for midlife motivational abilities, cognitive group, and time explaining depression (N = 137).

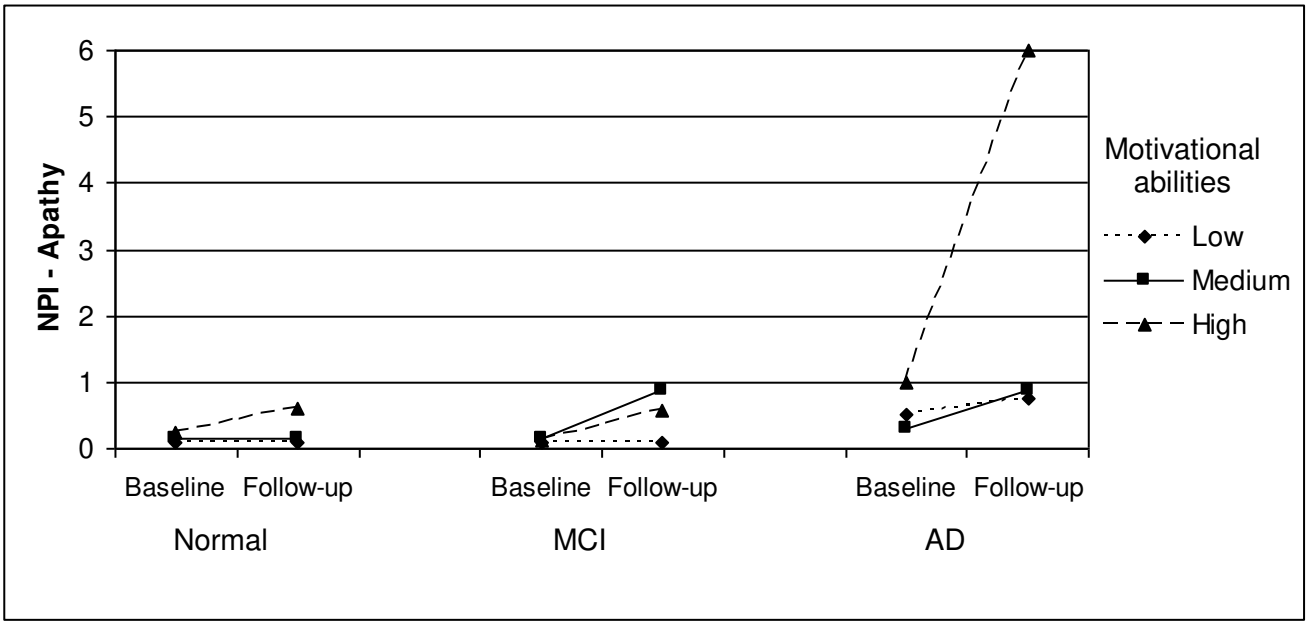
Source	*df*	F	η	p
Between subjects				
Time	1	1.97	0.02	0.163
Time x cognitive group	2	0.17	0.003	0.841
Time x motivational abilities	2	1.31	0.02	0.274
Time x cognitive group x motivational abilities	4	0.66	0.02	0.619
Error (Time)	124	(1.11)		
Within subjects				
Cognitive group	2	7.77	0.11	0.001***
Motivational abilities	2	6.39	0.09	0.002**
Cognitive group x motivational abilities	4	2.67	0.08	0.035*
Error	124	(2.81)		

Note: Age, gender, education, and midlife cognitive abilities were controlled.
Values enclosed in parentheses represent mean square errors.
*p < .05; ** p < .01; *** p < .001

12.7.5. Figure 1. Flow chart describing sample size.



12.7.6. Figure 2. Apathy over time (baseline, follow-up), for cognitive group (normal cognition, MCI, AD) and for midlife motivational abilities (low, medium, high).



Note: Subgroup sample sizes (low, medium and high motivational abilities) for each cohort are provided in Table 2.

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14. Curriculum Vitae Moyra Elizabeth Mortby, MSc

Date/ Place of Birth: 15 November 1984/ Basel, Switzerland

Nationality: British/ Swiss

Academic Career/ Education

June 2008 – May 2011 **PhD candidate** at the Department of Psychology, Division of Psychopathology and Clinical Intervention, University of Zurich, Switzerland, under the supervision of Professor Dr. Dr. Andreas Maercker.

June 2008 – May 2011 **Research assistant** at the Department of Psychology, Division of Psychopathology and Clinical Intervention, University of Zurich, Switzerland, on the project: *Motivational Reserve as protective psychological factor in mild Alzheimer's disease and mild cognitive impairment*.

August 2008 – August 2010 **External Doctoral student** with "The Life Course: Evolutionary and Ontogenetic Dynamics (LIFE)" Graduate Training program: a collaborative doctoral program between the Max Planck Institute in Berlin, Freie University Berlin, Humboldt University, University of Virginia, University of Michigan and Zurich University. LIFE speaker from 2008-2009.

May 2009 – September 2009 **Guest research stay, University of Michigan, Ann Arbor, USA** under the supervision of Professor Jacqui Smith as a voluntary component of the external doctoral program LIFE to work on the longitudinal Aging, Demographics and Memory Study.

October 2007 – March 2008 Transferable skill development (organization, leadership, communication): 6 month individual travel (Hong Kong, Australia, New Zealand and USA).

September 2006 – September 2007 **MSc in Psychological Research Methods**, Keele University, United Kingdom. A research and analytical degree, providing essential skills in research planning, conduct, analysis and evaluation using both qualitative and quantitative analytical methodology. Researcher on the project: '*The investigation of episodic memory and executive functions in visually and non-visually hallucinating Parkinson's disease patients*'.

September 2006 – September 2007	**Research Apprenticeship,** Keele University, United Kingdom. A component of the MSc in Psychological Research Methods, on the project: '*An investigation into the cognitive consequences of naturalistic hangover with focus on executive functioning in fully blinded participants*'.
September 2003 – June 2006	**BSc in Criminology and Psychology (dual honours)**, Keele University, United Kingdom. A dual honours course providing the foundation in research and theory for both subjects of criminology and psychology. For the Criminology component, a large-scale literature review on '*Electronic Monitoring: reconciling an effective measure of Community Punishment with Human Rights, Ethical Considerations, and Social Norms*' was conducted. For the Psychology component: researcher on the project '*A study investigating the role of semantic memory in supporting impaired episodic memory in a thalamic lesion patient*'.
March 2000 – June 2003	**Bilingual International Baccalaureate Certificate**, International School of Basel, Switzerland. Higher level subjects: Biology, German and History. Standard level subjects: English, Mathematical Methods and Information Technology in a Global Society.

Publications and Conference Presentations

Publications and Published Abstracts

Mortby, M. E., Maercker, A., Drobetz, R., Fankhauser, S. and Forstmeier, S. (submitted). Midlife Motivational Abilities: A Predictor of Apathy and Depression in Mild Cognitive Impairment and Early Alzheimer Disease.

Mortby, M. E., Maercker, A. and Forstmeier, S. (2011). Apathy: a separate syndrome from depression in dementia – a review. Aging Experimental Research. DOI: 10.3275/8105.

Forstmeier, S., **Mortby, M**. and Maercker, A. (2011). Kognitive Verhaltenstherapie im höheren Lebensalter: Ein Überblick. Psychotherapie im Alter, 1.

Mortby, M. E., Maercker, A. and Forstmeier, S. (2011). Midlife Motivational Abilities predict apathy and depression in Alzheimer's disease: The Aging, Demographics and Memory Study. Journal of Geriatric Psychiatry and Neurology.

Forstmeier, S., **Mortby, M**. and Maercker, A. (2011). Kognitive, behaviorale und achtsamkeitsbasierte Interventionen in der Alterspsychotherapie. In R. D. Hirsch, T. Bronisch and S. K. D. Sulz (eds.). Das Alter birgt viele Chancen – Psychotherapie als Türöffner. München: CIP-Medien.

Mortby, M. E., Maercker, A. and Forstmeier, S. (2010). Motivationale Fähigkeiten des mittleren Lebensalters als Moderator des Zusammenhangs zwischen kognitivem Status und Apathie sowie Depression. Zeitrschrift für Gerontologie + Geriatrie, Band 43, Sonderheft 1, September 2010, pg. 79.

Forstmeier, S., **Mortby, M**. and Maercker, A. (2009). Kognitive, behaviorale und achtsamkeitsbasierte Interventionen in der Alterspsychotherapie. Psychotherapie in Psychiatrie, Psychotherapeutischer Medizin und Klinischer Psychologie, 14. 2, 277-285.

Edelstyn, N.M.J., Drakeford, J.L., **Mortby, M**. and Ellis, S.J. (2007). Visual object processing, reality monitoring, reasoning and visual hallucinations in Parkinson's disease. Psychobiology Section of The British Psychological Society, Winter 2007 1, pg. 18.

Conference Presentations and Posters/ Invited talks

Forstmeier, S., **Mortby, M**., Pfeifer, L. and Maercker, A. (2011). Apathie und Motivationsregulation kognitiv beeinträchtigter älterer Menschen und das Belastungsleben ihrer Angehörigen. 7. Workshopkongress Klinische Psychologie und Psychotherapie, Berlin (2nd-4th June).

Mortby, M., Maercker, A. and Forstmeier, S. (2011). Midlife motivational abilities: Predictor of apathy and depression in dementia. 26th International Conference of Alzheimer's disease International, Toronto (26th-29th March).

Mortby, M., Maercker, A. and Forstmeier, S. (2010). Motivational Reserve: A Moderator of Apathy and Depression in Dementia in a US-Representative Sample. Gerontological Society of America (GSA) 63rd Annual Scientific Meeting, New Orleans (19th-23rd November).

Forstmeier, S., **Mortby, M**. and Maercker, A. (2010). Differential Effects of Acute Stress and Social Anxiety on Self-Control in Younger and Older People. Gerontological Society of America (GSA) 63rd Annual Scientific Meeting, New Orleans (19th-23rd November).

Forstmeier, S., **Mortby, M**. and Maercker, A. (2010). Do Midlife Motivational Abilities Predict Cognitive Decline and Alzheimer's Disease? Gerontological Society of America (GSA) 63rd Annual Scientific Meeting, New Orleans (19th-23rd November).

Mortby, M. (2010). Depressed mood in MCI and Alzheimer's disease: The role of premorbid motivational characteristics. Invited Talk at the APS PAIG Ageing Interest group of the Australian National University, Canberra, Australia (20th October).

Mortby, M., Maercker, A. and Forstmeier, S. (2010) Motivationale Fähigkeiten des mittleren Lebensalters als Moderator des Zusammenhangs zwischen kognitivem Status und Apathie sowie Depression. Deutsche Gesellschaft für Gerontologie und Geriatrie (DGGG), Berlin, Germany (15th-17th September).

Mortby, M., Maercker, A. and Forstmeier, S. (2010). Midlife motivational abilities: a moderator for apathy but not depression. LIFE Academy, Charlotteville, Virginia, USA (12th-18th May)

Mortby, M., Maercker, A. and Forstmeier, S. (2009). Pre-morbid motivational abilities and apathy and depression: predictive of the progression of dementia? Deutsche Gesellschaft für

Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), Berlin, Germany (25th-29th November).

Mortby, M., Maercker, A. and Forstmeier, S. (2009). Occupational Experience as a protective factor in later life Mental Health. Society for the Study of Human Development (SSHD), Ann Arbor, USA (18th-20th October).

Mortby, M., Maercker, A. and Forstmeier, S. (2009). Pre-morbid motivational abilities, apathy and depression in dementia. LIFE Academy, Ann Arbor, Michigan, USA (16th-20th October).

Mortby, M. (2009). Apathy: a separate syndrome from depression? LIFE Academy, Zurich (25th-29th May).

Mortby, M. (2008). Association Between Pre-morbid Motivational Abilities and Apathy and Depression in Alzheimer's Dementia: A Planned Study. LIFE Academy, Berlin (16th-20th October).

Edelstyn, N.M.J., Drakeford, J.L., **Mortby, M.** and Ellis, S.J. (2007). Visual object processing, reality monitoring, reasoning and visual hallucinations in Parkinson's disease. Proceedings of the Psychobiology Section Annual Scientific Meeting (3rd-5th September).

Scholarships and Grants

16. 03. 2009	Fakultäres Mentoring Auslands-Kurz-Mentorate and der Philosophischen Fakultät, University of Zurich to support a research stay at the University of Michigan, Ann Arbor, USA (30th May – 4th September, 2009). Grant received for CHF 2,000.
16. 03. 2009	International Max Planck Research School on the Life Course University of Michigan Grant, to support a research stay at the University of Michigan, Ann Arbor, USA (30th May – 4th September, 2009). Grant received of US$2,250.

Ad hoc Reviewer

International Psychogeriatrics

Memberships

British Psychological Society – Graduate Basis for Chartered Membership
Geriatric Society of America
International Society to Advance Alzheimer's Research and Treatment