Mindfulness and aging

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Exploring mechanisms and interventions

Lotte Berk

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Maastricht University

"Someone once told me that time
was a predator that stalked us all our lives.
I rather believe that time is a companion
who goes with us on the journey and
reminds us to cherish every moment,
because it will never come again.
What we leave behind is not as
important as how we've lived"

Jean-Luc Picard

CONTENTS

1

General introduction, thesis aims and outline

General introduction

For millennia, mortality has been the bane of humankind. The 5th century BCE historian, Herodotus described the Fountain of Youth, full of enchanted water that gave people exceptionally long life. This mythology has been mirrored in similar stories throughout history. Today, with the world population rapidly aging, and news story after news story about the coming "dementia tsunami," research institutions around the world are seeking out a cure or a way to postpone age-related cognitive decline with a focus on well-being. Mindfulness is often portrayed as one such Fountain of Youth. Not only has mindfulness gained popularity in the mainstream media, but the body of research has also expanded exponentially over the last two decades[1] (**Figure 1**).

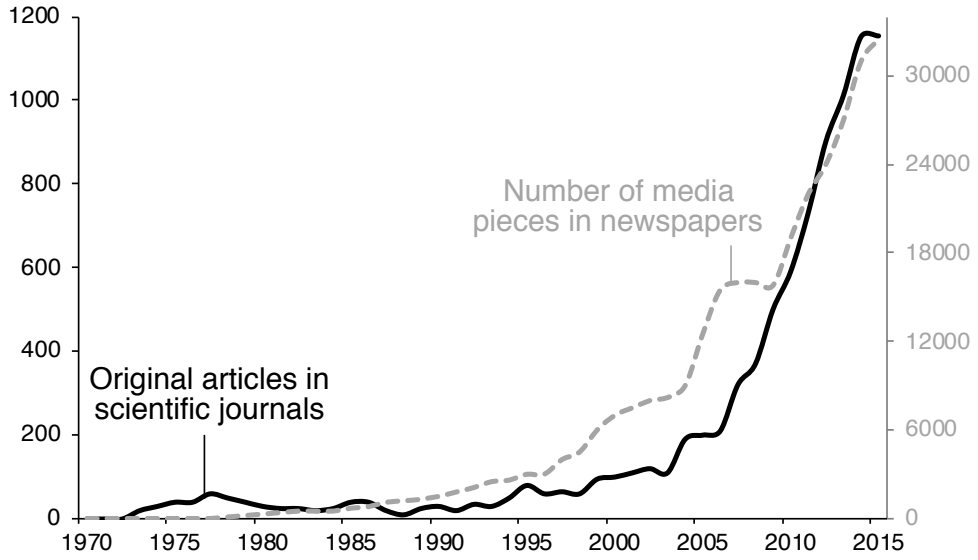

Figure 1. Scientific and news media articles on mindfulness and/or meditation by year from 1970 to 2015. Adapted from: van Dam et al., 2017

There is a growing interest in the application of mindfulness-based interventions as a preventative intervention targeting older adults. This fits with the recent shift towards "positive health," which departs from the WHO definition of health as complete well-being, and proposes a new definition of health as the ability to adapt and self-manage (**Box 1**)[2]. Mindfulness-based interventions might present a promising avenue toward the improvement of positive health.

This thesis investigates mechanisms and interventions of mindfulness and aging. In this chapter, an overview of what mindfulness is, and how it is measured is given. Further, the potential mechanisms of how mindfulness can influence aging are discussed. Finally, the aims and outline of the thesis are given.

Box 1. Definition of Health

WHO's definition of health, 1948:
Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

Proposed definition of positive health Huber et al., 2011:
Health as the ability to adapt and to self-manage, in the face of social, physical and emotional challenges.

What is mindfulness?

Mindfulness, an ancient Buddhist concept, has been described as awareness that emerges through paying attention to the present moment (attention), on purpose (intention), and in an open and nonjudgmental way (attitude)[3]. These three components (intention, attention, and attitude) are the core components of the practice of mindfulness, and occur simultaneously[4]. Mindfulness is typically cultivated in the context of an 8-week program that includes meditative exercises. A growing body of literature supports the efficacy of mindfulness-based interventions for health benefits and psychological well-being for both healthy and clinical populations[5,6]. One of the proposed mechanisms through which well-being is promoted is that, through attention and awareness, people are given a way to deal with uncontrollable negative situations, negative feelings, and stressful thoughts[3]. That is, by paying attention to thoughts, bodily sensations, and feelings, people create the space to choose how to react to stressors and prevent the onset or increase of an automatic reaction such as rumination[7]. Mindfulness can refer either to a trait (or disposition) or a state someone is in at the moment[8]. Dispositional mindfulness occurs at varying levels within the population and can be increased by mindfulness-based interventions[8,9]. Recently, a meta-analysis showed that dispositional mindfulness is associated with increased psychological health[10].

The most common mindfulness-based interventions are the Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) programs. MBSR was developed in the 1970s by Jon Kabat-Zinn to help patients cope with chronic conditions, such as chronic pain[3]. The MBSR is an eight-week program, consisting of weekly 2.5-hour long sessions. The program includes the following meditative exercises: body scan, gentle yoga, sitting meditation, and walking meditation. Participants are asked to practice for 45 minutes daily. Besides this homework, participants are invited to integrate mindfulness in their daily lives by bringing awareness to mundane activities such as brushing their teeth. A few decades later, in 2002, Zindel Segal, Mark Williams,

and John Teasdale developed MBCT by integrating components of cognitive behavioral therapy for depression into MBSR to aid recovery from depression and prevent relapse[7].

How is mindfulness measured?

Dispositional mindfulness is measured with a self-report questionnaire. There are several questionnaires to measure mindfulness. The Mindful Attention Awareness Scale (MAAS) is the most commonly used, and the Five Facet Mindfulness Questionnaire (FFMQ) is the second most used[10]. In a review of mindfulness questionnaires, the FFMQ received the highest possible rating for internal consistency and construct validation by hypothesis testing[11]. The FFMQ assesses five facets of mindfulness: *observing* refers to noticing or attending to sensory experiences, *describing* refers to describing emotions and feelings, *acting with awareness* refers to attending to one's activities in the present moment, being *non-judgmental* refers to taking a non- evaluative attitude toward one's thoughts and feelings, and being *non-reactive* refers to allowing thoughts and feelings to come and go[12,13].

As described above, mindfulness can refer to a disposition, but the state of how mindful a person is can vary from moment to moment. For example, one might be more mindful when they wake up at the beginning of the day, and less mindful when tired. One way to get insight into mindfulness state is the experience sampling method (ESM). ESM is a structured diary method for assessing subjective experiences and events at the moment they occur in their natural setting, so that ecological validity is maximized and retrospective recall biases can be avoided[14]. Moreover, with ESM, temporal relationships between variables and daily fluctuations in subjective experiences can be explored[15].

Mindfulness and aging

Cognitive decline with age is inevitable. While not all cognitive abilities decline with age, the general pattern of development is a downward slope. However, individuals can have different trajectories within this general downward trend due to different factors such as behavior, environment, and genetics[16]. **Figure 2** shows examples of individual trajectories with the same starting point, but different developments. Perhaps mindfulness-based interventions can influence one's late-life trajectory by decelerating or delaying the decline (curve C).

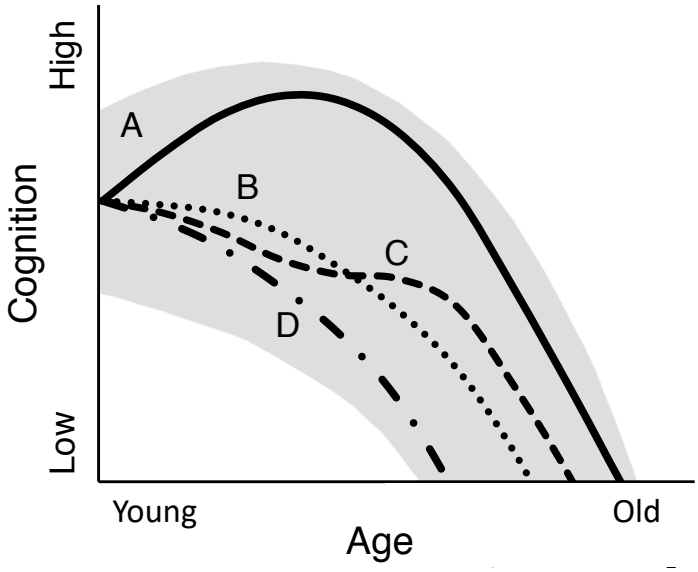

Figure 2. Depiction of the zone of possible cognitive development for a given individual (grey area). The four developmental curves (A, B, C, & D) indicating specific possible outcomes. Each possible curve has different trajectories as a function of interactions among behavioral, environmental, and genetic influences that allow vertical movement within the zone at different points in the life span. Adapted from: Hertzog et al., 2008[16]

While more methodologically rigorous studies are required, preliminary studies indicate that mindfulness meditation might reduce age-related cognitive decline[17]. These conclusions are drawn from both cross-sectional studies (e.g. comparing meditators versus controls) and longitudinal studies with differences in duration and type of meditation training. Several mechanisms have been proposed by which mindfulness may promote healthy aging. These include enhanced attentional control, preserved neural functioning, improved psychological well-being, and reduced systemic inflammation[18,19] (**Figure 3**).

One review showed that mindfulness meditation induces changes in brain structure and in the function of regions involved in regulation of attention, emotion, and self-awareness[20]. Stress reduction might be an important pathway for the beneficial effects of mindfulness meditation[21]. Recently, a meta-analysis showed that meditation reduces several physiological markers of stress, such as cortisol, C-reactive protein, tumor necrosis factor-alpha, blood pressure, and heart rate[21]. Moreover, mindfulness-based interventions in older adults may impact risk factors associated with age-related cognitive decline such as depression[22–25]. Mindfulness meditation has also corresponded with improvements in psychological well-being[5,26], although not without limitations[27].

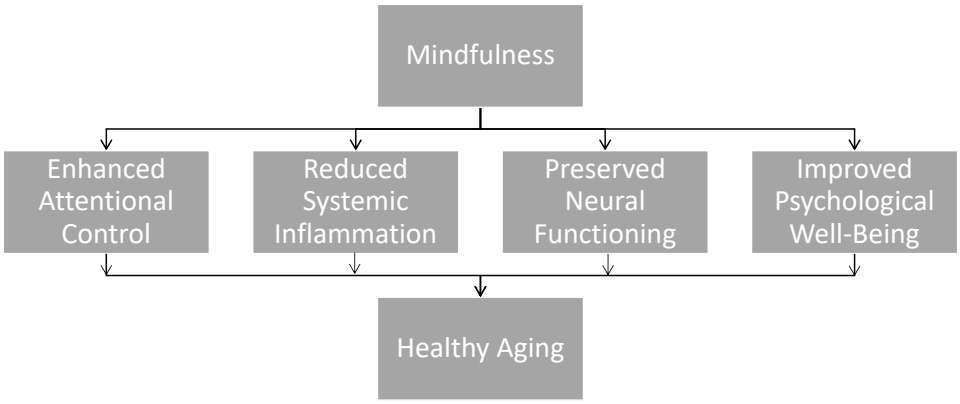

Figure 3. Schematic model for the effects of mindfulness training on healthy aging. Adapted from Fountain-Zaragoza & Prakash, 2017[19]

The Mindfulness-to-Meaning Theory proposes a mechanism by which mindfulness increases psychological well-being[28]. Through mindfulness practice, a nonjudgmental state of present-moment awareness is developed, which affects how stressful life events are interpreted. This broadened awareness, mental flexibility, and the ability to see distressing thoughts and emotions as events that will pass (instead of being the truth), reduces the negative impact of stressful events. Promoting positive emotions activates a virtuous cycle of positive psychological processes (as described in the broaden-and-build theory[29]), which increases psychological well-being[30]. Mindfulness is associated with positive emotions. People that are in a mindfulness state compared to a non-mindful state report more positive emotions[31,32]. Moreover, MBCT increases momentary positive emotions[33]. However, more research is needed to get insight into the interplay of mindfulness and positive affect.

Age is the biggest risk factor for the development of dementia, and with the world population aging, the prevalence of dementia is increasing[34]. Mindfulness-based interventions might be able to help people with dementia and their caregivers after a dementia diagnosis, a time filled with stress and uncertainties of the future. Studies have shown that mindfulness-based interventions are feasible and improve the mental health of caregivers of persons with dementia[35–37]. Mindfulness-based interventions that include both persons with dementia and caregivers also show feasibility and improvement in quality of life[38,39]. More research is needed to investigate whether people with dementia and their caregivers could participate as a dyad in one group together, and whether they benefit from this type of intervention.

Thesis aims and outline

The general aim of this thesis is to gain insight into the mechanisms of mindfulness on aging, to assess how mindfulness fluctuates in daily life and if it can be boosted with brief exercises. Moreover, this thesis explores a mindfulness-based intervention to support people with dementia and their caregivers. The following questions will be addressed:

Part I Mechanisms

Can mindfulness-based interventions influence cognitive functioning in older adults?
Chapter 2 provides a systematic literature review on whether mindfulness-based interventions can influence cognitive functioning in older adults. This review discusses potential mechanisms and current available evidence.

Does positive affect predict cognitive decline?
In **Chapter 3** we study the association between positive affect and cognitive decline. Positive affect was measured at baseline and memory, executive function and information processing speed were assessed over a twelve-year period in participants from the Maastricht Aging Study.

Is dispositional mindfulness associated with inflammation and with diabetes-related distress?
In **Chapter 4** we investigate the association between dispositional mindfulness and low-grade inflammation in participants from the Maastricht Study. This association is examined in participants with and without type 2 diabetes, and we examined which components of mindfulness drive this association. Moreover, we investigated whether higher mindfulness might be associated with less diabetes-related distress in participants with diabetes.

Is a mindful state associated with positive affect in daily life, and do short exercises influence this?
In **Chapter 5**, experience sampling method is used to investigate how mindfulness state might fluctuate in daily life and how this is associated with positive affect. Additionally, we looked at the items that were used to measure mindfulness to get insight into which in particular were predictive of positive affect in the next moment. Furthermore, we studied the effect of brief mindfulness exercises on mindfulness state.

Part II Interventions

Is a mindfulness-based intervention feasible for individuals with subjective memory problems?

Chapter 6 describes a mixed-method study to investigate whether the 8-week mindfulness-based stress reduction is feasible in older-adults with subjective memory problems. Interviews with participants were conducted to get insight into the benefits and barriers of the intervention, and whether adjustments should be made.

What is the current available evidence for the use of mindfulness-based interventions in people with dementia and their caregivers?

Chapter 7 gives an overview of existing literature on mindfulness-based interventions for caregivers and people with dementia and mild-cognitive impairment, and to gain insight into whether caregivers and people with dementia could participate together in a group.

Is a mindfulness-based intervention for people with dementia and their caregivers feasible and effective?

In **Chapter 8** we describe a mixed-methods study of an 8-week program, based on the mindfulness-based stress reduction (MBSR) training, for people with dementia and their caregivers together. The interviews conducted with the participants informed us about the effects of the training, and the experience of participating in the training in a group as a couple.

Chapter 9 describes the main findings of this thesis and provides a general discussion.

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Part I
Mechanisms

2

Can mindfulness-based interventions influence cognitive functioning in older adults? A review and considerations for future research

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Martin van Boxtel
Jim van Os

Aging & Mental Health, 2017

Abstract

Objectives An increased need exists to examine factors that protect against age-related cognitive decline. There is preliminary evidence that meditation can improve cognitive function. However, most studies are cross-sectional and examine a wide variety of meditation techniques. This review focuses on the standard 8-week mindfulness-based interventions (MBI) such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT).

Method We searched the PsychINFO, CINAHL, Web of Science, COCHRANE, and PubMed databases to identify original studies investigating the effects of MBI on cognition in older adults.

Results Six reports were included in the review of which three were randomized controlled trials. Studies reported preliminary positive effects on memory, executive function and processing speed. However, most reports had a high risk of bias and sample sizes were small. The only study with low risk of bias, large sample size and active control group reported no significant findings.

Conclusion We conclude that 8-week MBI for older adults are feasible, but results on cognitive improvement are inconclusive due a limited number of studies, small sample sizes, and a high risk of bias. Rather than a narrow focus on cognitive training per se, future research may productively shift to investigate MBI as a tool to alleviate suffering in older adults, and to prevent cognitive problems in later life already in younger target populations.

Introduction

A growing body of literature supports the efficacy of mindfulness-based interventions (MBI) in promoting health benefits and psychological well-being for both healthy and clinical populations[1,2]. Recently, the potential of MBI to contribute to successful aging has gained interest, also in the context of dementia prevention by targeting stress and other risk factors. This interest was sparked by research in young adults suggesting that mindfulness training could benefit cognitive functioning (see review[3]). Studies on the effects of meditation on age-related cognitive decline reported effects on attention, memory, executive function, processing speed, and general cognition[4]. However, these studies involved a variety of meditation techniques and had a cross-sectional design, making it hard to draw firm conclusions.

There are several pathways by which MBI can influence cognitive aging (**Figure 1**). There is preliminary evidence that stress influences the biological aging process[5]. Several studies have shown association between MBI, stress, arousal (e.g. high cortisol) and cellular aging[6]. Mindfulness meditation may result in increased telomerase activity[7]. Telomerase enzyme activity influences telomerase length, which is associated with health and mortality[5]. Moreover, a randomized controlled trial showed that a Mindfulness-Based Stress Reduction (MBSR) program in lonely older adults down-regulated pro-inflammatory gene expression[8]. MBI in older adults may also impact other risk factors associated with age-related cognitive decline such as depression[9–12] and vascular risk factors, such as hypertension[13]. Mindful meditation may influence brain structure and function[14] and a review reported some evidence that meditation may slow down age-related brain degeneration[15]. Recently, a study showed reduced age-related degeneration of the hippocampal subiculum, an area known to show reduction of gray matter with normal aging, in long-term meditators[16]. Moreover, a study on adults with Mild Cognitive Impairment (MCI) reported that participants in a MBSR program showed increased functional connectivity in the default mode network compared to control participants[17]. In addition, MBSR participants showed a trend towards less bilateral hippocampal volume atrophy than controls. These preliminary results, that require replication and systematic review, indicate that in adults with MCI, MBSR may have a positive impact on the regions of the brain most related to MCI and Alzheimer disease. Some studies also report indirect evidence by investigating the protective effect of trait mindfulness. For example, the negative effect of life stress on mental health was weakened for those individuals with higher levels of trait mindfulness[18].

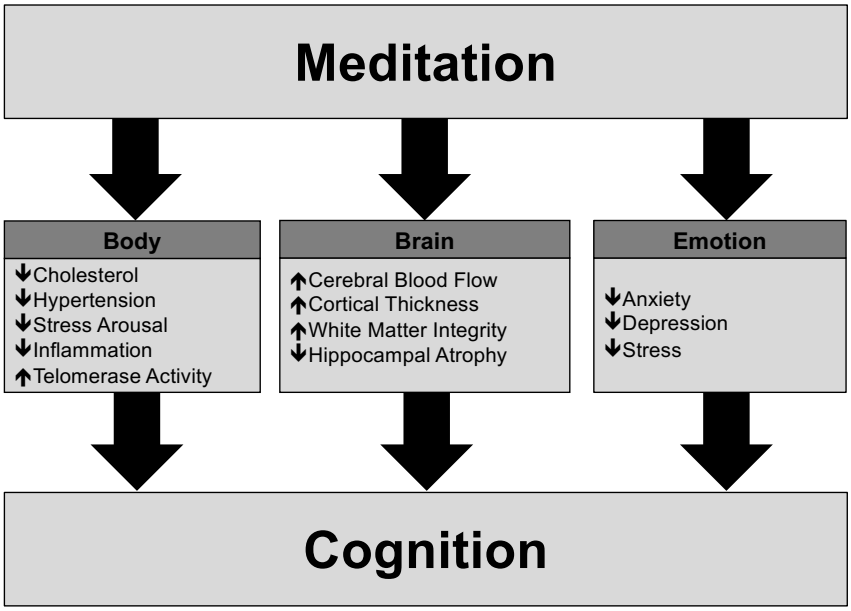

Figure 1. Schematic model for the effects of meditation on cognition. Adapted from Marciniak et al. (2014).

Even though these early reports suggest preliminary evidence that meditation can influence age-related cognitive decline, it remains unclear what can be expected from a standard 8-week mindfulness-based intervention such as MBSR and Mindfulness-Based Cognitive Therapy (MBCT), which have typically been used in health research. Both of these 8-week programs cultivate mindfulness, an ancient Buddhist concept described as awareness that emerges through paying attention to the present moment, in an open and nonjudgmental way[19]. MBCT was developed from MBSR and includes more information on depression and cognitive therapy-based exercises. The MBSR/MBCT training consists of eight group meetings lasting two and a half hours each, plus one full day during the sixth week of the course. Both trainings incorporate the following formal meditative exercises: body scan, gentle yoga, sitting meditation, and walking meditation[19,20].

This review focuses on these two interventions (MBSR; MBCT) because they have been the most widely studied methods to induce mindfulness in clinical and nonclinical samples[21], involve a systematic approach, have a standard protocol, are accessible, and give attention to practical application in daily life. First, we report our review of research on MBI and cognition in older adults. Then, we discuss the potential of MBI to contribute to successful cognitive aging.

Methods

Eligibility Criteria

For inclusion in the review, studies were required to have used MBSR or MBCT as intervention. Minor adjustments in session time to accommodate an older population were allowed as long as the training remained 8 weeks. Studies in peer-reviewed journals with samples with a mean age of 65 years or older, that used cognitive tasks as outcome measures were included. These eligibility criteria were assessed first at the level of the title, then the abstract, and finally the full article.

Study search and selection

The electronic databases Pubmed, PsychINFO, CINAHL, Web of Science and Cochrane Library, from the first available date until August 24, 2016, were used to search for relevant literature. The search included the following terms [("aging") AND ("MBSR" OR "MBCT" OR "mindfulness")]. The term "cognition" was not used for the search to include papers which did not focus on cognition but did report on cognitive test outcomes. In addition to database searches, additional relevant studies were identified from the reference lists of examined articles. **Figure 2** represents a flow diagram of the study selection process according to the Consort statement 2010 (www.consort-statement.org).

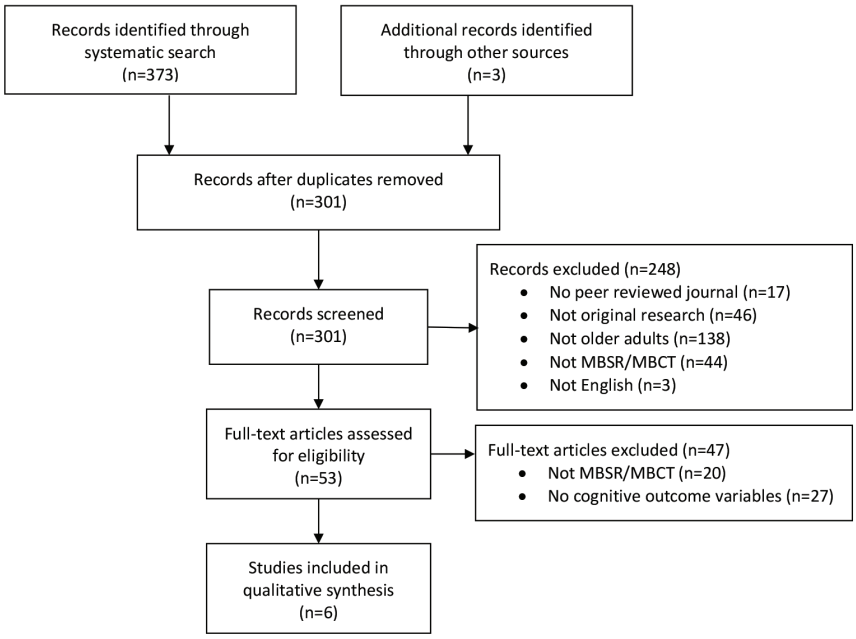

Figure 2. Flow diagram review

Data extraction and risk of bias assessment

A summary of the data extraction of the reviewed studies is shown in **Table 1**. Risk of bias was assessed with the Cochrane Risk of Bias Tool[22] (**Table 2**). Data extraction was conducted by L.B. The risk-of-bias evaluation was conducted by L.B and M.v.B.; for all ratings, a consensus was reached.

Results

The literature search resulted in a total of 373 records, 370 through the databases (Pubmed 62, PsychINFO 77, CINAHL 17, Web of Science 23, Cochrane Library 191), and three through cross-referencing the examined articles. After screening and full-text assessment, six studies were selected for final review. **Table 1** presents characteristics of these studies.

Ernst et al. (2008) investigated the feasibility and effects of MBSR on nursing home residents in Germany[23]. Cognitive state was assessed pre- and post-intervention with the Mini-Mental State Examination (MMSE[24]). Other outcome variables were health-related quality of life (Short-Form General Health Survey; SF-12[25]), depressive symptoms (Geriatric Depression Scale Residential; GDS-12R[26]), activities of daily living (Barthel Index[27]), and visual analogue scales of satisfaction with life, physical pain and major complaints. A semi-structured interview was conducted at the end of the course to inquire which elements of the course were helpful and which ones were difficult, and whether the course had been a strain on the participant.

This non-randomized study included fifteen participants (mean age: 80 years) in the MBSR group and seven participants (mean age: 89 years) in the non-intervention group. The intervention group was self-selected: those who wanted to participate could, and those who were only willing to participate for the assessments were the non-intervention group. The MBSR was adjusted by shortening the sessions from 120 min to 90 min, and the physical exercises were simplified to be less strenuous for the elderly participants. Also, the homework assignments were reduced and there was no full day retreat. Nine out of fifteen participants completed the MBSR course.

Change score of outcome measures were compared for the completers of the MBSR group and the non-intervention group. The MBSR group showed significant improvements in health-related quality of life and depressive symptoms. The non-intervention group had more major complaints at baseline than the MBSR group and showed a decrease of major complaints to the level of the MBSR group.

The MMSE score did not show a significant difference, however the score stayed the same in the MBSR group (pre and post score: 29) and decreased in the non-intervention group (pre: 27; post 24).

As acknowledged by the authors, several limitations were apparent. The groups were self-selected, there were demographic differences between the groups at baseline (age, nursing status and major complaints), no active control group, and attrition was relatively high (40%) in the MBSR group.

Lenze et al. (2014) studied the effects of MBSR on mindfulness, worry, and cognition in older adults with anxiety-related distress and subjective cognitive dysfunction[28]. Thirty-four participants (mean age: 71 years) were assigned to either a standard 8-session MBSR group or to an extended 12-session MBSR group. The retreat day was shortened to one-half day and the intensity of the yoga was reduced. Pre- and post-intervention measurements were carried out. A follow-up at 3 and 6 months after completion was conducted to assess continued use of MBSR techniques. A cognitive battery assessed memory and executive function. Verbal memory was measured with the immediate and delayed list and paragraph recall tests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS[29]) and California Verbal Learning Test (CVLT[30]) Executive function was measured with the Delis-Kaplan Executive Function Scale (DKEFS) verbal fluency test[31]. The RBANS digit span test and DKEFS color-word interference test were administered only for half of the participants and then discontinued. There were no significant differences between the 8-session and 12-session MBSR participants and the scores of both groups together were reported. Participants showed a significant improvement on list delayed recall, paragraph immediate recall, paragraph delayed recall, verbal fluency, and color-word interference. No significant changes were found for list learning and digit span test. Participants showed significant improvements in worry severity (Penn State Worry Questionnaire-Abbreviated; PSWQ-A[32]) and mindfulness using the Cognitive Affective Mindfulness Scale-Revised (CAMS-R[33]) but not on the Mindful Attention Awareness Scale (MAAS[34]). The drop-out rate was low (6%). The majority of participants reported continued use of mindfulness techniques at 3 and 6-month follow-up.

Table 1. Characteristics of studies

Author (year)	Design	ITT N (%male)	Completers N (%ITT)	Population	Mean age (SD)	Intervention	Cognitive tests findings	Other findings
Ernst et al. (2008)	Not Random Two groups; MBSR and CON Two time points: Pre- and post-intervention measurements	EXP: 15 (20) CON: 7 (43)	EXP: 9 (60) CON:7 (100)	Nursing home residents	EXP: 80[a] CON: 89[a]	MBSR Adjustments: -No retreat, -90 min sessions -Physical exercises simplified -No obligatory time for homework set -Possibility of practice in group twice a week CON: No intervention	No sign. differences between groups: -MMSE	Sig. greater improvement in physical health (SF-12), depression (GDS-12R), and severity of major complaints
Lenze et al. (2014)	Two EXP groups: 8wk and 12wk (only 8 wk results reported here) Two time points: Pre- and post-intervention measurements Pre, midway, post, 3 month and 6 month FU for clinical	EXP(8wk): 16 (31) EXP(12wk): 18 (22)	EXP(tot): 32 (94)	65+ with worry symptoms and subjective cognitive dysfunction	EXP(8wk): 70.9(4.5) EXP(12wk): 70.7(4.9)	MBSR (8wk and 12wk) -Half day retreat -Reducing intensity of yoga CON: No Control group	No sign. differences pre- and post-intervention: -List learning -Digit span test* Sign. improvement post-intervention: -List delayed recall -Paragraph immediate recall -Paragraph delayed recall -Verbal fluency -Color-word interference* *half of participants completed these tests	Worry reduction (PSWQ-A), Increased mindfulness (measured by CAMS-R, but not MAAS), Feasibility (attendance, satisfaction rating)
Mallya et al. (2015)	RCT Two groups: MBSR and CON Pre- and post-intervention measurements	EXP: 57 (23) CON: 40 (30)	EXP: 53 (91) CON: 33 (70)	65+ healthy	EXP: 68.8(4.6) CON: 69.7(4.9)	MBSR Adjustments: -Half-day retreat -30min instead of 40min daily homework CON: Active control (reading and relaxation)	No sign. differences pre/post between groups: MMSE CVLT-LDFR TMT A TMT B COWAT-FAS COWAT-Animal	MAAS (CON>EXP) PSS (ns) Depression GDS (ns) QoL (EXP>CON) RSES (ns)

Table 1. (continued)

Author (year)	Design	ITT N (%male)	Completers N (%ITT)	Population	Mean age (SD)	Intervention	Cognitive tests findings	Other findings
Moynihan et al. (2013)	RCT Two groups: MBSR and CON Four time points: Pre- and post-intervention, 3 weeks later, 21 weeks later	EXP: 108 (38) CON:111 (38)	EXP: 105 (97) CON:103 (93)	Older adults	EXP: 73.3(6.7) CON: 73.6(6.7)	MBSR Adjustments: -120 min sessions -Adjusted yoga CON: Waiting List	Trail B/A Ratio: EXP sign. better than CON at post-intervention but not at FU1 or FU2	CES-D-R (*ns*) PSS (*ns*) MAAS (EXP>CON) Greater alpha asymmetry EXP Antibody response (EXP higher at FU1, but lower at FU2)
O'Connor et al. (2014)	Not randomized Two groups: MBCT and waitlist control Three time points: Pre- and post-intervention, and 5 month FU	EXP: 18 (28) CON: 18 (33)	EXP: 12 (67) CON: 18 (100)	Elderly bereaved people with loss-related distress	EXP: 76.7(4.5) CON: 77.0(4.1)	MBCT Adjustments: -120 min sessions -Psychoeduction on general negative affect instead of depressive symptoms -Booster session at 3 and 6 months -post-intervention CON: Waiting List	Letter number sequencing (trend EXP improved)	BDI (EXP improved compared to CON) HTQ (*ns*) ICG-R (*ns*)
Smart et al. (2016)[b]	RCT Two Groups: MBSR and psychoeducation (CON)	SCD: 23 (61) HC: 15 (27)	SCD: 22 (96) HC: 15 (93)	Older adults with and without SCD	SCD: 10.0 (3.45) HC: 69.60 (3.58)	MBSR Adjustments: 120min sessions CON: Psychoeducation on cognitive aging	No sign. differences between groups: Go/NoGo RT Go/NoGo accuracy EXP but not CON reduced: Go/NoGo RT IIV	P3 ERP (EXP>CON) CCI (*ns*) FFMQ-A (*ns*) GDS (*ns*) Memory self-efficacy (*ns)* PVBC (EXP>CON)

BDI: Beck Depression Inventory: CAMS-R: Cognitive Affective Mindfulness Scale-Revised; CCI: Cognitive Complaints Index comprised of complaints items from the GDS, Memory Complaints Questionnaire and Metamemory in Adulthood Questionnaire; CON: Control Group; COWAT: Controlled Oral Word Association Task; CVLT-LDFR: California Verbal Learning Test- Long Delay Free Recall; EXP: Experimental Group; FFMQ-A: Mindful Attention composite from Five Facet Mindfulness Questionnaire subscales Observe, Describe, and Act with Awareness; FU: Follow-up; GDS: Geriatric Depression Scale; GDS-12R: Geriatric Depression Scale Residential; HC: Healthy Control; HTQ: Harvard Trauma Questionnaire; ICG: Inventory of Complicated Grief –Revised; ITT: Intention to treat; MAAS: Mindful Attention Awareness Scale; MBCT: Mindfulness-Based Cognitive Therapy; MBSR: Mindfulness-Based Stress Reduction; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; *ns*: no significant difference between groups; PVBC: Percent Brain Volume Change; PSWQ-A: Penn State Worry Questionnaire-Abbreviated; QOLS: Quality of Life Scale; RCT: randomized controlled trial; RSES: Rosenberg Self-Esteem Scale; SCD: Subjective Cognitive Decline; SF-12: Short-Form General Health Survey; TMT: Trail Making Test.

[a]Median age, SD not available.

[b]This study compared healthy controls (HC) and SCD in both MBSR and CON. Only demographics per HC and SCD were reported, but results are shown for comparison MBSR with CON only.

Table 2. Risk of Bias Summary

Author (year)	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Treatment fidelity	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Ernst et al. (2008)	N/A	N/A	?	?	?	-	?
Lenze et al. (2014)	N/A	N/A	-	+	?	+	-
Mallya et al. (2015)	+	+	+	+	+	+	?
Moynihan et al. (2013)	+	?	?	+	?	+	-
O'Connor et al. (2014)	-	-	-	?	?	+	?
Smart et al. (2016)	?	+	-	?	?	+	?

? = Unknown risk; + = Low risk; - = High risk.

The major limitation of this study is the lack of a control group. There is a strong possibility that the neuropsychological testing with an 8-week interval was biased by practice effects. Moreover, the use of different tests for different groups makes the analysis complex and choosing to drop a test for half the participants but reporting the results for half the group may introduce bias.

Mallya et al. (2015) investigated the effects of MBSR on cognitive functioning and wellbeing in healthy older adults[35]. Participants were randomly assigned to either MBSR (n=57, mean age: 68.8 years) or an active control group (n=40, mean age: 69.7 years). The active control condition consisted of a reading component and relaxation component, and had the same number of sessions and homework as MBSR. Several cognitive domains were assessed. Global cognitive function was assessed using MSSE[24] to compare the groups at baseline. Executive function was assessed with the Trail Making Test (TMT) A and B[36]. Verbal fluency was assessed with Controlled Oral Word Association Task (COWAT[37]). Other measurements included Mindful Attention Awareness Scale (MAAS[34], Perceived Stress Scale (PSS[38]), the Geriatric Depression Scale (GDS[39]), Quality of Life Scale (QOLS[40]), and the Rosenberg Self-Esteem Scale (RSES[41]). Controlling for sex, education, and age, data were analyzed separately for the intention-to-treat (ITT) participants and the participants who completed the training (i.e. per protocol treatment (PPT)). The completion rate was marginally higher (but not significantly different) for the MBSR group (91%) than the active control group (70%). No significant differences were found on the cognitive scores in either the ITT or PTT analyses, although there was a trend for MBSR completers to improve performance on the delayed recall compared to active control. Also, no changes on the measurements of wellbeing were found. The authors suggested that these null-findings could be attributed to ceiling effects, given that the participants were healthy, high-functioning older adults. Perhaps there was no room for improvement in this sample, and the beneficial effects of MBSR only apply to those with high levels of distress.

This study is one of two randomized controlled trials (RCT) in the review with an active control group. The active control group was to control for nonspecific effects. However, the progressive muscle relaxation used in the control group requires attention and awareness, and may have some overlap with the MBSR program. Another limitation of the study is omission of an additional wait list control group for better comparison with previous studies. Despite these minor limitations, this study was the first well-designed and controlled study in healthy older adults.

Moynihan et al. (2013) studied the effects of MBSR on executive function, frontal alpha asymmetry and immune function in older adults[42]. Other measurements included mindfulness (MAAS[34]), perceived stress (PSS[38]) and depression, assessed with the Center for the Epidemiologic Studies Depression Scale-Revised (CES-D-R[43]). Executive function was assessed using the TMT B/A ratio. Participants (n=201) were randomized into an MBSR (mean age: 73.3 years) or waitlist control group (mean age: 73.6 years). The MBSR participants showed improved executive function with a significantly lower TMT B/A ratio compared to the control group at post-intervention but not at the 3-week or 24-week follow-up. No significant differences in trails A or B were found at any of the time points. The MBSR group had higher MAAS scores after the intervention ($p=0.023$) and at follow-up 24 weeks later ($p=0.006$). The immune response (measured by antibody response after antigen challenge) of the MBSR participants was greater than the control group immediately after the intervention. Contrary to the hypothesis, the MBSR group's immune response was lower 24 weeks after intervention.

This was the first RCT with a large sample of older adults, but it has some limitations. The study did not include an active control group and the control group differed from the MBSR group at baseline; scoring lower on perceived self-control and depression scores, and higher on mindfulness.

O'Connor et al. (2014) investigated the effects of mindfulness-based cognitive therapy (MBCT) on depressive symptoms (Beck Depression Inventory[44]), posttraumatic stress (PTSS; measured with Harvard Trauma Questionnaire – Part IV[45]), complicated grief (Inventory of Complication Grief – Revised[46]) and working memory (letter-number sequencing[47]) in elderly bereaved people with long-term bereavement-related distress[48]. These outcome measures were assessed pre- and post-intervention and 5 months after intervention. This non-randomized pilot study enrolled 18 participants in the MBCT group (mean age: 76.7 years) and 18 participants in a wait-list control group (mean age: 77.0 years). Twelve participants (67%) of the MBCT group completed the intervention, no significant differences were found between completers and intention-to-treat (ITT). A significant increase in working memory was found post-intervention

for the MBCT group, but not the waitlist group. This difference disappeared at 5-month follow-up. Furthermore, depressive symptoms decreased for the MBCT group, and not for the wait-list control group, at the 5-month follow-up, but not immediately after the intervention. No significant differences were found for PTSS or complicated grief scores.

This pilot study shows promising results in terms of improved working memory, but without lasting effects after the intervention. The authors note that most participants discontinued daily formal mindfulness practice, which may be the reason for the lack of persistence. One of the limitations of this study is that it is non-randomized due to practical reasons: the MBCT group consisted of persons living close to the place where the intervention took place.

Smart et al. (2016) investigated the feasibility and effects of MBSR on cognitive electrophysiology (P3 event-related potential (P3 ERP) component), attention, structural magnetic resonance imaging (MRI), and psychological functioning on older adults with and without subjective cognitive decline (SCD)[49]. This randomized controlled study included 15 older adults with SCD (mean age: 69.6) and 23 without SCD (mean age: 70.0). Two participants (one of each group) failed to complete the intervention and post-testing due to health reasons, bringing the total to 36 participants. Both groups were randomized to either 8-week MBSR or a 5-week psychoeduction program on cognitive aging. The assessment took place within four weeks before intervention and within two weeks after intervention. EEG was taken during the Go/NoGo task. The behavioral measures from this task (reaction time, accuracy and reaction time intra-individual variability (RT IIV) were measured. RT IIV was used to assess attention regulation and been proposed as an indicator of future pathological cognitive decline[50]. The self-report measures included an index of cognitive complaints from combined items of GDS, Memory Complaints Questionnaire[51], and items from the Metamemory in Adulthood Questionnaire[52]. Moreover, depression was assessed using the items on the GDS that were not cognitive complaints. Memory self-efficacy was assessed using the Memory Self-Efficacy Questionnaire[53]. Attention regulation was assessed with the three subscales from the Five Facet Mindfulness Questionnaire (FFMQ[54]) namely Describe, Observe and Act Aware. The structural MRI was used to measure percent brain volume change pre/post-intervention. This study compared both the interventions (MBSR or psychoeducation) and the groups (SCD or healthy control). Participants showed a reduction in cognitive complaints and depression, regardless of the intervention type. Mindfulness attention did not change after either intervention. Memory self-efficacy increased for SCD and decreased for the healthy controls after both interventions. Participants with SCD receiving MBSR, but not PE, showed increase P3 amplitude post-intervention, approximating scores of healthy controls. The behavioral results of the

Go/NoGo task showed that there was no effect on RT, and an increase in accuracy for all participants. Importantly, all MBSR participants showed a reduction in Go/NoGo RT IIV, indicating an increased ability in moment-to-moment regulation of attention. The authors suggest that being able to better regulate attention might compensate for memory difficulties in older adults with cognitive decline. The structural MRI with a subset (PE n=6, MBSR n=8) showed increase in brain volume in the MBSR group.

This pilot study is the only other RCT discussed in this review with an active control group (PE). It demonstrated the feasibility of MBSR with older adults with and without SCD. Attention regulation was improved in all MBSR participants. This well-designed study, including a rigorous screening process, can serve as an example for future studies with the addition of a follow-up assessment to see whether the observed changes remain stable in the long term.

Discussion

Summary

We reviewed six studies investigating the effects of MBI on cognition in older adults. The studies reported a variety of neuropsychological tests to measure global cognitive function, executive function and memory.

Tests that were used by more than one study were the MMSE[23,35], verbal fluency[28,35], and the TMT[35,42,55]. No effects on the MMSE were found. Lenze et al. (2014) reported improvements post-intervention on verbal fluency, however there was no control group. The RCT by Mallya and Fiocco (2015) did not report significant findings on verbal fluency. They also did not find significant differences on the TMT, however Moynihan et al. (2013) reported significant changes on the TMT (only when using the B/A ratio) at post-intervention compared to control. This difference disappeared at follow-up after 3 and 21 weeks[42]. Other findings include a trend of post-intervention improvement compared to controls on working memory[48] and improved regulation of attention[49]. Most neuropsychological tests did not show any differences between intervention and control groups. Although Lenze et al. (2014) reported significant improvement on several tests, but this study did not include a control group.

Three of the six reviewed studies were RCTs[35,42,49]. Most of the studies were conducted as pilot projects and can be interpreted as evidence of feasibility of MBI interventions in older adults. It was demonstrated that no major adjustments to the standard protocol of MBSR/MBCT are necessary. Also, there is no support for the notion that increasing the length of the intervention is beneficial[28].

The study with the highest quality showed no differences between MBSR and the active control group on several cognitive measures[35]. However, the sample consisted of high functioning adults and therefore ceiling effects cannot be excluded. One of the strengths of this study was the inclusion of an active control group, however some of the exercises had overlap with the mindfulness exercises (e.g. relaxation). It may be productive for future studies to compare MBI with a group-based psychoeducation intervention such as used by Smart et al. (2016). The Mallya and Fiocco study (2015) can serve as an example of how future studies may be conducted, extending the sample to populations of older adults with cognitive complaints or depressive symptoms. For example, a meta-analysis showed significant effects of MBCT in individuals with elevated levels of depression and anxiety, but smaller effects in non-clinical populations[56]. Of course, it remains to be examined if this holds for cognitive outcomes in older adults. Regarding cognitive complaints, Smart et al. (2016) showed in a well-designed pilot study that older adults with subjective cognitive decline reported less cognitive complaints and increased memory self-efficacy following MBSR. Future studies that incorporate follow-up and larger samples will show whether these effects are robust.

Limitations

Several problems with these studies were identified. Most studies had a high risk of bias ratings. Only one study[35] had more 'low' risk bias ratings than 'unclear' or 'high' risk (**Table 2**). Different neuropsychological tests were used, and most did not include an elaborate battery of tests or used measures that were not very sensitive (e.g. MMSE), making it difficult to draw conclusions. Lack of statistical power is another problem. According to a review on MBSR trials, 33 participants per group are required in a two group design to achieve an 80% chance of detecting medium-to-large treatment effects[57]. Only two of the six studies in this review have a sample size that can be considered adequate. Moreover, only two studies used an active control group. The studies included different groups of older adults, ranging from healthy individuals to people with cognitive complaints or bereaved individuals with loss-related stress.

Conclusions

This review highlights the need for more rigorous studies that examine the effect of a standard 8-week MBI on cognition in older adults, because current evidence is not sufficient to draw a conclusion. Feasibility and acceptability have been demonstrated, and the shift has to be made toward well-designed studies to advance knowledge in this area. The use of a standardized intervention format, active control group, large sample size and extensive neuropsychological test battery is recommended.

It is recommended that future studies on cognitive functioning also include measurements on daily life functioning. Improved performance on a neuropsychological test might not always be indicative of improved functioning in daily life. That is, other studies on cognitive training with older adults have shown small effects, and the problem is that even though individuals may score higher on a test, this may not impact daily life functioning in any way. The strength of MBI may not necessarily lie in improving objective cognitive performance but in how people relate to their cognitive problems in daily life situations, to what extent wellbeing improves and how individuals are helped in making better life style choices. There is growing evidence of improved wellbeing in older individuals after MBI, such as substantial reductions of emotional stress in older adults with depression and anxiety after MBSR[9]. Future research could focus on the mechanisms of this process to get a deeper understanding of why and for whom this intervention may be beneficial. For example, the experience sampling method[58] may be used to investigate the effect of MBI on stress reactivity.

Regular meditation over a prolonged period of time may have a protective effect on cognitive aging[15,59]. Prevention in the preclinical stage may be the most effective way to decrease the incidence of age-related cognitive decline. MBI could work at two different stages of life. The first would begin early in life as prevention, possibly slowing down age-related cognitive decline by affecting brain network efficiency (brain reserve) and making healthy life style choices. The second approach would deploy MBI at a later stage in life, to reduce suffering in response to mental symptoms that may come with getting older. Moreover, MBI has the advantage of being inexpensive, and easy to teach and perform. However, in order to substantiate such supposed benefits of MBI, more well-designed studies with standardized protocols are required.

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3

Positive affect and cognitive decline: a 12-year follow-up of the Maastricht Aging Study

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Abstract

Objective In cross-sectional studies, positive affect (PA) has been associated with higher levels of cognitive functioning. This study examined whether positive affect (PA) is associated with change in cognitive function over 12 years in an adult population sample.

Methods Participants (n=258), aged 40 to 82 years, were drawn from a subsample of the Maastricht Aging Study (MAAS) and assessed at baseline, 6 years and 12 years. PA was measured at baseline with a Dutch translation of the Positive and Negative Affect Schedule (PANAS). PA scores and associations with cognitive decline were tested in random-effects models.

Results Controlling for demographics and depressive symptoms, there was no significant association with PA scores and decline in memory (χ^2=1.52; df=2; P=0.47), executive functions (χ^2=0.99; df=2; P=0.61) and information processing speed (χ^2=0.52; df=2; P=0.77) at 6- and 12-year follow-up.

Conclusions PA did not predict cognitive change over time. These findings question the extent of protective effects of PA on cognitive aging in adulthood, and are discussed in terms of age range and types of measures used for PA and cognition.

Introduction

With a rapidly aging society, there is an increased need to examine factors that confer protection against age-related cognitive decline. Specifically in older adults, cognitive decline may develop into mild cognitive impairment (MCI) and potentially dementia[1]. While studies show that negative affect (NA) is associated with a heightened risk for age-related cognitive decline and dementia[2], fewer studies have examined the role of positive affect (PA) in age-related cognitive decline. Recently, there has been a growing interest in positive psychology, and research has started to focus on the potential benefits of positive psychological states[3].

PA is a subjective state of mood reflecting to what extent a person experiences pleasurable engagement with the environment. High PA is characterized by feeling enthusiastic, active and alert, whereas low PA reflects a state of sadness and lethargy[4]. NA, on the other hand, reflects the extent to which someone feels distress and other unpleasant moods such as guilt, fear, and nervousness. Low NA is described as a state of calmness. PA and NA are not merely two opposite mood factors on a single continuum, but can be better considered as distinctive orthogonal dimensions[4]. Although originally thought to be completely independent[4], a confirmatory factor analysis of the widely-used Positive and Negative Affect Scale (PANAS) showed that it is best described with NA and PA as two distinct factors, however with a moderate negative correlation[5,6].

Higher levels of positive emotions have been associated with reduced risk of stroke and cardiovascular mortality[7,8], delayed onset of frailty[9], hypertension[10], and increased longevity[11] – although recent research did not confirm this[12]. Studies on biological correlates of PA have focused on potential mechanisms such as reduced activation of the neuroendocrine, autonomic, immune and inflammatory pathways (e.g. lowering of cortisol levels and cytokines)[13]. Importantly, these correlates are specifically related to PA, that is, these relationships are independent of NA. Mechanisms such as these may also support brain health. In addition, the PA dopamine hypothesis suggests that PA promotes the release of dopamine in the brain[14] which may facilitate processes such as attention, working memory, and memory consolidation, as well as creative problem solving. This may be mediated by dopamine activating brain regions such as the prefrontal cortex and anterior cingulate, facilitating cognitive processes.

The biological correlates of PA suggest that PA could also influence cognitive decline. Most research in this area has been done at the behavioral level. That is, PA influences cognition with studies showing improved performance on problem solving, working memory and creativity[14,15]. The majority of these studies use an experimental design where positive affect is temporarily induced (e.g. by giving participants an unexpected

gift or exposure to positive words) before testing performance in the cognitive domain. One study investigated dispositional PA and decision making and showed that those with high PA performed better than those with low PA[16]. However, most research has focused on state PA, from the perspective that PA enhances cognitive function by broadening the scope of attention and thought-action repertoires[17,18].

In sum, several indications exist that PA could serve as protective factor in cognitive decline by improving general health (including brain health) on the one hand, and enhance cognitive functioning via increased dopamine levels on the other hand.

Surprisingly, little research has been carried out into the relationship between PA and cognition in older adults. One cross-sectional study showed that higher PA was associated with better free memory recall in the older (65 to 82 years) age group[19]. Another study showed that PA predicted greater sustained attention in older adults[20]. In both studies, the contribution of PA to the proportion of variance explained was small (1-3%). One longitudinal study in older adults showed that baseline PA differentiated persons with MCI from controls at baseline and after a 4-5 year follow up[21]. To the best of our knowledge, no study to date has investigated the potential predictive effect of dispositional PA on age-related cognitive development over time. Getting insight into the possible protective effects of PA on cognitive decline during normal aging is crucial because PA can be altered. For example, mindfulness based interventions (MBI) increase positive affect[22–24].

We set out to investigate the relationship between PA and cognitive decline in a 12-year longitudinal study on cognitive aging. We hypothesized that individuals with higher PA scores would show less age-related cognitive decline in memory, executive functions, and information processing speed.

Methods

Participants

The sample consisted of individuals enrolled in the Maastricht Aging Study (MAAS), a longitudinal study of determinants of cognitive aging. Details of the study have been published elsewhere[25]. In MAAS, 1,823 participants underwent a baseline assessment between 1993 and 1996. Participants were stratified according to age, sex, and level of occupational achievement. Individuals with conditions known to affect cognitive function (e.g. dementia or other neurological and psychiatric disorders) were excluded. This prospective cohort study examining the relationship between PA and cognitive change included participants aged 40 years or older in whom PA was assessed in one

of the four panel studies of MAAS. The final study sample consisted of 258 participants. The local ethics committee of the Maastricht University Medical Center approved the MAAS study, and all participants gave informed consent.

Measures

Positive Affect

PA was measured using the Dutch translation of the Positive and Negative Affect Schedule (PANAS[4,26]). The PANAS is a 20-item scale with 10 items assessing PA (e.g. enthusiastic, alert) and 10 items assessing NA (e.g. distressed, upset). Participants were asked to rate their mood in the last two weeks on a five-point Likert scale ranging from "not at all" = 1, to "extremely" = 5. Similar to the original version, the Dutch version of the scale has a high internal consistency, with Cronbach's alpha of 0.84 for the PA scale and 0.80 for the NA scale[19].

Neuropsychological Assessment

Neuropsychological tests were administered by psychologists and trained test-assistants at baseline and at 6- and 12-year follow-up. Three neuropsychological tests were selected from the core test battery of MAAS that index verbal memory, executive function and information processing speed.

Verbal memory was assessed with the Visual Verbal Learning Test (VVLT[27]). This test is a word-list learning task in which 15 unrelated monosyllabic words are presented on a computer screen over five consecutive learning trials. Immediately following each trial is a recall phase (immediate recall) and a delayed recall phase 20 minutes after the test (delayed recall). The total number of correctly reproduced words at the delayed recall was used for the memory score in the present study.

The Concept Shifting Test (CST) was used to index executive function[28]. In three trials, participants have to cross out as fast as possible 16 digits in ascending order (part A), 16 letters in alphabetical order (part B), and 8 digits and 8 letters in alternating order (part C). The score used is the shifting score that is calculated by subtracting the average time needed to finish part A and B from the time needed to finish part C.

The Letter Digit Substitution Test (LDST) was used to measure information processing speed[29]. Participants have to match digits to letters as quickly as possible, according to a key where each number is paired with a different letter. The total score is the number of correct substitutions made in 90 seconds.

The Mini–Mental State Examination (MMSE) measures several domains of cognitive functioning and was used to assess global cognitive functioning[30].

Covariates

Several variables that might influence the association between PA and cognitive change over time were taken into account by including them as covariates in the model. These included the demographic covariates age, sex, and educational level (low, middle, high). Depressive symptoms were assessed with the 16-item depression subscale of the revised Symptom Checklist-90[31].

Statistical Analysis

The scores for the VVLT were negatively skewed, therefore a square root transformation was used to normalize the distribution. The scores on the CST were positively skewed, and a natural logarithm transformation was used.

The association between PA and cognitive change over time was tested in random-effects models. This analysis models individual growth curves that take into account within-subject correlation between repeated measures. By using full maximum likelihood, missing data can be considered to be missing at random if covariates that are associated with missingness are included in the analyses. We did this by including variables such as age and depression in the reported analyses. Random effects for the intercept and slope with unstructured correlation matrices were specified because likelihood-ratio testing suggested that this fitted the data better than specifying random intercepts only. To model the association between PA and cognitive decline, a PA-by-Time interaction term was included, with time entered as dummy variables for each of the 2 follow-ups, thereby allowing for nonlinear effects. Also, we tested a model that included age^2 to allow for nonlinear effects of age on cognition. The fully adjusted model included fixed effects for PA, time, PA*time, age, age^2, sex, level of education, and depressive symptoms.

Moreover, we tested a model that included continuous PA scores divided by their tertiles in order to classify participant categorically as either low, middle, or high PA. Research on PA often uses a median split or tertile groups of the PA scores (e.g.[19]).

To test whether dropout rates could be predicted by the observed variables, a logistic regression with “participant in the study at follow-up” (yes/no) as a dependent variable was performed at both follow-ups. All tests were 2-sided with an α-level of 0.05 and were performed in Stata 12.1 (StataCorp, TX).

Results

At baseline, 258 participants (aged 40.0-82.2 years) filled out the PANAS questionnaire (see **Table 1** for characteristics). PA scores were normally distributed. At 6-year follow-up, 172 (67%) participants were still in the study. At 12-year follow-up, 151 (59%) participants completed the assessment. The odds of dropping out of the study increased with being older at both the 6-year follow-up (odds ratio=1.11, 95% confidence interval=1.05-1.17) and the 12-year follow-up (odds ratio=1.12, 95% confidence interval=1.07-1.19), and with having a lower baseline MMSE score at for 12-year follow-up only (odds ratio=0.78, 95% confidence interval=0.63-0.96).

Table 1. Baseline characteristics of study sample

Characteristic	n=258
Age, mean (SD)	61.0 (12.0)
Female, n (%)	138 (54)
Education, n (%)*	
Low	123 (48)
Middle	93 (36)
High	42 (16)
PA, mean (SD)**	32.1 (6.4)
NA, mean (SD)	18.3 (6.6)
MMSE, mean (SD)	27.5 (2.0)
Depression score, mean (SD)	21.7 (7.2)
Memory, mean (SD)	8.4 (3.1)
Executive function, mean (SD)	14.7 (15.7)
Processing speed, mean (SD)	43.8 (11.4)

PA = Positive Affect; NA = Negative Affect; MMSE = Mini-Mental State Examination

*P<0.05.

**P<0.01.

Baseline PA and 12-year cognitive decline

Table 2 summarizes the Pearson's bivariate correlations between cognition and PA. Results of the association between PA at baseline and cognitive change over time are shown in **Table 3**. This model included fixed effects for PA, time, PA*time, age, sex, level of education, and depressive symptoms. A second model, including age^2, did not provide different results and was therefore omitted (data not shown).

Table 2. Pearson's bivariate correlations between positive affect and cognition at baseline, 6- and 12-year follow-up

	Positive Affect
Baseline	
Memory	0.07
Executive Functions	0.02
Processing Speed	0.05
6-y Follow-Up	
Memory	-0.02
Executive Functions	-0.10
Processing Speed	0.05
12-y Follow-Up	
Memory	-0.10
Executive Functions	0.07
Processing Speed	-0.01

Note: Positive affect measured at baseline.

Table 3. Baseline positive affect (PA) as predictor of cognitive functioning at 6-year and 12-year follow up

	From baseline to 6-y Follow-Up		From baseline to 12-y Follow-Up		
Parameter	**Decline**	**95% CI**	**Decline**	**95% CI**	**PA×Time[a]**
Memory[§]	-0.60	-1.75 to 0.55	-0.67	-1.92 to 0.59	1.52
Executive Functions[¶]	-0.01	-0.03 to 0.02	0.01	-0.02 to 0.03	0.99
Processing Speed[#]	0.02	-0.11 to 0.16	0.06	-0.10 to 0.21	0.52

All P>0.05
Model: PA×time, age, sex, education, and depressive symptoms. CI = Confidence Interval; PA = Positive Affect
[a]Test of interaction between PA and time (baseline, 6-y follow-up, 12-y follow-up): χ2 statistic with 2 df
[§]Visual verbal learning test – delayed recall. Higher scores indicate better performance. Scores are quadratic transformations.
[¶]Concept shifting test, interference index. Lower scores indicate better performance. Scores are logarithmic transformations
[#]Letter-digit substitution test. Higher scores indicate better performance.

The overall interaction between PA and time was not significant for memory (χ^2=1.52; df=2; P=0.47), executive function (χ^2=0.99; df=2; P=0.61), and information processing speed (χ^2=0.52; df=2; P=0.77) after 6 and 12-year follow-up in fully-adjusted models, suggesting similar age-related cognitive change over time. The estimated Cohen's f^2 effect sizes for PAxTime were small (<0.01) for change in memory, executive functioning, and processing speed.

The analysis of PA tertile groups (PAlow n=95; PAmiddle n=87; PAhigh n=77) showed similar results. Compared to PAlow as the reference category, neither PAmiddle nor PAhigh had a different rate of cognitive change over time for memory (PAmiddle: χ^2=4.20; *df*=2; *P*=0.17, PAhigh: =0.17; *df*=2; *P*=0.92), executive function (PAmiddle: χ^2=0.24; *df*=2; *P*=0.89, PAhigh: χ^2=0.24; *df*=2; *P*=0.89), or information processing speed (PAmiddle: χ^2=0.24; *df*=2; *P*=0.89, PAhigh: χ^2=0.24; *df*=2; *P*=0.89). The trajectories of the cognitive change as a function of PA group are represented in **Figure 1**. Both PAlow and PAhigh showed some improvement in performance at the 6-year follow-up compared to baseline on tests of memory and information processing, probably due to test-retest effects. At the 12-year follow-up, this shifted towards a trend for a decline. The scores on executive function showed a decline for both groups at the 6-year follow-up, but this decline slowed down at the 12-year follow-up.

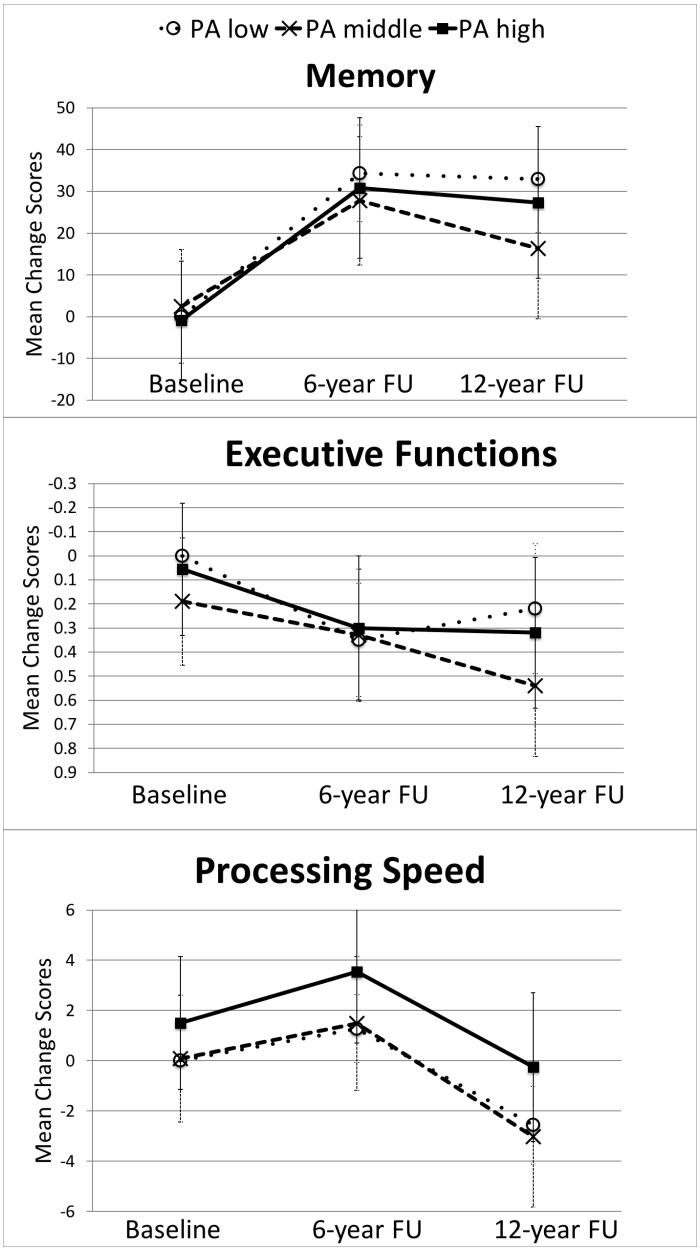

Figure 1. Plotted mean change scores (for memory, executive functions, and processing speed) and 95% confidence intervals from baseline to 6-year, and 12-year follow-ups for individuals with low PA (dotted line), middle PA (dashed line) and high PA (solid line) at baseline. Higher scores indicate better performance for memory and processing speed, whereas lower scores for executive functions indicate better performance (note: the y-axis is flipped to show that a decreasing line reflects decreased performance).

Discussion

We investigated whether PA has a protective effect on age-related cognitive change over a span of 12 years in a healthy adult sample. Contrary to expectation, PA was not associated with cognitive change over time in memory, executive function, and information processing speed.

We additionally examined the association between PA as a trichotomous variable (PA low, middle, and high) and cognitive performance at baseline and over time, but the result of this analysis also revealed no longitudinal associations. This analysis showed a trend for the high PA group to perform better on tasks of memory and information processing speed. Unfortunately, the sample size was too small to make finer, possibly more sensitive, PA strata.

The age range of the sample included was relatively wide (40+). Previous studies examining differences in cognitive performance related to PA were often restricted to older (65+) adults. Due to the limited sample size, we were not able to compare the young-old versus the older-old.

Since it might be possible that depressive symptoms are taking away the variance explained by PA, we additionally compared models with and without depressive symptoms as a covariate. However, these models also were not significant.

The PANAS was only administered at baseline so there was no repeated measurement available for PA. Therefore, we could not control for possible changes in PA. However, PA has been shown to be relatively stable in older age, with little change until the age of 60, and a minor decrease in older participants[32], although some studies show a slight increase in PA with age[33]. Therefore, there is no strong evidence that PA would change substantially over time and would alter our findings. Interestingly, in this study we did not find an age difference between individuals with high and low levels of PA.

The measurement we used for PA might explain the discrepancies with previous research finding an association between cognition and PA. We used the PANAS, whereas other studies have used other methods to measure PA. For example, items of reversed Negative Affect scale have been used[7], or only a single item to probe PA 'how often do you feel happy?'[12]. When reviews describe the effects of PA they summarize studies with different measurements. Yet, it is unclear whether PA defined simply as happiness is similar to a PA measured with a scale consisting of several items. A study using several measurements of PA could shed light on whether the items used impact the association between PA and cognition.

The distinction of PA as a state or as dispositional PA could be differentiated in the time indication in the instructions. For example, the items can relate to how someone feels 'in general' or 'in the last two weeks'. In our study, the latter time indication was used and assumes that it is an indication of PA trait. One might argue that the time frame of 'two weeks' is more indicative of state than trait. However, Watson, Clark, & Telliggen (1988) investigated the differences of PANAS ratings on two different occasions for seven time frames (*moment, today, past few days, past few weeks, year, general)*. No significant differences were found for stability values between the rated time frames. Moreover, every time frame showed a significant level of stability, even in the shortest time frame ('moment'). This suggests that even momentary moods are reflections of a person's general affective level[4]. Thus, these findings reflect the strong dispositional component of PA. However, PA can be altered by interventions (e.g.[22]) and if our results would have indicated that PA would serve as a buffer in the aging process, interventions to increase PA would be indicated.

Other studies with older people have used different measurements of cognitive performance. Hill et al. (2005) found an effect on free recall (and not delayed recall) in their cross-sectional study. They used the same data set as the current study, but different outcome measurements and only looked at the outcome at baseline. Another study with older adults showed that PA predicted greater sustained attention, but did not find effects of PA on recognition memory, spatial working memory and reaction time[20].

Our study has several strengths. The observational period was long enough to study age-related cognitive decline, with a 6-year and 12-year follow up. The neuropsychological battery involved different cognitive domains with tests sensitive to change. Finally, the statistical methods allowed for modeling time trajectories without restricting the analyses to study completers.

Our study also has some limitations. First, the sample size was too small to explore in more detail differences in age groups or gender. A trend was found for participants with a lower PA to be more likely to drop out of the study, leading to a selection bias. However, this was partially accounted for by using mixed model analysis. Another limitation (inherent to a longitudinal design) is the retest effect, which seems most apparent in the change from baseline to year 6. Considering the long time between the tests, this is likely to be due to aspecific effects (e.g. being familiar with the procedure) rather than a learning effect on the test itself. Moreover, previous work has shown that retest effects are no longer detectable after 7 years[34]. The PANAS is a self-report measure and one

of several instruments to measure PA. As discussed above, PA was only measured at baseline and not at the other time points.

In summary, no significant protective effects of PA on cognitive change over time in normal aging were found. These findings question the extent of the hypothesized protective effects of high PA on age-related cognitive decline, although more research is needed. Future research should use a larger sample size so that effects in subgroups (age groups, sex) can be investigated in more detail. Moreover, measuring PA at multiple time points would ensure that there is no substantial change in PA that confounds the results.

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Associations of low-grade inflammation with mindfulness in individuals with and without type 2 diabetes

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Do brief meditation exercises boost state mindfulness and positive affect in daily life? An experience sampling pilot study

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Submitted

Part II
Interventions

6

Mindfulness-based stress reduction in middle-aged and older adults with memory complaints: a mixed-methods study

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Abstract

Objectives In a rapidly aging world population, an increasingly large group faces age-related decline in cognitive functioning. Cognitive complaints of older adults are often related to worries and concerns associated with age-related functional decline. Mindfulness-Based Stress Reduction (MBSR) can successfully target stress, worry and ruminative thinking, but the applicability of this method in middle-aged and older adults with memory complaints is unclear.

Method Patients of a university hospital memory clinic (n=13), aged 45-85 years, with memory complaints but no diagnosis of cognitive disorder, participated in a standard 8-week MBSR program, consisting of weekly group meetings and a one-day silent retreat. After completion, semi-structured qualitative interviews were conducted. Questionnaires (administered before, one week after and five weeks after the intervention) assessed quality of life, psychological distress (stress, anxiety and depressive symptoms), mindfulness, self-compassion, and subjective memory functioning. Neurocognitive functioning was assessed online, before and after the intervention.

Results The qualitative analysis showed positive effects of the training (e.g. increased serenity), many participants worrying less about memory complaints. The self-reported measures were in line with the results of the qualitative analysis.

Conclusion This exploratory mixed-methods study suggests that MBSR is feasible and well received among older individuals with cognitive complaints.

Introduction

As the world population ages, an increasingly large group faces age-related cognitive decline and reduced quality of life. This presents both human and economic challenges. Cognitive complaints in older individuals are often related to worries and concerns associated with age-related decline[1,2]. Several cognitive interventions have been developed, however with limited success[3]. Rather than cognitive training, meditation interventions may be promising. Mindfulness-Based Stress Reduction (MBSR) can successfully target stress, worry and ruminative thinking[4,5], however the feasibility in older individuals with memory complaints is unclear.

There is preliminary evidence that stress affects the biological aging process and that mindfulness based interventions (MBI) may influence metabolic stress and cellular aging[6]. Mindful meditation may influence brain structure and function[7], and a systematic review suggested that meditation can offset age-related decline[8]. A few studies have started to investigate the feasibility and effects of MBSR in older individuals. However, most studies include healthy adults[9,10]. A recent review reported that it is unclear whether MBI can influence cognitive functioning in older adults, because of the limited amount of methodologically sound studies[11]. One randomized controlled trial reported improved stress, mood, well-being, sleep and quality of life in adults with subjective cognitive decline, which was sustained at 6 months follow-up[12]. However, the meditation program (Kirtan Kriya Meditation) differs from the MBSR in content, length and amount of daily practice. A few studies have focused on MBSR with participants with subjective memory complaints. Recently, one study reported cognitive and psychosocial benefits in older adults with subjective memory complaints[13]. Another study randomized participants with subjective memory complaints to an MBSR program or psychoeduction[14]. Both groups showed reduction in cognitive complaints and depression, and only the MBSR group showed memory self-efficacy. Although these were small studies (n=34 and n=38), the focus was on quantitative results.

In order to develop more insight into whether the standard MBSR is suitable for older individuals with cognitive complaints, a complementary qualitative approach may reveal which aspects of the training program could be adjusted to better meet the needs of this specific population. Qualitative studies to analyze the experiences of the participants on MBI have been conducted with a variety of other populations, such as participants with breast cancer[15], depression[16], and Parkinson's disease[17]. Themes that emerge are often related to the pillars of mindfulness such as coping with stress and accepting things as they are. Moreover, the support of the group is often mentioned as a positive experience.

The primary goal of the present study was to determine the feasibility and acceptability of an 8-week MBSR program in middle-aged and older adults with cognitive complaints, including a qualitative assessment of the experiences with the intervention. The secondary objective was to conduct hypothesis-generating analyses on cognitive and psychological indicators of sensitivity to the MBSR program. Outcomes focused on quality of life, psychological distress (stress, anxiety and depressive symptoms), mindfulness, self-compassion, and subjective memory functioning.

Methods

Participants

Health professionals at the Maastricht University Medical Centre memory clinic referred patients who experienced subjective memory complaints but who were not diagnosed with cognitive impairment (including mild cognitive impairment) after a standard clinical workup (see Aalten et al., 2014 for details)[18]. Subjective memory complaints were ascertained during intake.

Other eligibility criteria included being interested in the program, able to communicate in Dutch, able to attend at least seven out of eight meetings, agree to make homework assignments and having access to a personal computer at home. Also, people who took medication that could interfere with the treatment were excluded from participation. All study procedures were reviewed and approved by the Ethics Review Committee of the Maastricht University Medical Center and all participants gave written informed consent. The study was registered in the Dutch Trial Register database (#NTR4749).

Study Design

A mixed method qualitative-quantitative design was used in order to gain in-depth knowledge about the experiences and effects of MBSR in older people with cognitive complaints. Qualitative data were collected through a semi-structured interview after the training and quantitative data were gathered with questionnaires. The qualitative data explored the experience of the training in a thorough way in order to uncover areas to be explored in future studies; the quantitative data provided preliminary insight in the effects of the MBSR.

Participants completed an online cognitive test battery before and after the MBSR course. Self-report questionnaires were also administered before and after the MBSR and also included a follow-up, five weeks after the course ended. The semi-structured interview was conducted one to two weeks after the intervention. **Figure 1** shows the study timeline.

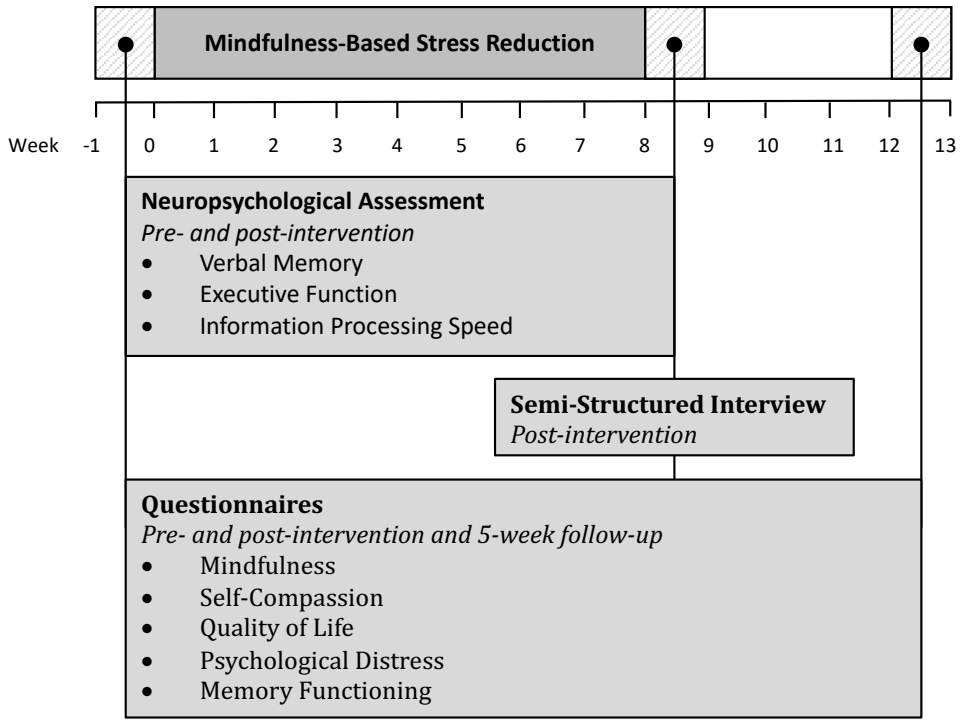

Figure 1. Study timeline and measurements for both groups

Intervention

The MBSR program was based on the program developed by Jon Kabat-Zinn[19]. The intervention consisted of eight weekly 2.5 hour sessions and a 6-hour silent retreat on a separate day in week six. Participants were expected to engage in homework activities (45-60 min) on at least 6 of 7 weekdays. Background information about the content of training sessions and forms for the homework assignments were handed out each week. The training aimed to cultivate mindfulness, an attentional quality that supports the participant to welcome all experiences that arise in the moment, with a mild and friendly curiosity and letting go of tendencies to judge the experience. In the sessions, participants engaged in formal group exercises to cultivate mindfulness (sitting meditation, body scan, and mild hatha yoga) and exchanged experiences about what the exercises brought about. The MBSR groups were conducted by a certified MBSR trainer (MvB) who had formal training and maintains an on-going personal practice.

Measures

Feasibility and Acceptability

Feasibility was indexed through attendance and completion rate. Further, the amount of daily practice was reported. Acceptability was measured through the qualitative data of the semi-structured interview, in which participants reported experiences with the program and provided feedback. Moreover, the uptake rate (i.e., ratio screened/enrolled participants) and reasons for refusal to participate were recorded[20].

Quantitative Data Collection – Psychosocial Measures

The questionnaires were administered immediately before (baseline), as well as 1 week and 5 weeks after the MBSR course (follow-up 1 and 2, respectively). The questionnaires provided an overview of quality of life, mental health, levels of mindfulness, self-compassion and subjective memory functioning of participants.

Mindfulness

The Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF) was used to assess dispositional mindfulness[21]. This 24-item questionnaire, based on the original 39-item FFMQ[22], measures five components of mindfulness: *observing* (noticing or attending to sensory experiences), *describing* (describing emotions and feelings), *acting with awareness* (attending to one's activities in the present moment), *being non-judgmental* (taking a non-evaluative attitude toward one's thoughts and feelings), and *being non-reactive* (allowing thoughts and feelings to come and go). The FFMQ-SF was shown to be reliable and valid in Dutch samples, Cronbach's α ranging from 0.69 to 0.90[21,23].

Self-Compassion Scale - Short Form (SCS-SF)

This is a short form of the self-compassion questionnaire that measures three components of self-compassion: self-kindness versus self-judgement, common humanity versus isolation, and mindfulness versus over-identification[24]. Participants were asked to mark how often they experienced these states on a 5-point Likert scale. Examples of these states are: "When I feel bad, I think that most other people are happier than I am", and "I try to see failures as a common part of life". Only the total score of the short form is used, since the subscale forms are less reliable with the short form[25].

Quality of Life

Health-related quality of life was measured using the EuroQol, in which the participants could select a number on a scale between 0 (= worst imaginable health condition) and 100 (= best imaginable health condition) to rate their health condition at that moment[26].

Psychological Distress

The 21-item Depression Anxiety Stress Scales (DASS-21) was used to measure

psychological distress[27]. This questionnaire is a short form of the 42-item self-report measure[28]. Internal consistency of the DASS-21 is acceptable for all three scales with Cronbach's α ranging from 0.82 to 0.90[27].

Subjective memory functioning

Subjective memory functioning was assessed with four subscales of the Dutch version of the Metamemory in Adulthood Questionnaire (MIA[29]). Metamemory is a term used to describe one's self-knowledge and self-belief about one's own memory functioning. The subscale Change indicates perceived change in memory functioning (e.g. "The older I get the harder it is to remember things clearly"). The Capacity subscale indexes perceived memory capacity (e.g. "I am good at remembering names"). The Anxiety subscale measures the degree of feelings of anxiety and stress in relation to memory functioning (e.g. "I do not get flustered when I am put on the spot to remember new things"). The three scales (Change, Capacity, Anxiety) are combined into a measure of Memory Self-Efficacy and is associated with future memory performance in older adults (MSE[30,31]). The locus of control subscale indicates perceived sense of control over memory (e.g. "Even if I work on it, my memory ability will go downhill").

Quantitative Data Collection – Neuropsychological Assessment

Neuropsychological tests were administered online before and after the MBSR program. There was no assessment at follow-up, since these two test moments provided all the information necessary for a proof of concept. Participants received instructions to ensure that they would not be disturbed during the assessment. The online test battery was developed and implemented by NeuroTask BV (www.neurotask.com). Three measures were used to assess verbal memory, executive function and information processing speed. For the post measurement, a parallel version of the verbal learning test was used. After the assessment, participants were able to write comments in a text box. The prototypical versions of the employed tests are described below.

Verbal memory

Verbal memory was assessed with the Verbal Learning Test[32]. Fifteen monosyllabic words were presented on participants' computer screens over five consecutive trials. After each trial, the participant had to write down as many of the fifteen words they remembered (immediate recall). The fifteen words were presented in identical order across all trials. After an approximate 20 min delay, there was another recall trial (delayed recall). This was followed by a recognition trial in which the participants had to select the 15 words out of a list of 30. The total number of correctly reproduced words at the delayed recall task was used for the memory score in the present study.

Executive Function

Trail Making Tests A and B (TMT[33]) were used to assess cognitive speed, visuomotor tracking and cognitive flexibility. TMT-A requires participants to connect circled numbers by clicking on them in consecutive order. TMT-B requires participants to alternate between letters and numbers in sequential order (i.e., 1-A-2-B-3-C, etc.). The outcome is the amount of time to complete. We also include the B/A ratio as an outcome measure to compare with other research[10].

Information Processing Speed

An adapted version of the Symbol Digit Modalities Test (SDMT) was used to measure information processing speed[34]. A key was presented to the participants in which the digits 1-9 were each paired to a different symbol. This key was visible during the whole test period, lasting 90 seconds, in which the participants had to replace the randomized symbols with the matching digit as quickly as possible. The score is calculated by totaling the number of correct answers.

Qualitative Data Collection

The semi-structured interviews, conducted by a trained research assistant (RH), were recorded and transcribed verbatim. The research assistant was familiar with the content of the training and research literature, but was not a mindfulness trainer. The interview style was informal and inviting. **Table 1** shows the questions for the interview, which were based on other studies and consultation with experienced researchers[35]. Ten interviews were done in person and two were done by telephone. One participant was not interviewed because she could not be contacted. The aim was to analyze the content of these semi-structured interviews using thematic analysis[36]. The research assistant (RH) and a researcher (LB) coded the transcripts independently, using the qualitative software package ATLAS.ti (Scientific Software Development GmbH, Berlin). From the codes, categories were identified independently and then discussed to reach consensus. This consensus process was verified by a third researcher (MvB). This process was repeated for the identification of themes, until consensus was reached.

Data Analysis

The descriptive statistics of the questionnaires and neuropsychological assessment was calculated with SPSS 22.0 (IBM Corporation, Armonk, NY). Paired t-tests were performed to examine the difference between scores at baseline, directly after and 5 weeks after the MBSR training. Moreover, effect sizes are reported to inform future researchers for a-priori power analyses and meta-analyses.

Table 1. Qualitative interview questions structured around the three phases of participation.

Before	Why did you take part in this training?
During	What was your experience working in a group?
	What aspects of the training did you find difficult?
	What aspects of the training did you find beneficial?
	Did you encounter specific obstacles during the training or homework assignments?
	Should anything be changed to make the training more supportive?
After	Has anything changed for you with regard to your general health?
	Has anything changed for you with regard to your memory complaints?
	Do you feel better able to cope with stressful events than before you started the training?
	Has the training affected your personal life (i.e. life-style changes)?
	Are there any techniques you continue to use?
	Would you recommend this training to people with memory complaints?
	Do you have any further comments?

Results

Thirty people in total were screened and interviewed by the trainer. In the process, 17 participants were excluded. The most common reason for exclusion was being unable or unwilling to invest the time required (n=9). Other reasons included planned medical procedures (n=2), use of antidepressants (n=2), no interest after reading information about the training (n=3), and the partner objecting to participation (n=1). Two groups were started, six months apart (the first in March, the second in October 2015). The second group was deemed necessary to ensure data saturation in the qualitative study[37]. Group one had seven participants, group two had six participants. The mean age of all the participants was 59 years (range: 45-85). The average years of education was 13.2 years (SD: 2.2) and 6 out of 13 were female.

Feasibility and Acceptability

Almost a third of the screened participants (30%) refused to participate in the study, mostly due to the time investment. The MBSR is a time intensive program, and thus difficult for participants, in particular with this study's limited options (two start dates). All thirteen participants who started the course finished it with completing an average of 91% of all sessions (range: 4-9 sessions). Participants reported an average of 44.4 min a day of home practice (SD=14.6) during the 8-week MBSR program.

Table 2. Group means and standard deviations (SD) of psychosocial outcomes at pre- and post-intervention and 5-week follow-up.

	Baseline (BL) mean (SD) N=13	Follow-up 1 (FU1) mean (SD) N=12	Intervention change (BL-FU1) d	Follow-up 2 (FU2) mean (SD) N=10	Overall change (BL-FU2) d
DASS-21 depression	12.92 (10.25)	9.31 (8.46)a	0.46	9.40 (11.00)	0.36
DASS-21 anxiety	8.15 (5.97)	7.95 (5.04)a	0.05	7.60 (7.47)	0.08
DASS-21 stress	15.31 (9.79)	14.73 (8.16)a	0.42	12.60 (11.08)	0.29
FFMQ-SF observing	13.23 (2.98)	13.83 (3.51)	0.19	14.03 (4.61)	0.26
FFMQ-SF describing	15.23 (3.81)	15.42 (3.94)	0.23	16.70 (3.89)	0.68
FFMQ-SF act with awareness	14.92 (3.66)	13.33 (3.20)	0.32	16.20 (4.59)	0.33
FFMQ-SF non-judgment	14.28 (4.17)	15.08 (3.94)	0.35	16.90 (4.18)*	0.78
FFMQ-SF non-reactivity	14.50 (3.98)	14.33 (4.31)	0.12	15.90 (4.56)**	1.31
FFMQ-SF total	72.16 (10.53)	72.00 (10.46)	0.12	79.73 (14.16)	0.71
MIA capacity	2.56 (0.41)	2.67 (0.51)	0.32	2.73 (0.63)	0.34
MIA change	2.39 (0.64)	2.32 (0.63)	0.04	2.56 (0.68)	0.11
MIA anxiety	3.49 (0.75)	3.47 (0.63)	0.12	3.40 (0.80)	0.19
MSE	2.49 (0.46)	2.51 (0.39)	0.16	2.63 (0.60)	0.20
MIA locus	3.05 (0.45)	3.13 (0.42)	0.20	3.07 (0.47)	0.36
SCS-SF total	2.59 (1.03)	2.79 (0.93)	0.56	3.13 (0.90)	0.67
Quality of Life	62.25 (14.31)	66.64 (9.45)	0.18	70.10 (12.33)	0.65

[a] n=11 due to missing data for one participant; d Cohen's d effect size; DASS-21, 21-item Depression Anxiety Stress Scale; FFMQ-SF, Five Facet Mindfulness Questionnaire - Short Form; MIA, Metamemory in Adulthood Questionnaire; MSE, Memory Self-Efficacy; SCS-SF, Self Compassion Scale - Short Form.
*$p < 0.05$, **$p < 0.01$.

Quantitative Data Results – Psychosocial Measures

Table 2 shows the mean scores and standard deviations for each of the questionnaires at baseline, follow-up 1 and follow-up 2. Effect sizes are reported between baseline and follow-up 1 and baseline and follow-up 2. After the MBSR training (follow-up 1) the mean scores of depressive symptoms decreased and quality of life increased, although these changes were not significant. No significant changes were found for scores on stress and depressive symptoms, mindfulness, self-compassion and subjective memory. Five weeks after the MBSR training (follow-up 2) compared to baseline, the mean scores of all the mindfulness subscales and total score increased, with a significant change for the non-judgment and non-reactivity subscales. Although mean scores for self-compassion and quality of life increased, and stress and depressive symptoms decreased; these changes were not significant. Furthermore, no significant changes at follow-up 2 were found for anxiety symptoms and subjective memory.

Quantitative Data Results – Neuropsychological Assessment

Table 3 shows the neuropsychological assessment pre- and post-intervention. All participants (n=13) completed the pre-intervention assessment. The post-intervention assessment was not completed by two subjects. Furthermore, one outlier was identified and not included in the overview (**Table 3**), as there were indications that the assessment was not performed in a single session and furthermore was not carried out correctly. It is likely that this person would have benefitted from extra instructions or supervision during the assessment. All mean scores improved after the MBSR training, with a significant increase for verbal memory.

Table 3. Neuropsychological test scores pre- and post-intervention.

	Baseline Mean (SD) N=12	Post-intervention Mean (SD) N=10	Intervention change *d*
VLT delayed recall, total correct	10.83 (2.48)	12.20 (2.35)*	0.98
TMT-A (s)	43.51 (14.76)	37.00 (8.58)	0.26
TMT-B (s)	86.22 (52.53)	64.35 (27.19)	0.21
TMT ratio B/A	1.97 (1.02)	1.73 (0.54)	0.08
SDMT, # total correct	34.58 (10.77)	37.30 (8.91)	0.15

d, Cohen's *d* Effect Size; VLT, Verbal Learning Task; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.
*p < 0.05

Qualitative Data

From 30 categories, five themes were identified (**Table 4**). Each theme is described below.

Table 4. Themes and categories qualitative analysis.

Theme	Category
Motivations and expectations	There is no harm in trying
	Participating because of advice
	Positive expectations about the training
Group Process	Recognition
	Nice group
	Support by group
Positive effects of the training	Acceptance
	Serenity
	Decrease in worrying about memory complaints
	Decrease in complaints
	More awareness
	Behavioral change with respect to stress
	Insight
	Positive experience exercises
	Positive experience of the training in general
	Observational change with respect to stress
	Continuation of mindfulness exercises
	Self-compassion
Difficulties	Busy life-style
	Inner pressure
	Personal obstacles
	Demanding society
	Low level of self-discipline
Considerations	Guided exercises necessary during the training
	Obstacles during exercises
	No decline in complaints
	No behavioral change
	Longer period of training
	More time for questions and discussion about experiences
	Challenges after the training

Motivation and expectations

Many participants held neutral expectations for participating in this course or showed uncertainty.

> *"There is no harm in trying."*
> *"I don't know if my memory will improve or if I would worry less [about memory problems]."*

For most participants, the main motivation was that it had been suggested by the health professional at the memory clinic. A few participants hoped to learn either to deal with memory complaints or even improve their memory. Besides memory complaints, two of participants also mentioned that they felt very busy and thought that the training would be beneficial.

> *"I'm always running and working. My mind is always busy."*

A few participants had heard positive things about mindfulness and mentioned this as a motivation to participate.

> *"People around me who had done mindfulness exercises recommended them. When I heard I could participate in this study, I thought to myself: 'This is your chance!'"*

Group Process

Most participants were positive about the training being a group training. Most had worked in groups at work. Participants mentioned that the group was friendly and provided a safe environment. They recognized themselves in stories of others and felt supported by the group.

> *"It was a pleasant experience and it was useful to work in a group, because you experience you are not the only one [with these problems]. When I heard the stories of other people in the group, I thought to myself: 'you just need to change the name and then the story is about me'."*

> *"Not being alone gives you more strength. The support of the group strengthened me and the others in the mindfulness training."*

One participant mentioned that even though working in a group was acceptable, he did not feel like participants were all on the same wavelength. This feeling was increased after hearing about the personal struggles of some other participants. However, this did not keep him from taking part in the group process.

Positive Effects of Training

All participants reported positive effects and wanted to continue the mindfulness exercises after the training. Most participants reported general positive feelings and felt sorry it was over.

> *"In general, I am happy I participated in the training. I would do it again immediately. It is too bad it had to end."*

The meetings also helped with motivation to do the homework exercises. The majority of the participants mentioned serenity as a positive effect of the training.

> *"The movement exercises were useful. Although you are active, they have a calming effect. I thought that was a strange effect in the beginning, as I have done handball and basketball and during these sports I felt even more excited afterwards. But these exercises create serenity, not only in your head, but also in your body."*

> *"I learned from the training to be calm. Serenity has a healing effect. It creates creativity, reduces stress, improves your health, and it helps you to handle difficult situations better. We all need this rest."*

Another benefit reported by participants was the realization of how they coped and thought about situations in a suboptimal way.

> *"I am aware now that I can pull the breaks whenever I want, even though I am tempted to keep racing. Now I have more self-control. I have never experienced that before. I am more aware of my fatigue which led to the insight that I should take more moments of rest."*

Several participants mentioned increased attention and linked it to decreased memory problems. One participant explained that before the training, he was constantly distracted by other things instead of being focused on what he was doing or what somebody was telling him. Because of this increased focus, he felt that his memory improved, or at least that there were fewer situations in which he forgot something.

> *"I have learned that when you handle situations with more awareness, it also enters your memory better. My greatest complaints were my memory complaints. Now I see that it was not technically my memory that was impaired, but that something went wrong in imprinting the memories."*

Several participants worried less about their memory complaints, and linked this to a higher level of acceptance.

> *"[Before the training] I wanted to remember and know everything, now I am better able to let this go. I accept that the way I function now is how I function. That's it. Not wanting more."*

In this way, participants were also able to accept situations (in which there was stress or they forgot something) and themselves as they were, rather than as they wished they were. A higher level of acceptance resulted in more self-compassion for two participants as well.

> *"Along the way it is getting easier to think: 'Ok, today I couldn't work on it, but I can do it tomorrow.' So, I got less demanding towards myself."*

Other benefits from the training that were mentioned by several participants involved a different approach towards stressful situations. Most participants mentioned that they reacted to stressful situations differently after the training.

> *"I try to take more distance from the stressful event and do nothing about it for a while, so that when I do something about it, I am less irritated or agitated."*

Difficulties

Participants mentioned several difficulties during the training. The majority of the participants reported problems planning their homework exercises.

> *"It was a great challenge for me to fit the homework exercises in my daily pattern. I was astonished how busy my daily schedule actually is."*

In addition to their busy schedules, many participants experienced inner pressure.

> *"From the moment I get out of bed I feel like I have to do all these things, while no one is actually pushing me. It is only my own idea that I need to complete everything that day."*

Some participants mentioned the role society has on this pressure to perform:

> *"Stress is in our society, but definitely also in yourself and we all participate in it. Before you know it, you go and join the rat race with everybody else."*

In addition to these difficulties, several participants mentioned physical impairments as an obstacle. For example, participants with a lumbar hernia, arthritis or a dislocated shoulder reported that it was difficult for them to participate in all the movement exercises. A number of participants also mentioned that lack of sleep (already present before the training) made it hard to concentrate during exercises because of fatigue.

Considerations

Several participants mentioned that the guided audio recordings were necessary for them to complete the mindfulness exercises.

> *"I tried to do the body scan without the CD, but I fell asleep after five minutes. So, I really need the CD, otherwise I cannot finish the exercise."*

Several participants mentioned that since the training ended, it was significantly harder to keep up with the exercises and that the training sessions were motivating. Half of the participants suggested that the training should be longer. Even though the intention is there, many participants realized it will be difficult to maintain their practice without the sessions.

> *"Yes, I have the intention to not let it go. But now I think to myself: 'How often have I actually done these exercises [since the course ended]', and that is pretty disappointing".*

One participant stated she would have liked to have a few more meetings to ask more questions or share experiences. A number of participants suggested that, for this reason, the time of the sessions could be extended. Another participant mentioned that sometimes she could not hear the trainer because of her hearing impairment, but she indicated that this was resolved during the training.

Discussion

The aim of this study was to determine the feasibility and acceptability of the 8-week MBSR program in middle-aged and older adults with cognitive complaints. The results suggest that the 8-week MBSR program is feasible and acceptable, with all participants reporting benefits of the study. In addition, participants showed reduced scores on depressive and stress symptoms, and an increase in quality of life and mindfulness.

No major adjustments seem necessary for this training to fit the needs of these middle-aged and older adults. Even though participants reported cognitive complaints, there were no indications that they were not able to process the information of the training. The difficulties that were mentioned in the interviews were not specific to the nature of their complaints but involved problems generally experienced by participants such as finding the time to practice. This indicates that there is no need to increase the length of the training. This is in line with a study that found no added benefit of a 12-week compared to an 8-week MBSR course for older adults[13].

Interestingly, few participants addressed their memory complaints in the interview. All participants had more concerns with daily stress and being overwhelmed. The training helped them with stress management, to become more aware, find serenity and learn when and how to take a break when a situation is overwhelming. Several participants reported increased acceptance and self-compassion. This is in line with other qualitative research in other populations, where similar themes have been reported (e.g. Hoffman et al., 2012)[15].

The self-reported quantitative data supported the qualitative data. They showed a decrease in depressive and stress symptoms and an increase in quality of life and mindfulness. However, only for the two subscales of non-judgment and non-reactivity were these changes significant. Even though this study cannot rule out non-specific effects associated with attention, general group support, hope or expectations, which may all have contributed to these improvements, there is a large body of evidence in other patient groups that report similar findings[38]. Perhaps symptoms of stress and depression were related to participants' cognitive complaints, and the relief of these symptoms helped improve their functioning. Future studies with larger samples are required to disentangle general effects from specific mechanisms.

No improvement in the subscales of MIA was found to indicate that subjective memory improved. There was a very slight improvement of the MSE, but it is unclear whether memory self-efficacy increased due to the training. A randomized controlled trial investigating the effects of a memory training on the MSE also did not find a change in memory self-efficacy[39]. However, unlike the current analysis, this report did observe changes in the subscales Change and Anxiety. Thus, measures of anxiety and depression appear to be sensitive to change after an intervention.

The proof of concept for the neuropsychological test battery showed that it was feasible to administer cognitive tests online. However, there are disadvantages to online testing. Without supervision, it is difficult to verify if the participant adheres to the instructions. Other factors such as the ability to use the mouse with accuracy could influence the test results and might have a steep learning curve. Moreover, without a normative dataset for online assessment it is difficult to draw conclusions about their cognitive level (i.e. the scores cannot be compared to the regular normative set). Despite these disadvantages, online testing would be particularly helpful in the collection of follow-up data for large scaled studies: decreasing the burden for participants (e.g. no travel to a testing site) and research staff. Although all cognitive measures showed improvement (with a significant change only in verbal memory), it is likely that these are due to test-retest effects. Future research should control for the test-retest effects of online testing

by including a control group. Perhaps a pre-baseline test to familiarize participants with test procedures and to ensure that the change in scores is due to the intervention is required. Moreover, parallel versions of the tests should be used to attenuate retest effects[40].

The results of the present study should be interpreted with care due to several limitations. The sample size of the study was small and therefore lacked power, had an increased risk of type 1 error due to multiple comparisons and did not have a control group. However, the focus of this study is on the qualitative results. Another limitation is that fidelity to the MBSR program was not confirmed by, for example, taping and reviewing the session. Future studies ideally should include a fidelity measure, in particular if it involves a large study with multiple trainers. In addition, future studies should take into account that one of the biggest obstacles in recruitment is the time investment for participants. This might induce a bias and should be controlled for. In spite of these limitations, the results of the present study are encouraging and may inform future research.

This study was a pilot study without a control group to assess acceptability and feasibility. The thematic analysis showed that participants reported benefits from the interventions and no adjustments for the training seem to be necessary for middle-aged and older adults with cognitive complaints. However, it might be worthwhile to investigate the use of booster sessions. The participants indicated a need for continuation of supervised practice, which could be addressed with extra follow-up sessions. Furthermore, future studies may consider a cost-effectiveness analysis of delivering MBSR to this demographic. The initial cost of the training might prevent service use because of an increase in well-being. The standard 8-week MBSR may be effective in targeting stress and depressive symptoms in older adults with cognitive complaints, improving quality of life and cognition, but this remains to be tested in a randomized controlled trial with an active control group.

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7

Mindfulness training for people with dementia and their caregivers: rationale, current research, and future directions

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Abstract

The world population is aging and the prevalence of dementia is increasing. By 2050, those aged 60 years and older are expected to make up a quarter of the population. With that, the number of people with dementia is increasing. Unfortunately, there is no cure for dementia. The progression of symptoms with no hope of improvement is difficult to cope with, both for patients and their caregivers. New and evidence-based strategies are needed to support the well-being of both caregiver and patient. Mindfulness training is a body-mind intervention that has shown to improve psychological well-being in a variety of mental health conditions. Mindfulness, a nonjudgmental attention to one's experience in the present moment, is a skill that can be developed with a standard 8-week training. Research has shown preliminary but promising results for mindfulness-based interventions to benefit people with dementia and caregivers. The aim of this review is (a) to provide a rationale for the application of mindfulness in the context of dementia care by giving an overview of studies on mindfulness for people with dementia and/or their caregivers and (b) to provide suggestions for future projects on mindfulness in the context of dementia and to give recommendations for future research.

Introduction

The world population is aging and the prevalence of dementia is increasing. By 2050, those aged 60 years and older are expected to make up almost a quarter of the world's population[1]. People who develop dementia mainly express concerns about memory loss, but also experience difficulties with communication, loss of control and autonomy. Informal caregivers have an important role in the care for people with dementia[2]. Informal caregivers of people with dementia experience providing care as stressful, and show higher levels of psychological distress than caregivers of physically frail elderly people and non-caregivers[3]. From the moment of the diagnosis of dementia, both the person with dementia and the caregiver will enter a time with stress and uncertainties.

Current interventions to support people with dementia and caregivers often focus on one or the other group, rather than the dyad[4]. New strategies are needed to support the well-being of both caregiver and person with dementia. Mindfulness training is an intervention that has shown to improve psychological well-being in both healthy and clinical populations[5–7]. Mindfulness based interventions (MBI) have received increasing empirical support, suggesting it increases well-being of older adults and caregivers in particular.

The aim of this review is (a) to provide a rationale for the application of mindfulness training in the context of dementia care by giving an overview of studies on mindfulness for people with dementia and/or their caregivers, and (b) to provide suggestions for future projects on mindfulness in the context of dementia and to give recommendations for future research.

Mindfulness-Based Interventions: General Overview

Although there is a wide variety of interventions that include components of mindfulness (e.g. Acceptance and Commitment Therapy), this review focuses on the two programs with the largest evidence base, the Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT). These group-based programs have been studied in healthy populations and in those with mental or physical disorders, showing satisfactory to good efficacy[7–9].

The main characteristic of these standardized programs is the cultivation of mindfulness: being able to direct attention in the present moment, in a nonjudgmental way, to allow one to act with awareness. Mindfulness is both a characteristic with a population distribution and a skill that can be trained by practicing mindfulness meditation[10]. The standard program consists of eight weekly group meetings with a duration of 2-2.5 hours each plus a one-day class during the sixth week, and homework for approximately

45 minutes a day. The programs incorporate meditative exercises such as the body scan, hatha yoga, sitting meditation, and walking meditation[11,12]. As with any skill, it is important that participants continue the practice after the program has ended, so that they can continue to develop mindfulness and might use it in future difficult situations.

Mindfulness and Aging

Recent research on MBI and aging show positive effects on cognitive, emotional and psychological domains. There is preliminary evidence that mindful meditation may improve attention, memory, executive function, processing speed and general cognition[13,14]. Moreover, studies show that meditation influences brain structure and function, particularly in areas involved in attentional control, self-awareness and emotion-regulation[15–17]. Although more systematic research is needed, preliminary results indicate that meditation might reduce age-related cognitive decline[18]. These conclusions are drawn from both cross-sectional studies (e.g. comparing meditators versus controls) and longitudinal studies with differences in duration and type of meditation training.

Several mechanisms have been proposed by which mindfulness may promote healthy aging. These include enhanced attentional control, preserved neural functioning, improved psychological well-being, and reduced systemic inflammation[19,20].

The Mindfulness-to-Meaning Theory proposes a mechanism through which mindfulness increases psychological well-being[21]. Through mindfulness practice, participants develop a nonjudgmental state of present-moment awareness, which has an effect on the interpretations of stressful life events. This developed broadened awareness, mental flexibility, and the ability to see distressing thoughts and emotions as events that will pass, instead of being the truth, reduces the negative impact of stressful events. Promoting positive reappraisal activates an upward spiral of positive psychological processes as specified in the broaden-and-build theory[22], which increases psychological well-being[21]. Support for an upward spiral where state mindfulness and reappraisal enhance each other has been found in several studies such as a study using autoregressive latent trajectory modeling[23]. Another study showed an upward spiral in which state mindfulness and positive affect enhanced each other[24].

Moreover, the reduction of stress may result in increased telomerase activity, lower blood pressure and heart rate[25]. Furthermore, a recent review suggests that mindfulness meditation may increase cognitive reserve capacity and may mitigate age-related cognitive decline[26].

These mechanisms have been proposed as a general pathway to possibly reduce the risk of developing dementia and to slow the process of neurodegeneration. Although studies on improving cognition in older adults with MBI are inconclusive[27], there is preliminary evidence that MBI increases psychological well-being in older adults, although not without limitations[28]. The majority of this support comes from feasibility studies without a comparison group. These studies reported benefits on pain, attention, sleep, mood elevation and global quality of life[29], emotional well-being[30], anxiety, ruminative thoughts, sleep problems, depressive symptoms[31], and emotional distress[32]. One of the two randomized controlled trials (RCT) in the area of aging reported greater reductions in loneliness in the MBSR participants than the wait-list group[33]. The other RCT reported improvement on disability, pain severity and psychological functioning for both the MBSR and education group[34].

In the following sections, we provide a review of research on MBI for caregivers (section *Mindfulness and Caregivers*) and patient and caregiver dyads (*Mindfulness for Caregiver and Patient Dyads*). In the sections thereafter, we focus on research involving people with dementia with a review of research on MBI for people with dementia (*Mindfulness for Persons with Dementia*), caregivers of people with dementia (*Mindfulness for Caregivers of Persons with Dementia*), and people with dementia and caregiver dyads (*Mindfulness for Dyads (Dementia & Caregivers together*). Studies were identified by searches of PubMed, Web of Science, and PsychINFO using the following search terms: "(mindfulness OR MBCT OR MBSR)" AND "(dementia OR alzheimer OR cognitive decline OR MCI OR caregivers)". Studies on mild cognitive impairment and subjective cognitive decline were included since individuals with these conditions have a high risk to develop dementia. Both qualitative and quantitative studies were included, and studies needed to include a standard MBI. In addition, additional relevant studies were identified from the reference lists of examined articles.

Mindfulness and Caregivers

Research on MBI to support informal caregivers suggests feasibility and potential benefit on mental health[35,36]. Most research involved uncontrolled trials for caregivers of a variety of conditions, ranging from terminally ill patients (e.g. patients with advanced-stage cancer) to chronic conditions (e.g. diabetes).

An uncontrolled pilot study with caregivers of elderly patients with cognitive or other functional impairment underwent an adjusted MBSR program (with shorter 90-minute sessions) and showed improvements in depression symptoms, but no improvements in mindfulness[37]. One RCT on caregivers of patients with chronic conditions showed an improvement on depression, which was the primary outcome, compared to an active

control[38]. Moreover, an improvement in anxiety, self-efficacy and mindfulness were found. However, no effects were found on stress, quality of life or self-compassion.

Mindfulness for Caregiver and Patient Dyads

Because the lives of caregivers and patients are closely related and MBI aims at being present without judgement with these (shared) life experiences, it may be that the beneficial effects of training could be enhanced by applying the intervention to the system of both patient and caregiver. There are several uncontrolled studies that recruited caregivers and patients to participate in the MBI together. In one pre-test and post-test design study, 21 patient-caregiver dyads completed an MBSR training and both caregiver and patients showed improvement in mood, stress and mindfulness[39]. A pilot study with an adapted MBSR (6 weeks: three in-person sessions, three audiotaped sessions) for caregivers of cancer patients included 26 dyads and reported improvement of stress and anxiety for patients, but no significant changes for the caregiver[40]. A mixed-method study included 19 lung cancer patients and 16 partners[41]. Caregiver burden decreased among the partners. However, no significant changes were found in mental distress among all participants. The qualitative analysis of the semi-structured interviews showed that the MBSR training started a process in which both patients and partners became more aware of, and gained more insight into, their thoughts, feelings and bodily sensations. Moreover, participants reported that it was helpful to participate together with their partner. They encouraged each other to perform the exercises, and it led to better mutual understanding.

Mindfulness and Dementia

Mindfulness for Persons with Dementia

Studies with persons with mild cognitive impairment (MCI) or subjective cognitive decline (SCD) have looked at the effect of MBI. This is informative for dementia research, since individuals with MCI have an increased annual conversion rate of 5%–17% to Alzheimer's disease[42], and approximately 60% over a 15-year period of persons with SCD will continue to develop Alzheimer's disease[43].

Studies with persons with mild cognitive impairment (MCI) or subjective memory complaints have looked at the effect of MBI. One pilot study was a randomized trial with 14 people with MCI, which found a trend toward improvement of cognition, quality of life, and well-being for people in the mindfulness condition[44]. An RCT with 22 people of MCI, showed that the participants in the MBI group showed less memory deterioration and greater decrease in depressive symptoms compared to the control group[45].

Besides these studies on MCI, three other studies involved persons with subjective cognitive decline (SCD). One pilot study included 34 older adults with SCD and showed improved worry severity[46]. Another study on MBSR for people with SCD involved an RCT that included 14 older adults with and 22 without SCD[47]. The participants with SCD reported a decrease in cognitive complaints and increase in memory self-efficacy. Attention regulation was improved in all MBSR participants. Recently, a feasibility mixed-methods study in middle-aged and older adults with SCD reported that participants after MBSR worried less about their memory complaints[48]. Moreover, an RCT with older adults with stress disorders and subjective neurocognitive problems compared MBSR to health education, with the primary outcomes being memory and cognitive control[49]. Participants receiving MBSR showed greater improvement in memory, but not cognitive control. Moreover, the MBSR group improved on measures of worry, depression, and anxiety, and decreased cortisol level for those with high baseline cortisol.

Although these studies demonstrate feasibility of MBSR with older adults with SCD and MCI, and preliminary evidence for memory improvement, more research is necessary to investigate whether MBI can influence cognitive decline. Such studies are beginning to be developed. Recently, a protocol mixed-methods longitudinal study for mindfulness with persons with MCI was published. This study will investigate whether a customized MBI will improve cognitive function, mental health, mindfulness and functional abilities in daily life activities of persons with MCI, with a one-year follow-up[50].

Mindfulness for Caregivers of Persons with Dementia

A recent systematic review reported that caregivers of persons with dementia show elevated stress, and poorer attention and executive function performance[51]. Moreover, caregivers of persons with dementia show increased levels of anxiety and depression[52,53]. Studies have reported that caregiving for a person with dementia may be particularly stressful compared to other forms of caregiving[54,55].

Three RCTs have investigated the effects of MBI in caregivers of persons with dementia[56–58]. One study divided 31 caregivers over an adapted MBCT (90 minute sessions, 7 weeks) and two control groups: education and respite only[56]. Both MBCT and education improved the primary outcome of caregiver stress compared to the respite-only group. No effects were found on the secondary outcome measures of cognition and mindfulness. Another study randomized 78 caregivers of persons with dementia into a MBSR or active control group[57]. Caregivers in the MBSR group showed greater improvement in overall mental health, stress and depression. Both interventions improved anxiety, social support and burden. In another RCT, 38 family caregivers of persons with dementia were randomized to MBSR or standard social support control

condition[58]. The caregivers in the MBSR group reported lower levels of perceived stress relative to active control group, but not at the three-month follow-up.

Mindfulness for Dyads (Dementia & Caregivers together)

To date, only two studies have investigated MBI including both persons with dementia as well as their caregivers. One study with single-group, pre-test and post-test design, involved an adjusted MBSR for persons with progressive cognitive decline (n=17, majority with dementia) and 20 caregivers[59]. This study showed improvement in quality of life and depressive symptoms, but no significant findings on cognitive functioning for both patients and caregivers. Another pilot study involved 12 persons with dementia and 8 caregivers with a standard MBSR[60]. Interviews and observations indicated that some participants with dementia were able to learn mindfulness and experienced increases in quality of life. The caregivers were very positive in their evaluation in that it was helping them to cope better with life. Both groups showed improved quality of life after the intervention, but this was not maintained at the 3-month follow up.

These studies show that it is feasible and potentially beneficial to involve the person with dementia and their caregivers together in an MBI. Although the majority of studies have separated these groups, the well-being of a caregiver and the person with dementia should be considered in context because they influence each other. One study using both cross-sectional and longitudinal analyses investigated the role of suffering in 1222 persons with dementia and the well-being of their caregivers[61]. This study showed, in both cross-sectional and longitudinal analyses, that perceived suffering of the person with dementia contributes to caregiver depression and burden. Importantly, this was after controlling for the effects of cognitive and physical disability, memory problems, disruptive behaviors, and time spent on caregiving.

Future Directions and Considerations

Although current research supports the rationale for MBI with persons with dementia and their caregivers, only few RCTs have been conducted and more research is necessary (see **Table 1**). There are several recommendations for future research.

First, more methodologically rigorous trials (RCT with active control) are recommended. The active control is a particularly important component given the strong evidence of the Dodo bird verdict; that all psychotherapies are equally effective[62,63]. However, this does not mean that the effects are realized by the same mechanisms. Since a mindfulness intervention is a complex process, research projects should not only consider the outcomes of a trial, but also address the mechanisms by which the effects

are realized to gain more insight into applying mindfulness in the complex setting of a person with dementia and caregiver. Also, not much is known about the long-term effects, therefore follow-up measurements are recommended. Moreover, an active control for MBI should particularly control for the non-specific effect of "community" associated with mindfulness training. That is, the active control condition needs to provide the same degree of personal contact, being together with other people and feeling of "community".

Second, it is unclear if and what kind of adjustments are necessary for people with dementia and their caregivers. In several studies, adaptation of the MBSR or MBCT protocol to the context of a person with dementia and caregiver is frequently practiced, but it is unclear what the effects of specific adaptations are or what the rationale is. For example, many studies adjust the standard MBSR or MBCT protocol to reduce the duration of the sessions (e.g. Ernst et al., 2008)[64] the number of elderly people is increasing. The aging process and associated stress diminishes their quality of life. Mindfulness-based stress reduction (MBSR, the duration of homework (e.g. Mallya & Fiocco, 2015)[65], or do not include a silent day (e.g. Paller et al., 2014)[59]. Another study increased the duration by spreading out the 8 sessions over 8 months[66]. However, one study compared an extended 12-week MBSR to an 8-week MBSR in older adults with worry symptoms and subjective cognitive dysfunction, and they found no difference in effects for the different duration of the MBSR[46]. Another study showed that a shorter 4-week MBSR with 1-hour sessions improved caregiver burden[67]. With different adjustments and different outcome measures it is difficult to tell which elements are crucial. Moreover, other programs that have major adaptations to an MBSR or MBCT protocol have been developed for people with dementia[68], and a pilot study showed its feasibility in care homes[69].

Other longer forms showed benefits on cognition in people with Alzheimer's Disease over a two-year period, including three weekly sessions based on mindfulness, cognitive stimulation therapy and progressive muscle relaxation[70].

Instead of general adjustments, there may be large inter-individual differences driving the need for adjustment within the training group. Therefore, it might be useful to approach the training with a certain amount of flexibility, both from the trainers and the participants. There might not be a "one size fits all" approach. Keeping that in mind, future research should investigate which modifications are beneficial. For example, practical strategies to support home practice and choice in personalized materials should be considered. Perhaps more exercises dedicated to compassion and self-compassion would be a valuable addition. This, however, is ideally investigated with a three-armed

RCT (MBI with and without extra compassion, and an active control). Investigating components of the MBI have recently been a topic of discussion, not just for people with dementia and their caregivers. Recently, essential characteristics of MBI and teachers of MBI have been described[71]. However, it does not touch upon the optimal amount of practice time in the sessions and time spent on homework assignments. Investigating home-practice could lead to different guidelines (i.e. less time) for homework, since the amount of time practiced seems to not be related to the positive outcomes of the program[72]. These and other studies measuring practice time, rely on self-report. However, similar results were found using objective electronic measurement in a six-week MBCT-based program that showed that adherence to practice (length, frequency, and type of meditation chosen) did not relate to outcomes[73]. Recently, a first study to directly compare an 8-week with a 4-week MBI showed improvements compared to controls in mindfulness and positive affect, but not between the 4-week and 8-week MBI[74]. Thus, abbreviated MBI might be similar to a standard MBI. These studies on length of the program and practice might guide future research on adjustment of the program. A shorter program or shorter sessions might be just as effective, and would make it more accessible for a larger number of people. In particular, time investment could be a major obstacle for caregivers with people with dementia, and a shorter program could increase the likelihood of participation.

Third, future research could investigate whether it is desirable to have people with dementia and their caregiver participate in the MBI together. Although it seems feasible (e.g. Paller et al., 2014)[59], caregivers may feel conflicted when they are invited to pay attention to themselves and focus on their own needs, preventing them from fully benefitting. For example, a few of participants in a study with MBSR for couples facing lung cancer indicated that they felt worried and distracted about the well-being of their partner (van den Hurk et al., 2015)[41]. Moreover, caregivers might be reluctant to discuss their fears. Perhaps a program that allows the dyad to separate at specific times could be investigated.

Fourth, future research should consider the following outcome measures to gain more insight into the effects of the MBI. Perhaps it is more fruitful to not only focus on cognition but also on other aspects, such as positive health[75]. Measuring the influence of compassion on the relationship of the caregiver and person with dementia could be investigated since MBI can improve compassion and that, in turn, might improve couple functioning. One dyadic study with lung cancer patients and their partners showed that more self-compassion was related to less psychological distress in individuals with low levels of self-compassion[76]. Unfortunately, compassion was not measured in most studies. However, research has shown self-reported increases in self-compassion after

meditation, impacting mental health[77]. Increasing self-compassion among persons with dementia and caregivers might be particularly valuable since it helps to buffer against anxiety and is associated with increased well-being[78]. It thus may boost personal resources to supply care for others. In addition, meditation enhances compassionate responding; thus, acting to relieve a person's suffering[79,80]. Increased caregiver compassion could support the person with dementia. Measuring caregiver management strategies and the impact of MBI might also be interesting for future research since caregivers characterized by non-acceptance was associated with behavioral problems in people with dementia[81]. MBI is thought to increase acceptance and therefore, it might also have an influence on the caregiver style. Future studies could investigate cost-effectiveness in order to make the training program more interesting for reimbursement (e.g. via health insurance). Another important direction of future research is to identify, understand and develop strategies to overcome barriers to participation, such as time, finances and personal convictions; not only at the individual level, but also what the strategies and barriers are to deliver the program on a larger scale.

This review focuses on older adults since dementia is an age-related disease, however, the essential adjustments to the training are not particularly age-driven. That is, MBI would also be suitable for persons with early onset dementia. A major concern in this field of research is that there are many forms of meditation. Although this review is focused on MBSR/MBCT, other programs with a mindfulness component are developed and researched. It is important to investigate the potential mechanisms and carefully consider the reasons for adjustments.

Conclusions

In sum, current research supports the rationale for MBI with persons with dementia and their caregivers, shows that it is feasible with dyads, and shows preliminary support for improvement in their well-being. In applying interventions for people with dementia and caregivers, their well-being should be considered in context and how dyads influence each other. MBI may offer the couple a skill that they can both use in the future challenges that accompany the context of living with dementia, thus enhancing resilience and autonomy. However, more research is necessary, in particular with respect to what adjustments are beneficial and necessary, and the use of outcomes measures related to positive health.

Table 1. Overview of MBI studies with caregiver and patient dyads, and MBI studies with persons with SCD, MCI or dementia.

Author (year)	Design	Sample	Care recipient relationship	Adjustments to MBSR/ MBCT	Outcome Measures	Results
Berk et al. (2017)	UCT	Older adults with SCD (n = 13), age (M = 59, range 45-85), 54% male	NA	8 weekly sessions, 2.5-hr, day long retreat.	FFMQ-SF, SCS-SF, EuroQol, DASS-21, MIA, VLT, Trail Making Test A and B	Improved verbal memory (delayed recall). Participants reported positive effects; e.g. worried less about memory complaints.
Birnie, Garland, & Carlson (2010)	UCT	Cancer patients and their partners (n= 82) 47.6% male, age patients (M = 62.9, SD = 7.37) age partners (M = 62.8, SD = 9.34)	Spouse (n = 20) Common-law (n = 1)	No details	POMS, C-SOSI, MAAS	Significant reductions in mood disturbance, muscle tension, neurological/GI and upper respiratory symptoms. Partner's mood disturbance scores were positively correlated with patients' symptoms of stress and negatively correlated with patients' levels of mindfulness
Brown, Coogle, & Wegelin (2016)	RCT	Caregivers of family members with dementia, n = 38 (MBSR = 23, CON = 15), age (M = 61.14, SD = 10.41), 15.8% male, CON = social support	Parent (n=19) Spouse (n=16) Other (n=3)	8 weekly sessions, 1.5-2-hr, day long retreat.	PSS, AAQ, POMS, SF-36, ZBI, FCI-MS, salivary cortisol.	MBSR lower levels of perceived stress and mood disturbance post-intervention compared to SS control, at 3 month FU no difference between groups. No differences in diurnal cortisol response change of the course of the study
Larouche et al. (2016)	RCT	Older adults with MCI, n=22 (MBI=11, CON =11), age (M = 71.6, SD=7.6), 63.6% male	NA	NS	verbal free-recall memory test, geriatric depression scale, WHO quality of life.	Post-intervention, MBI less objective memory deteriorations, greater decrease in depressive symptoms, increased quality of life
Leader et al. (2013)	UCT	People with dementia (n=12) and caregivers (n=8)	NS	8 weekly sessions, 2.5 hr.	WEMWBS, qualitative	Increase in WEMWBS, not maintained after 3 month FU. Interviews showed people with dementia able to learn mindfulness and experienced increased quality of life; the caregivers evaluated positively and helped with coping.

Table 1. (Continued)

Author (year)	Design	Sample	Care recipient relationship	Adjustments to MBSR/ MBCT	Outcome Measures	Results
Lengacher et al. (2012)	UCT	Cancer patients and their family caregivers (n=52)	Family caregivers: 53.8% lives with patient	Modified for 6-week program. Three in-person sessions and three audiotaped sessions (content validity index score of .944), 2-hour sessions	PSS, CESDS, STAI, MSAS, MOS-SF-36, Cortisol and immune (IL-6)	Post interventions, patients improved on stress and anxiety. Both patients and caregivers lower IL-6
Lenze et al. (2014)	UCT	Two MBSR groups, n=34. 8-week program (n =16), 12-week program (n=18), 12-week age (M = 70.7, SD = 4.9) 22% male, 8-week age (M = 70.9, SD = 4.5) 31% male	NA	8 weekly sessions, 2.5 hr. sessions and daylong session. 12-week reduced day-long retreat to 2.5 hr.	List learning, digit span test, verbal fluency, color-word interference, PSWQ-A, CAMS-R, MAAS	Sign. improvement post-intervention List delayed recall Paragraph immediate recall Paragraph delayed recall Verbal Fluency Color-word interference, worry reduction (PSWQ-A), mindfulness (measured by CAMS-R, but not MAAS),
Oken et al. (2010)	RCT	Three groups: MBCT (n=10, age (M = 62.50, SD = 11.61) 20% male, education class (EDU), n=11, age (M = 67.09, SD = 8.36), 27% male; respite only (CON), n = 10, age (M = 63.80, SD = 7.93), 10% male	Parent (n = 8) Spouse (n = 23)	6-weekly 90-minute group sessions	RMBPC, PSS, CESD, SF-36 Fatigue, MAAS, FFNJ, GPSE, ESS, NPI total, Caregiver appraisal, CRI, Cortisol, IL-6, TNF-α, hsCRP, Stroop interference, ANT, Word list immediate and delayed recall.	improved caregiver self-efficacy (RMBPC) for both MBI and EDU compared to CON

Table 1. (Continued)

Author (year)	Design	Sample	Care recipient relationship	Adjustments to MBSR/ MBCT	Outcome Measures	Results
Paller, et al. (2015)	UCT	People with progressive cognitive decline (=17) and caregivers (n=20), 19 were part of patient-caregiver dyad. Age patients (M = 72), age caregivers (M = 62.5). Diagnosis patients: Dementia (AD: n=9, FTD: n =1), MCI (n=2), memory loss due to strokes (n=2), memory complaints (n=3)	Parent (n=5) Spouse (n=13) Other (n=2)	8 weekly sessions, 1.5 hr. Elements of dialectical behavior therapy and acceptance and commitment therapy	QOL-AD, GDS, PSQI, BAI, Trail Making Test A and B, RBANS,	Increased quality of life, fewer depressive symptoms, better subjective sleep quality.
Smart et al. (2016)	RCT	Older adults with (n = 14, mean age 70.0 (SD 3.45, 61% male) and without SCD (n = 22, mean age 69.6 (SD 3.58, 27% male) randomized into MBI or psychoeducation	NA	8 weekly sessions, 2 hr.	CCI, MSEQ, FFMQ	SCD participants showed decrease in cognitive complains and increase in memory self-efficacy after intervention. Attention regulation was improved in MBSR participants.
Van Den Hurk et al. (2015)	UCT	Lung cancer patients (n=19, mean age 61.7 (range 54-77), 53% male) and partners (n=16, mean age 60.9 (range 30-76, 44% male)	Partners (n=16)	8 weekly sessions, 2.5 hr. sessions and day long retreat.	HADS, QLQ-LCI, CIS-F, IES, PSWQ, MAAS, SPPIC, CRA-SE	Caregiver burden in partners decreased after MBSR.

Table 1. (Continued)

Author (year)	Design	Sample	Care recipient relationship	Adjustments to MBSR/ MBCT	Outcome Measures	Results
Wetherell et al. (2017)	RCT	Older adults with SCD randomized to MBSR (n = 47, mean age 70.4 (SD 4.1, 13% male) or health education control condition (n = 56, mean age 73.3 (SD 6.1, 27% male)	NA	8 weekly session, 1.5 hr., half-day meditation retreat.	Memory (immediate, delayed paragraph and list recall), Verbal Fluency Test and Color Word Interference Test (DKEFS), PSWQ, CGI-I, PROMIS, CAMS-R, cortisol	MBSR group improved on worry, depression symptoms at post intervention and worry, depression and anxiety symptoms. MBSR participants showed decreased cortisol level for those with high baseline cortisol.
Wells et al. (2013)	RCT	Older adults with MCI (n = 14) randomized into MBSR, age (M= 73, SD = 8) or CON, age (M=75, SD = 7).	NA	8 weekly sessions, 2 hr., and one daylong retreat day.	ADAS-cog, RAVLT, COWAT, RS, PSS, QOL-AD, HHI, LOT-R, CES-D, MAAS	Control subjects performed better than the MBSR group on the Trails A and B tests. Non-significant trends that suggested improvement with MBSR vs. control were detected for quality of life, cognition and well-being.
Whitebird et al. (2012)	RCT	Caregivers of family members with dementia randomized in MBSR (n = 38, age (M = 57.2, SD = 9.6), 13.2% male) or active control (CCES: n = 40, age (M = 56.4, SD = 10.2), 10% male)	Parent (n = 58) Spouse, sibling or friend (n = 20)	8-week, 2.5-hr, and a 5-hr retreat day.	PSS, CESD, STAI, MBCBS, MOSSSS	MBSR improved overall mental health, reduced stress, decreased depression compared to CCES. Both interventions improved caregiver mental health and improved anxiety, social support and burden.

AAQ: Acceptance and Action Questionnaire II, ADAS-cog: Alzheimer's Disease Assessment Scale cognitive subscale, ANT: Attentional Network Test, BAI: Beck Anxiety Inventory, CAMS-R: Cognitive Affective Mindfulness Scale-Revised, CESD: Center for Epidemiologic Studies Depression Scale, CIS-F: Checklist Individual Strength-Fatigue, CON: Control group, COWAT: Controlled Oral Word Association Test, CRA-SE: Caregiver Reaction Assessment-Care-derived Self-Esteem, CRI: Coping Responses Inventory, C-SOSI: Calgary Symptoms of Stress Inventory, ESS: Epworth Sleepiness Scale, FCI-MS: Mutuality Scale of the Family Care Inventory, FFNJ Five Factor Mindfulness Questionnaire Nonjudgement Subscale, FU: Follow-up, GDS: Geriatric Depression Scale, GPSE: General Perceived Self-Efficacy, HADS: Hospital Anxiety and Depression Scale, HHI: Herth Hope Index, hsCRP: high-sensitivity C-reactive protein, IES: Impact of Event Scale, IL-6: interleukin-6, LOT-R: Life Orientation Test-Revised, MAAS: Mindful Attention Awareness Scale, MBCBS: Montgomery Borgatta Caregiver Burden Scale, MBCT: Mindfulness Based Cognitive Therapy, MBSR: Mindfulness Based Stress Reduction, MBI: Mindfulness Based Intervention, MCI: Mild Cognitive Impairment, MOSSSS: Medical Outcomes Study Social Support Survey, NA: Not Applicable, NPI: Neuropsychiatric Inventory, NS: Not Stated, POMS: Profile of Mood States, PSQI: Pittsburg Sleep Quality Inventory, PSS: Perceived Stress Scale, PSWQ-A: Penn State Worry Questionnaire-Abbreviated, PSQI: Pittsburgh Sleep Quality Index, QIQ-LC: Quality of Life Questionnaire - Lunch Cancer, QOL-AD: Quality of Life-Alzheimer's Disease, RAVLT: Rey Auditory Verbal Learning Test, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, RMBPC: Revised Memory and Behavior Problems Checklist, RS: Resilience Scale, SCD: Subjective Cognitive Decline, SD: Standard Deviation, SPPIC: Self-Perceived Pressure from Informal Care, TNF-α: tumor necrosis-α, WEMWBS: Warwick Edinburgh Mental Well-being Scale, UCT: uncontrolled trial, ZBI: Zarit Burden Interview

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8

Mindfulness-based intervention for people with dementia and their partners: Results of a mixed-methods study

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Abstract

Objectives Studies have shown preliminary support for mindfulness-based interventions benefitting people with dementia and their caregivers. However, most studies focus on these two groups separately. This study examined whether it would be possible for people with dementia and their caregiver to jointly undergo an adjusted Mindfulness-Based Stress Reduction (MBSR) training, named TANDEM.

Method The 8-week MBSR training was adjusted based on a literature review and interviews with experts (clinicians and mindfulness trainers). Seven couples (a person with early-stage dementia and their caregiver) participated together in the 8-week TANDEM program. Semi-structured qualitative interviews were conducted after completion. Questionnaires (administered before and after the intervention) assessed the primary outcomes of quality of life and psychological distress (stress, anxiety and depressive symptoms). Secondary outcomes were mindfulness, self-compassion, positive mental health, worrying, and perceived burden (for caregivers).

Results All participants completed the program and reported beneficial effects (relaxation, awareness, acceptance, and resilience). Most managed to integrate exercises into their daily lives and planned to continue their practice. Participating in a group was considered valuable and supportive. Furthermore, it was appreciated that participants could follow the training together (as a couple). The quantitative results showed a small effect on increased quality of life for caregivers. No substantial decrease in psychological distress was apparent. Caregivers displayed a large increase in mindfulness.

Conclusions The results of this mixed-methods study suggest that an adjusted mindfulness program is feasible and well-received among couples of persons with early-stage dementia and their caregiver, warranting further research in this area.

Introduction

Receiving a diagnosis of dementia has a major impact on psychological well-being, both for the persons with dementia (PwD) as well as the caregivers[1]. Caring for a person with dementia is associated with higher levels of distress, illness and decreased quality of life[2].

Interventions to support caregivers and PwD often focused on each category separately, rather than including a dyad (PwD and caregiver together)[3]. However, a jointly experienced intervention to support dyadic well-being may be more effective. Dyadic approaches in interventions for chronic disease are more effective than those only focused on patients[4]. Mindfulness-based interventions represent a promising option to support PwD and caregiver together. Mindfulness is a skill that can be developed with a training and is defined as an awareness that arises through paying attention, on purpose, in the present moment, and non-judgmentally[5]. Mindfulness-based interventions have shown to improve psychological well-being in both healthy and clinical populations[6–8]. Most common variations are the Mindfulness-Based Stress Reduction (MBSR[5]) and Mindfulness-Based Cognitive Therapy (MBCT[9]). Both are an 8-week group training where participants practice mindfulness meditation. Mindfulness-based interventions fit in the recent shift to define health from a positive perspective; as an ability to adapt and self-manage in the face of social, physical, and emotional challenges[10]. This is particularly relevant to PwD and caregivers facing a future with no cure possible.

Because of the growing evidence of the positive impact of MBSR and MBCT on well-being, recent studies have investigated the effects on caregivers, as well as people with mild cognitive impairment and dementia. Although this research is still in its infancy, studies suggest that mindfulness-based interventions could benefit both PwD and caregivers[11]. While these studies have provided tentative support for the effectiveness in both groups separately, more research is needed to investigate if it is feasible to have the caregiver and PwD participate together in a group training. Moreover, qualitative research can explore the experience of PwD and their caregivers and the mechanisms through which mindfulness may bring about improvement. The current study used a mixed-method approach to investigate whether (1) an adjusted MBSR program is a feasible intervention for PwD and their caregivers and (2) whether this MBSR program improves the quality of life and reduces psychological distress in PwD and their caregivers.

Methods

Study Design

To explore the feasibility and effectiveness of and adapted MBSR program in PwD and caregivers, a mixed-methods pilot study was conducted. Participants completed self-report questionnaires before and after the TANDEM program. The semi-structured interviews were conducted individually, one to three weeks after the intervention. The Ethical Review Committee Psychology and Neuroscience of Maastricht University approved the protocol. All participants gave written informed consent.

Participants

Participants were recruited through regional case managers, flyers, and an advertisement in a local paper. Participants were included when they were part of a dyad consisting of a person diagnosed with any form of dementia, and a caregiver. Other inclusion criteria included (1) the ability of the PwD to participate in the training, assessed during an intake with the trainer which included a short mindfulness exercise (2) able to understand and use the Dutch language (3) no psychiatric comorbidity requiring medical treatment (4) willingness to attend the training together (5) participation in at least 6 out of 9 sessions. Both trainings took place in the homelike environment of regional centers for informal care for people with cancer.

Adapted MBSR program: TANDEM

The TANDEM training (an acronym that, in Dutch, stands for "Attention Training for People with Dementia and their Caregivers") was based on the original MBSR program as developed by Kabat-Zinn[5]. Several adjustments were made to make the intervention more suitable for PwD and caregivers. The workbook materials were written in an easy to follow language and icons were used to mark different sections. Theme cards were developed to accompany the workbook. Also, topics such as acceptance and communication were given extra time in the training since this was deemed an important theme for PwD and caregivers. Moreover, the movement exercises were modified to be less strenuous. The program was discussed with mindfulness trainers and experts on dementia and caregivers. The TANDEM program consisted of eight sessions of 2.5 hours each, a 4-hour silent day and daily homework assignments of 45 min per day. A range of exercises were taught during the program to cultivate mindfulness, such as the body scan, sitting meditation, gentle yoga exercises, mindful walking, and the 3-minute breathing space. During the meetings, home practice and the application of mindfulness in daily life were discussed as well as psycho-education about stress and communication.

Participants received a workbook with information for each session and a USB or CD with recordings to guide home practice. Also, cards with the theme of the week were given as a reminder (e.g. to be placed on the dining table at home). The two trainers of the TANDEM program were qualified and experienced mindfulness trainers.

Measures

Feasibility and Acceptability

Feasibility was measured with attendance and completion of the program. Acceptability was assessed with semi-structured interviews, in which participants were asked about their experiences and provided feedback (see **Table 1**).

Table 1. Topic list of semi-structured interview

1.	General impression
2.	Beneficial and difficult aspects of the training
3.	Materials (i.e., workbook), difficulty
4.	Length of the sessions and training
5.	Home practice
6.	Changes due to the training (i.e., dealing with difficulties)
7.	Future (i.e., plans to continue practice)
8.	Participation with peer group
9.	Participation with partner
10.	Recommendations for adaptations

Quality of Life

Quality of life was the primary outcome measure and was assessed using the World Health Organization Quality of Life assessment (WHOQOL-Bref[12,13]). The four categories physical health, psychological health, social relationships, and environment were averaged to calculate a total quality of life score.

Caregiver Burden

The Self-Perceived Pressure from Informal Care (SPPIC), a nine-item questionnaire, was used to assess the extent to which caregiving was experienced as a burden[14]. To add positive aspects of caregiving, the subscale Care-Derived Self Esteem of the Caregiver Reaction Assessment (CRA-SE) was added[15].

Self-compassion

Self-compassion was measured using a short 12-item form of the Self-Compassion questionnaire[16,17].

Positive Mental Health

The Dutch Mental Health Continuum Short Form (MHC-SF) is a 16-item questionnaire that was used to measure emotional, psychological and social well-being[18,19].

Worry

The 16-item *Penn State Worry Questionnaire (PSWQ)* was used to measured worry[20,21].

Psychological Distress

The 21-item Depression Anxiety Stress Scales (DASS-21) was used to measure psychological distress[22].

Mindfulness

The Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF) was used to assess mindfulness[23]. The FFMQ-SF has been validated in older adults[24].

Statistical and Qualitative Analysis

Data were analyzed using SPSS 22.0 (IBM Corporation, Armonk, NY). Cohen's d_z, the standardized mean difference effect size for within-subject designs, was calculated[25]. No other formal statistical evaluations were calculated, given the explorative nature of the study, insufficient power and absence of a control group.

The content of the interviews was analyzed using deductive content analysis. The transcripts were coded independently by two researchers (LB and AS), using the qualitative software package ATLAS.ti (Scientific Software Development GmbH, Berlin). The codes where clustered within categories, based on the semi-structured interview, independently and discussed to reach consensus. This consensus process was verified by a third researcher (MdV).

Results

Participants

A total of 14 people participated in the training, or seven couples. All caregivers were the partners of the PwD. The age of participants ranged from 56 to 81 years. **Table 2** gives an overview of participants' characteristics.

Feasibility

All participants attended six or more sessions of the TANDEM training, with an average of 7.3 out of the eight weekly sessions. All participants completed the post-training questionnaires. Five out of seven participants with dementia indicated that their partner had helped them with filling out the questionnaires.

Table 2. Characteristics of people with dementia and partners at baseline

	Total (n = 14)	**Persons with dementia (n = 7)**	**Partners (n = 7)**
Age, mean (SD)	71.11 (7.45)	71.46 (7.41)	70.75 (8.14)
Gender (n, % female)	7 (50)	2 (29)	5 (71)
Level of education (n, %)			
Low	3 (21)	1 (14)	2 (29)
Middle	8 (57)	4 (57)	4 (57)
High	3 (21)	2 (29)	1 (14)
Type of dementia[a] (n, %)			
Alzheimer's disease		4 (57)	
Vascular dementia		2 (29)	
Frontotemporal dementia		1 (14)	
Time since diagnosis (in years), mean (SD)		1.89 (1.69)	

[a]For some participants the diagnosis was probable AD and they did not pursue further diagnostic procedures.

Qualitative Evaluation

All participants completed the interviews after the training ended, with the exception of one couple. They had received bad news and did not want to participate in the interviews anymore but did fill out the questionnaires. Their case-manager reported that they had enjoyed the training, in particular that all participants were respected, the materials were good, and that many relevant topics were discussed. A total of twelve participants were interviewed.

The results from the interviews were divided into four topics: experiences, participating with partner, effects, and practical feasibility. These topics are described below and clarified by quotations from the interviews (C = caregiver, PwD = person with dementia).

Experiences

In general, participants were very positive about the TANDEM training. Participants mentioned several aspects they appreciated about the training such as the good atmosphere in the group, pleasant location, practical, logical structure, sharing experiences with group members, becoming calmer, and the training being very useful in general. All participants expressed satisfaction with their trainer. They felt supported

and connected because of the trainer, and the trainer's voice was experienced as pleasant.

> *"I was really impressed [with the training]. In particular, the complete structure of the training, the direct applicability of everything, the space that everyone had to express themselves. I have the feeling that all those other couples, that we really got to know them… There is truly a back-and-forth. The homework. Everything felt right." (C3)*

> *"[The trainer was great because] she was very harmonious and friendly in the way she interacted with us. …. But what we also experienced (when we were at home, put the iPad on the table, and sat down to do the exercises) that she had such a pleasant voice. Yes, that did a lot for me." (PwD3)*

Participants started the training with different expectations. Some participants had the need to learn new tools to cope with the diagnosis of dementia, or to get help with specific problems (e.g. difficulty sleeping). Other participants had some doubts and started the training with a critical attitude because they did not know if and how it could help them or thought it might be too 'new-age' for them.

> *"I actually started [the training] reluctantly. We had signed up for it. …. Thinking, 'We will at least start it. Start it, try it. And then see if it does anything for us.'" (C6)*

Different experiences with practice during the training were reported. Whereas a few participants found a daily routine to practice, most did not practice every day and tended to prefer shorter exercises such as the three-minute breathing space. Participants experienced relaxation, falling asleep during practice, and having difficulties doing the exercises at home. The longer exercises (45 min) were more difficult to plan but were recognized as beneficial.

> *"The longer exercises had a high threshold, so I had a hard time getting started. Even though I would be the first one to say, 'If you start such a long exercise and you experience the calmness that comes with it, it is very pleasant.' Even though the cost was high, the reward was definitely there." (C4)*

One participant frequently experienced sadness while practicing. Although she appreciated a new-found connection with her emotions, she also struggled with how to deal with this.

"And then you got the assignment to see if you could apply the exercises when things don't go well. 'What do you feel? How does that feel? What stands in the way? And if something is in the way, do nothing with it. It is there and it can be there.' And what happened with me, in that phase of the training, is that I was confronted with my sadness. …. As a rational human being you try to solve things that are unsolvable. You can be confronted with things that you can solve. But not the whole story [of dementia]. And at first you try to reflect on it as little as possible. But that is doomed to fail, because that isn't how it works. You try to find a way … you can't get around it. So, I increasingly got very sad, but not in a negative way." (C4)

Participating in a Group with their Partner

All participants felt positive about participating in a group, which was a safe place where one could be oneself and share one's experiences. The group was considered a very valuable aspect of the training; participants felt connected to the group members and felt less alone because of them. Some participants shared more in the group than others. A few participants noticed differences when comparing themselves to the group. One PwD noticed that other PwDs were worse off than he was. One caregiver noticed that everyone was dealing with the diagnosis in their own way.

"[Participating in a group] was marvelous ... Of course, it is in the back of your mind, 'what will happen [in the future regarding the diagnosis]?' … The fear. And then you hear from other people how they felt and what they experienced. I learned a lot and I got a lot out of it." (C1)

"We were a good group together. It felt right for us. We got along. We felt a camaraderie. It really was good. Everyone shared with each other except for me. I'm not much of a talker." (PwD1)

Participation of both PwD and partners in one group was perceived as valuable. Couples enjoyed it. Some mentioned a feeling of solidarity and liking that their partners heard their experiences in the group. None of the participants felt the need to do the training without their partner. One caregiver mentioned that even though she could imagine that a group with only caregivers could be valuable, she would still prefer doing the training with her partner. One PwD was concerned before the training started that his partner would say negative things about him during the training.

"Well, what went through my mind [before the training started] was, 'She's not going to say unpleasant things about me, is she?' That wasn't the case." (PwD3)

"[Participating with my partner was] very pleasant. Just because we can talk about it well, doesn't mean that everything comes up in conversation. Just because it doesn't come up. Not because it's taboo. But a lot of things come up [in the training] that made me think, 'that's good for him to hear.'"

Couples practiced together as well as separately. They encouraged each other to do the exercises. One caregiver had a hard time not getting angry when her partner did not want to do the exercises with her.

Most of the time he reminded me [to do the exercises]. (laughter) I would think, 'Should I skip today..?' .... But he was the instigator. (PwD6)

We did the [homework] together. After the morning coffee, my husband was the one to get everything ready, as if to say, 'come on.' I really liked that I didn't have to make him do it." (C3)

Some participants reported that the training had influenced their relationship as a couple. Caregivers were better able to prevent or deal with quarrels. They felt more connected. One caregiver mentioned that they had more physical contact. Several participants mentioned that the communication between them had improved.

"[My partner] is very fast. When she talks she jumps from one thing to the next. [I'll say:] 'What are you talking about?' 'Oh, wait,' she says. She didn't used to do that. That has completely changed over the last month. .... She says, 'Let me explain,' and then she does explain it. And she really does. And that makes her so much happier, and me too. So that works. Not always. But usually we do it like that." (PwD4)

"I ask him more questions. I don't assume as much anymore. And I used to be very good at assuming. And now I just ask, 'What is that like for you?' This is much more useful to him. He participates more. That has changed." (C3)

Effects

The training brought beneficial changes to all participants, with the exception of one PwD who said that nothing had changed. Participants mostly report increased calmness and relaxation. The training helped both caregivers and PwD to cope with and accept the diagnosis. They reported an increased awareness and spending less time on automatic pilot and instead being in the moment. Some participants reported increased self-care. Moreover, participants learned new ways to deal with difficulties.

"At night, sometimes I wake up in a panic, and I used to stay up all night… awake with palpitations and feeling miserable. But now I know I can't change it. There's nothing that I can do about the situation. It is how it is and it will follow its course. And then I just focus on my breath. And I know I can't do anything to change this. This doesn't make it painless, but it helps me to keep going." (C3)

"I notice that I react better to the outside world. I'm on the board of a community center. Someone else on the board [said about me,] 'Typical, he probably forgot.' That gets under my skin…. It makes me mad. But now, mindfulness makes me calmer." (PwD2)

"I feel better. I'm a nervous Nellie. I'm someone who likes to be on time. I can't stand being late. That makes me a little nervous, but it got better. …. I think, 'Oh, let it go'. (PwD5)

Practical feasibility

The materials (the workbook and cards) were appreciated, however, most PwD did not use them. Some caregivers used the workbook but most considered it a reference book and did not use it much. The workbook was considered legible and accessible. Moreover, a few caregivers mentioned that the texts and poems were inspiring. The cards were put up in their houses as a reminder by most participants.

"[Reading] was difficult. I would read [the cards], but then I would forget what it said. They weren't really useful." (PwD4)

"We always put the cards on the table, every week a different one. It reminds you…a few sayings stick with you: [Grant me the serenity to accept the things I cannot change, courage to change the things I can, and wisdom to know the difference.]" (C2)

The length of the 8-week training was considered adequate by most participants. One participant would not mind if it were shorter, whereas another expressed a strong need for continued support with the practice. Although most participants would enjoy booster sessions the general impression was that the length was appropriate.

"The eight weeks. That was not something I was looking forward to, but apparently it was necessary to get through the material. In hindsight, I liked going. Last week [I was disappointed that it had ended]. Now I'm happy to have time for other things." (C5)

"Before [the training started], I thought to myself, 'Geez Louise, busy for two months!' And then you're also supposed to [do homework.] It wasn't as if I didn't want to do it, but I wasn't exactly enthusiastic. But already after the first meeting I wanted to continue. Yes, it was long, but I liked it very much." (PwD3)

The duration of the sessions (2.5 hours) was considered appropriate and feasible.

"I thought that [the length of the session] was good. At a certain moment it's enough. Your head is full. Full or empty. You start to notice one thing or another, and then I think it's enough. Then you want to go and digest it." (C2)

Different elements from the training were considered most useful, but only after the initial response that everything was considered useful. Participants mentioned elements such as taking care of oneself and finding a balance between activities that consume or give energy, calmness that the exercises bring, the three-minute breathing space because it is easily applicable, the explanation about acceptance, and remembering quotes like "You can't stop the waves, but you can learn to surf." when dealing with difficult situations. One caregiver had an immediate answer when asked what was most useful, namely the analogy of biking on a tandem together.

"[The analogy of riding a tandem bicycle together] got through to me the most of anything in the training. I thought, 'Dang, that's it!' … This is what's happening. You are on the back seat of a tandem bicycle. You have to follow. Unfortunately, you have to follow, because she will not get better, it will only get worse. So, you will have to give in. You will have to accept it. That is difficult, but because of the training I have arrived at that insight." (C6)

Participants had a difficult time mentioning what specifically from the training was least useful. They responded that nothing in particular could be omitted. After that, sometimes a few personal experiences were mentioned such as disliking doing exercises on the floor or already having the knowledge of certain topics discussed. However, nobody reported that anything should be left out of the program.

"I worked in education and have experience with communication. That part [of the training] wasn't an eyeopener for me. …. Then you know how communication is heavily influenced by assumptions…. But it is good to have it in [the training], because there will be a lot of people that do not realize this." (C4)

When asked specifically if they thought adjustments were necessary, most participants did not have a specific answer. A few people wished that the training was closer to where they lived, that it would be helpful if there would be booster sessions, that the group should probably not exceed 10 people, and that health insurance should cover this training for caregivers and PwD. All participants had the intention to keep up with their practice, although one PwD would let it depend on his partner. In particular the breathing space and informal exercises (e.g., practicing awareness in daily activities) were mentioned.

Effectiveness

Table 3 shows the scores of the questionnaires before and after the TANDEM training. Caregivers' and PwD scores show different directions in changes. Changes with a large effect size ($d_z \geq 0.8$) were found with increased mindfulness in caregivers and reduced self-compassion in PwD. Small ($d_z = 0.2$) to medium ($d_z = 0.5$) effect sizes were found for reductions in mental health and quality of life in PwD, and reductions in worry and self-esteem, and an increase in quality of life in caregivers.

Table 3. Characteristics, baseline and post-intervention scores of persons with dementia and partners.

	Total					Persons with dementia					Partners				
	Baseline (n = 14)		Post (n = 14)			Baseline (n = 14)		Post (n = 14)			Baseline (n = 14)		Post (n = 14)		
	M	SD	M	SD	dz	M	SD	M	SD	dz	M	SD	M	SD	dz
QoL (WHOQOL-Bref)	16.01	1.34	16.07	1.33	0.09	16.43	1.33	16.26	1.74	0.29	15.51	1.31	15.85	0.70	0.47
Psychological distress (DASS-21)	8.48	7.20	8.14	8.03	0.03	6.00	5.05	6.29	5.77	0.04	10.95	8.51	10.00	9.91	0.07
Mindfulness (FFMQ-SF)	81.92	6.74	83.85	7.10	0.39	83.00	6.32	82.17	7.25	0.13	81.00	7.44	85.29	7.20	2.86
Self-compassion (SCS-SF)	3.49	0.84	3.29	0.45	0.23	4.01	0.63	3.22	0.51	1.11	3.05	0.76	3.35	0.43	0.39
Mental health (MHC-SF)	3.64	1.04	3.60	0.61	0.07	3.85	0.47	3.63	0.40	0.52	3.44	1.42	3.57	0.81	0.17
Worry (PSWQ)	48.71	11.18	48.43	12.90	0.03	42.43	11.76	44.57	11.72	0.18	55.00	6.35	52.29	13.73	0.25
Caregiver burden (SPPIC)											26.14	7.73	26.71	7.18	0.17
Caregiver self-esteem (CRA-SE)											24.57	4.86	23.57	4.58	0.46

d_z: Cohen's d standardized mean difference effect size for within-subject designs, CRA-SE: Caregiver Reaction Assessment - Care-Derived Self Esteem subscale, DASS-21: 21-item Depression Anxiety Stress Scale, FFMQ-SF: Five Facet Mindfulness Questionnaire - Short Form, PSWQ: Penn State Worry Questionnaire, MHC-SF: Mental Health Continuum - Short Form, QoL: Quality of Life, SCS-SF: Self Compassion Scale - Short Form, SPPIC: Self-Perceived Pressure from Informal Care, WHOQOL-Bref: World Health Organization Quality of Life assessment

Discussion

This study showed that participating in the TANDEM training, an adjusted MBSR, was feasible for PwD and their partners. All participants completed the training. Quantitative data showed a small effect for an increase in quality of life in caregivers and a decrease for PwD. Participants did not show a substantial reduction in psychological distress, but the levels were not elevated at baseline. Caregivers showed a large increase in mindfulness. No large effects were found for PwD. The qualitative analysis showed that for most participants, the training seemed to increase calmness, awareness, acceptance, and resilience (e.g., dealing with difficult situations). Participating in a group together with their partner was considered very valuable and had a positive influence on their relationship. These results suggest that the training provides tools to both PwD and caregiver to cope with dementia and to support each other.

In a qualitative study on the needs of early-stage dementia caregivers, caregivers reported the importance of acceptance to be able to adapt to the situation[26]the needs of early-stage dementia caregivers (EDC. However, caregivers also indicated the lack of knowledge, difficulty acknowledging changes, and focus on loss interfered with the process of acceptance. In our study, participants reported that acceptance was what they gained from the TANDEM training. It seems that the training might fulfill an important aspect needed to adapt to the disease.

Increased acceptance can potentially influence caregiver management strategies. Caregiver management strategies can be characterized by a high or low level of acceptance of the caregiving situation and dementia related problems[27]. Future research could investigate whether the TANDEM training might positively influence a non-adaptive care management strategy that is characterized by a low level of acceptance and high level of neuroticism in the caregiver. Mindfulness has an inverse association with neuroticism[28]. Successful interventions that target neuroticism and a non-adaptive caregiver strategy could result in lower levels of negative emotions, such as depression, in the caregiver and lower levels of behavioral changes, such as hyperactivity, in the person with dementia[27].

All participants felt positive about the trainer. Even though the groups had two different teachers, similar aspects were mentioned such as liking the voice and the way the trainer interacted with the group. It is likely that the trainer is a crucial element in the training, by facilitating the group process and providing a safe environment. Although elaborate teacher training and meditation experience is considered essential to ensure that the mindfulness training is delivered properly and effectively[29], little research has been done on the importance of trainer experience and competence. Recently, one study

showed that trainer competence of MBCT was not associated with treatment outcome for depression[30], whereas another study showed that higher training levels of teachers were associated with positive outcomes in MBSR[31]. Although more research is needed, we recommend a trainer with in-depth teacher training and experience.

None of the participants mentioned that they would rather participate without their partner. However, it might be possible that caregivers would benefit from participating in a group with other caregivers only, since it is possible that during the training they are more preoccupied with the well-being of their partner instead of their own. A pilot study with lung cancer patients and caregivers showed that participants can feel distracted by the presence of their partner because they are concerned about their well-being[32]. The participants in our study did not report this, however, future studies should keep this potential issue in mind. Moreover, future research could investigate how the connection between PwD and caregiver will change over time while the illness progresses. Mindfulness may offer a tool to increase resilience to the unavoidable changes in their relationship that come with a diagnosis of dementia. It may offer people the flexibility to be with the loss of the known relationship and a willingness to explore love and connection in the changed relationship.

One participant reported that the training made her experience sadness. This was not a negative experience, but she did not know if it was going to pass. Although this is the experience of a single individual, it should be noted that the training might increase negative emotions by providing mental space for these during practice. It is crucial that trainers are aware of this possibility and that the participants are guided in this process.

The study has several limitations. The results may reflect a self-selection bias; where certain characteristics may motivate people to participate in the mindfulness training. Future research could interview potential participants that decide not to participate to get more insight into barriers to participate in a mindfulness training. Many PwD (71%) indicated that their partner helped them filling out their questionnaires. Therefore, it is unclear whether this might have influenced their answers to the questions. This study was a feasibility pilot without a control group. Future research could consider an active control group such as the Health Enhancement Program, which is similar to the MBSR but without the mindfulness component[33].

One of the strengths of the study is its mixed-methods design. By using both qualitative and quantitative methods we get better insight into whether this training is feasible and effective. Monitoring attendance and completion rates is indicative of the acceptance of the training, while information from the interviews can give more in-depth information

on why participants completed the training and what might need to be adjusted in the future. Moreover, comparing the results from the questionnaires and interviews, we can see whether they overlap and what might not be registered by questionnaires. The quantitative results did not show large changes in psychological distress or worry, even though participants indicate in the interviews many positive effects such as increased calmness, acceptance, and ability to deal with difficult situations. Mindfulness exercises have given them a tool whenever things get too much. Apparently, these benefits are difficult to assess with the outcome measures that were chosen. Our study showed a small increase in caregiver burden, and a small decrease in caregiver self-esteem. These results are in the opposite direction of what was expected. The standard deviation indicates that there was a high variability. This was not only the case for these two questionnaires, but for many other questionnaires. Participants might differ a lot in the changes they report. Future research might look into other options than retrospective questionnaires, such as experience sampling methodology to get more insight into individual processes[34]. Moreover, other questionnaires, such as the Applied Mindfulness Process Scale might be useful to get insight into how participants use their mindfulness practice to deal with negative or stressful events in daily lives[35].

To conclude, this study demonstrates that TANDEM, an adapted MBSR, is a feasible intervention for people with dementia and their caregivers, together in one group. Quantitative data showed a small effect on increase in quality of life for caregivers and a decrease for PwD, but no effects on psychological distress. Although specific benefits differed between participants, many beneficial aspects (increased relaxation, awareness, acceptance, and resilience) were shared by most caregivers and PwD. The training might help people with dementia and their caregivers to accept the diagnosis and deal with the changes ahead. Future research combining experience sampling methodology and qualitative research is important to obtain further insight into how to tailor interventions for this population.

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9

General Discussion

General discussion

Mindfulness is a promising avenue to support healthy aging. It might also benefit both people with dementia and their caregivers. The studies in this thesis use various methods to investigate how mindfulness can contribute to healthy aging.

In part I we looked at the potential mechanisms of mindfulness and aging. In **Chapter 2** we gave an overview of existing research and potential mechanisms on how mindfulness-based intervention (MBI) can influence cognitive functioning in older adults. In **Chapter 3** we investigated whether positive affect (PA) could serve as a buffer for cognitive decline over a period of twelve years. In **Chapter 4** we investigated whether mindfulness was associated with low-grade inflammation. To explore whether short mindful meditation exercises could increase mindfulness and PA, and how these concepts interact in daily life, we conducted an experiences sampling study in **Chapter 5**.

In part II we looked at mindfulness-based interventions for people with subjective cognitive decline, as well as people with dementia and their caregivers. In **Chapter 6** we examined the feasibility of MBI in individuals with memory complaints in a mixed-methods study. In **Chapter 7** we give an overview of studies using MBI with caregivers and people with dementia, and discussed the rationale behind giving MBI for people with dementia and their caregivers together. In **Chapter 8** we investigated the feasibility and effect of MBI on people with dementia and their caregivers in a project called TANDEM (in Dutch: Training AaNdacht voor mensen met DEmentie en Mantelzorgers).

This chapter integrates the main findings with previous research, discusses methodological considerations, and describes the implications for future research.

Main findings

Part I Mechanisms

Can mindfulness-based interventions influence cognitive functioning in older adults? (Chapter 2)

Results from previous studies indicate that mindfulness-based interventions (MBIs) are feasible for older adults. However, research on cognitive improvement is inconclusive. Of the six studies that were reviewed, three were randomized controlled trials. Most studies had a high risk of bias and the sample sizes were small. The study with a low risk of bias and large sample size reported no significant findings between the MBI and active control group on several cognitive measures. More rigorous studies are needed to examine the effect of MBIs on cognition in older adults. The use of a

standardized intervention format, active control group, large sample size and extensive neuropsychological test battery is recommended.

Does positive affect predict cognitive decline? (Chapter 3)
Positive affect (PA) was measured at baseline in participants from the Maastricht Aging Study. Memory, executive functions and information processing speed were assessed over a twelve-year period. Controlling for demographics and depressive symptoms, there was no significant association between PA and decline in memory, executive functions, and information processing speed at the 6- and 12-year follow-up. These results question whether PA has a protective effect on cognitive aging in adulthood.

Is dispositional mindfulness associated with inflammation and with diabetes-related distress? (Chapter 4)
In the population-based Maastricht Study, a cohort of individuals with and without type 2 diabetes were assessed on dispositional mindfulness. A standardized sum score for inflammation was created from the following plasma biomarkers of low-grade inflammation: high-sensitive C-reactive protein, serum amyloid A, soluble intercellular adhesion molecule-1, interleukin-6, interleukin-8, and tumor necrosis factor alpha. Higher mindfulness scores were associated with lower inflammation scores in individuals with and without type 2 diabetes. Moreover, in individuals with type 2 diabetes, higher mindfulness scores were associated with lower diabetes-related distress.

Is a mindful state associated with positive affect in daily life, and do short exercises influence this? (Chapter 5)
Momentary data was collected using experience sampling methodology (ESM). This study showed that it is feasible to prompt participants to do brief meditation exercises and collect ESM data. Most participants thought it was a positive experience and almost half would use the application to keep up with their meditation practice. The ESM data showed individual differences in variability in both mindfulness and PA. Higher momentary mindfulness predicted higher PA at the next moment, in both the intervention (ESM and brief meditation prompts) and control period (ESM only). The same pattern was seen for PA predicting mindfulness in the next moment. The item *non-judging* predicted PA, independent of PA at the previous moment. Daily mindfulness (as assessed by an evening questionnaire) did not predict PA.

Part II Interventions

Is a mindfulness-based intervention feasible for individuals with subjective memory problems? (Chapter 6)

The results of this study suggest that the eight-week mindfulness-based stress reduction (MBSR) program is feasible and acceptable. Participants reported positive effects of the training such as increased calmness and worrying less about their memory. Moreover, they showed reduced scores on depressive and stress symptoms, and an increase in quality of life and mindfulness. No adjustments to the training program seem necessary to fit the needs of individuals with subjective memory problems.

What is the current available evidence for the use of mindfulness-based interventions in people with dementia and their caregivers?

The literature on MBIs with caregivers and people with dementia shows that it is feasible with dyads (person with dementia and caregiver) and preliminary support for improvement in their well-being. Most research has examined the effect of MBIs with caregivers or people with mild-cognitive impairment. Few studies have investigated people with dementia or dyads. More research is recommended, in particular to investigate whether adjustments to the MBI are beneficial and necessary.

Is a mindfulness-based intervention for people with dementia and their caregivers feasible and effective?

Dyads, consisting of a person with early-stage dementia and their partner, participated in an adjusted MBSR training, named TANDEM. The results showed that the program was feasible. Small effects were found for an increase in quality of life in caregivers, and a decrease for people with dementia. No substantial reduction in psychological distress was found. A large increase in mindfulness was found for caregivers but not for people with dementia. In the interviews, participants reported increased calmness, awareness, acceptance and resilience. They considered participating in a group and with their partner valuable. The results suggest that the TANDEM training provides tools for both the person with dementia and their caregiver to cope with dementia and to support each other.

Measuring mindfulness

This thesis used the 24-item Five Facet Mindfulness Questionnaire (FFMQ) to measure mindfulness[1,2] (**Table 1**). In **Chapter 4**, the questionnaire was used to measure dispositional mindfulness, and in **Chapters 6** and **8**, it was used to examine whether a mindfulness-based intervention (MBI) increased mindfulness. In chapter 5, the highest loading item for each facet was used to measure state mindfulness.

Table 1. Example items for mindfulness facets from the Five Facet Mindfulness Questionnaire.

Facet	Example item
Observing	I pay attention to physical experiences, such as the wind in my hair or the sun on my face.
Describing	I'm good at finding words to describe my feelings.
Acting with awareness	I find myself doing things without paying attention. (R)
Non-judging	I tell myself that I shouldn't be thinking the way I'm thinking. (R)
Non-reactivity	When I have distressing thoughts or images, I just notice them and let them go.

Note: R = reverse-scored item

Several authors have questioned whether all facets in the FFMQ are important components of mindfulness, and whether all aspects of mindfulness are covered by the FFMQ[3,4]. The facets *observing* and *describing* are not as sensitive to change after an intervention as the other facets[1]. Moreover, in meditators, higher levels of *observing* were associated with better psychological adjustment (less psychological symptoms and higher well-being), whereas in non-meditators, an opposite pattern was shown[5]. This is in line with the results from **Chapter 4**, where higher *observing* scores were associated with more diabetes-related distress in individuals with diabetes (of whom 95% did not meditate). Moreover, another study with individuals with diabetes showed no negative association between *observing* and emotional distress, whereas other facets did show that assocation[6]. The interpretation of the *observing* facet should be done in context of whether the sample is meditating or non-meditating. Also, the interplay with other facets should be considered. Namely, it seems that acceptance is key for *observing* to have a positive impact. The Monitor and Acceptance Theory suggests that attention monitoring (measured by *observing)* is essential to improve attention to both positive and negative affective information, but that acceptance (measured by *non-reactivity)* is crucial to improve affective regulation[7].

The *describing* facet (the ability to label inner experiences with words) might be related to mindfulness rather than being a component of mindfulness[3]. Instead, *describing* might be a facilitator of the mindfulness process. That is, if one is good at describing one's inner experiences, it might be easier to become more mindful. However, *describing* is often not included in definitions of mindfulness[8]. It also is not included in the definition by Kabat-Zinn. More recently, Bishop and colleagues proposed a two-component model of mindfulness to establish a consensual operational definition of mindfulness[8]. The first component is self-regulation of attention, such that attention is directed to experiences in the present moment. The second component involves a particular orientation to one's experiences in the present moment, characterized by curiosity, openness, and acceptance. Also, *describing* is not included in this definition. The idea behind *describing* being a part of mindfulness is that labeling of experiences is used in mindfulness meditation[9]. However, the goal is not to give an accurate description of

one's experiences, but to label those experiences. For example, a feeling can be labeled as "sadness," or thoughts as "worrying about my job". The original intention to capture the skill of labelling in the questionnaire is suggested by the use of labeling in mindfulness meditation, and by research that suggests that verbal labeling of feelings reduces the response of the amygdala and other limbic regions (involved with emotional processing) to emotional stimuli[10]. However, when looking at the items, it is understandable that it is not interpreted this way. For example, the *describing* item "I can easily put my beliefs, opinions, and expectations into words", seems to assess whether someone is articulate instead of capable of labeling their experiences. Perhaps the facet *describing* would be better designated as *labelling*, and would include items adjusted to better capture this skill. Of course, the question remains whether non-meditators would be able to interpret these questions.

In addition to the concerns about the facets of the FFMQ, components of mindfulness might be missing. Although mindfulness can be developed with regular practice, and result in qualities such as insight, wisdom, compassion and equanimity[9], such aspects are not captured with the commonly used questionnaires. Perhaps this results from the adaptation of traditional mindfulness meditation practices for secular use[11]. Indeed, when Buddhists were interviewed to compare Buddhist mindfulness and mindfulness in psychology, several missing components were identified[4,12]. For example, the intention to return awareness to the present moment, and awareness of aversion and suffering were absent from the FFMQ[4]. Moreover, the absence of elements such as empathy and wisdom were also discussed[12]. Future research could investigate whether components such as wisdom and compassion are qualities that result from mindfulness practice or measures of mindfulness[13].

In **Chapter 5** experience sampling method (ESM) was used to track fluctuations of state mindfulness and positive affect. Several participants noted that the act of answering questions, when prompted by the application on their smartphone ten times a day, about how you are feeling at that moment was like a mindfulness intervention in and of itself. Self-monitoring creates awareness, which can increase self-insight, and can instigate a change in behavior[14]. In that sense, ESM itself can increase mindfulness. However, this mostly involves the aspect of awareness and other components of mindfulness, such as non-reactivity. Using ESM as an intervention might be particularly effective when combined with mindfulness training to ensure that self-monitoring, which might be similar to *observing*, has a positive effect. As discussed previously, according to the Monitor and Acceptance Theory, *observing* needs to be combined with *non-reactivity* to improve affect regulation. For example, *observing* was associated with more depressive symptoms among students with low levels of *non-reactivity*, whereas high levels of

observing was associated with less depressive symptoms in those with high levels of *non-reactivity*[15]. For instance, if the individuals with type 2 diabetes from **Chapter 4** would participate in an ESM study, it is possible that they would increase *observing* and the associated diabetes-related distress, whereas with a mindfulness training they could increase *non-reactivity* to turn *observing* into improved acceptance and emotional regulation.

To conclude, research uses different mindfulness questionnaires that have conceptual differences. Research that uses the questionnaires to optimize the intervention or assess the effectiveness, should do so with caution[16]. Future research would benefit from a consensus about the definition of mindfulness, its essential components, and how sensitive the components are to change by interventions.

Mindfulness and mechanisms of aging

In the introduction of this thesis, several mechanisms by which mindfulness may promote healthy aging were discussed: enhanced attentional control, preserved neural functioning, improved psychological well-being, and reduced systemic inflammation[17,18]. This thesis has contributed to insights into the role of mindfulness and psychological well-being as well as mechanisms in the aging process.

In **Chapter 3** we investigated whether positive affect (PA) was associated with change in cognitive function over 12 years in a sample of the Maastricht Aging Study. No significant associations were found with memory, executive function, or information processing speed. When the association between PA and cognitive performance was examined with PA as a trichotomous variable (PA low, middle, and high), there was a trend for the high PA group to perform better on memory and information processing speed tasks. Future research with a larger sample might be able to examine this association better. One of the limitations was that PA was only measured at baseline. While PA seems to be a relatively stable over time and could be considered a trait[19], it can be altered, for example by mindfulness-based interventions[20]. If PA were measured at several time points, it would be possible to examine whether a mindfulness-based intervention could increase PA. Consequently, the investigation would show if the trajectories of cognitive decline could be changed.

Chapter 4 showed that individuals with higher dispositional mindfulness had lower levels of low-grade inflammation. This association was accounted for by *non-reactivity*. It is possible that being non-reactive is important to reduce unhealthy behaviors (e.g., binge eating or smoking) as a reaction to a stressful event. The participants in the study

with higher mindfulness had a lower body mass index (BMI) and engaged in more physical activity but did not differ in smoking behavior compared to people with lower mindfulness (data not shown). The association between mindfulness and inflammation was independent of lifestyle factors, smoking, alcohol consumption, BMI, and physical activity separately. However, when all lifestyle factors were added to one model, mindfulness was no longer significant (data not shown), possibly indicating that the effect of mindfulness on inflammation is mainly driven through influence on lifestyle. Another possible pathway is that mindfulness reduces stress, thereby influencing the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which in turn influences inflammation[21]. Future research that includes a measure of stress can provide more insight.

Mindfulness-based interventions

Research has investigated the relationship between mindfulness and cognitive function since this might be a way to reduce the risk of developing dementia, and to slow the process of neurodegeneration. Most studies have been done with participants with subjective cognitive decline and mild cognitive impairment, since they are at high risk to develop Alzheimer's disease[22,23]. In line with these studies, the results from **Chapter 6**, a study in which participants with memory complaints completed a Mindfulness-Based Stress Reduction program, found that MBI showed promising results in this target group. In interviews, participants reported positive effects of the training such as increased calmness, and many participants worried less about their memory declining. Participants got more insight that helped them take better care of themselves. Moreover, they adopted a different approach towards stressful situations.

Few studies have been done with participants with dementia and caregivers[24,25]. In **chapter 8**, we included people with dementia and their caregivers as dyads together in one group. Participants were very positive about participating as a dyad, and would not prefer to follow a training separate from their partner (e.g., training specifically for caregivers only). As one caregiver specifically mentioned, there are not many interventions that involve both the person with dementia and the caregiver together. Since the person with dementia and their caregiver go through the process together, it might benefit them to participate in a training together. The participants experienced improved acceptance as a result of the training. Acceptance is an important aspect for adapting to the consequences of a dementia diagnosis[26]. Both people with dementia and their caregivers reported benefits of the training, suggesting that it provides tools that help in coping with dementia. Often participants reported increased calmness or relaxation. While a relaxation training might yield similar benefits, the other benefits

that participants reported were more unique to mindfulness training. For example, improved communication (among partners), better self-care because of increased awareness, or dealing with stressful situations. Future research should consider several follow-up assessments to investigate if these changes are long lasting. Perhaps in combination with interviews at follow-up, this could provide insights into the effects of MBI, and whether these effects remain when dementia has progressed, causing added stress and burden. Future research should also be aware of adverse effects. For example, in **Chapter 8** a caregiver reported in the interview that she became more aware of her sadness. On the one hand she appreciated the new-found connection with her emotions, on the other hand she expressed concern about whether this feeling would ever go away. It is important to realized that an MBI can evoke strong emotions, and although the training will also provide the tools to deal with them, the trainer might need to offer additional support.

Table 2. Six dimensions of health indicators, covering 32 aspects of health

Bodily functions	Mental functions and perception	Spiritual/existential dimension
• Medical facts • Medical observations • Physical functioning • Complaints and pain • Energy	• Cognitive functioning • Emotional state • Esteem/self-respect • Experiencing to be in charge/ manageability • Self-management • Resilience, sense of coherence	• Meaning/meaningfulness • Striving for aims/ideals • Future prospects • Acceptance

Quality of life	Social and societal participation	Daily functioning
• Quality of life/well-being • Experiencing happiness • Enjoyment • Perceived health • Flourishing • Zest for life • Balance	• Social and communicative skills • Meaningful relationships • Social contacts • Experiencing to be accepted • Community involvement • Meaningful work	• Basic ADL • Instrumental ADL • Ability to work • Health literacy

The quantitative results from **Chapters 6** and **8** did not show large effects in the hypothesized direction for most measures. Future studies could benefit from using intervention specific questionnaires that give insight into how participants use their mindfulness practice to deal with negative or stressful events in their daily lives such as the Applied Mindfulness Process Scale[27]. Moreover, future research could focus more on positive aspects that are in line with the new concept of positive health. As a first step towards an operationalization of the new definition of health, a mixed-methods study classified six dimensions of health (**Table 2**)[28]. The resulting radar chart is used in clinical practice as a tool to facilitate for communication between the patient and the general practitioner (**Figure 1**). As part of patient-centered care the patient can

then decide which aspect is most important to them. This tool has not yet been further developed as a measurement instrument for health (which could then be used for research) since the constructs are difficult to measure. Moreover, the effort is met with skepticism by patients, since they often do not recognize themselves in the outcomes of questionnaires[29].

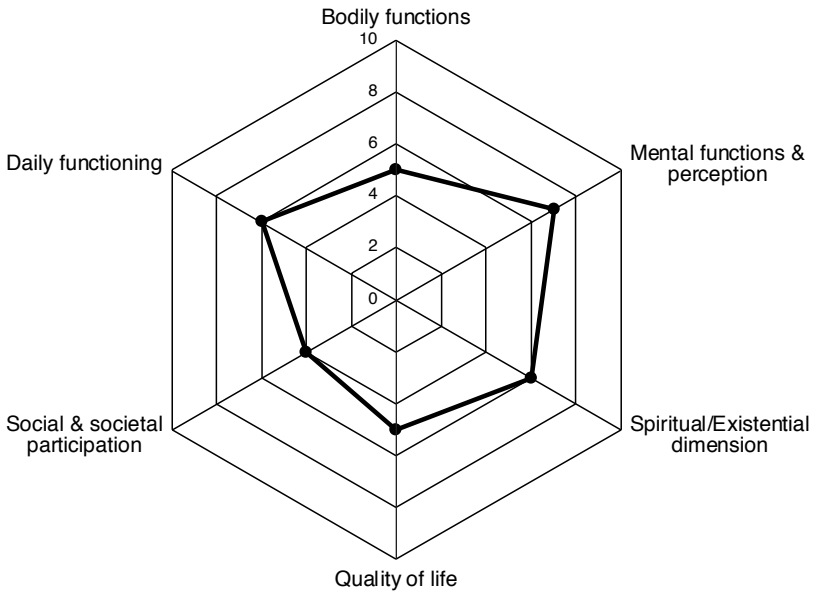

Figure 1. The six dimensions of positive health visualized on a subjective scale for practical use showing an example of a person's state. Adapted from: Huber et al., 2016[28]

The studies in **Chapter 6** and **8** both involved a small sample, and there were large individual differences. Particularly in a small sample, the mean change score does not give a good indication of what the effect of the intervention is (see **Figure 2** for an example from **Chapter 6**). In a larger sample, the individual variability will have a smaller influence. To evaluate interventions, both qualitative and quantitative evidence is necessary, and other methods such as experience sampling method are important[30,31].

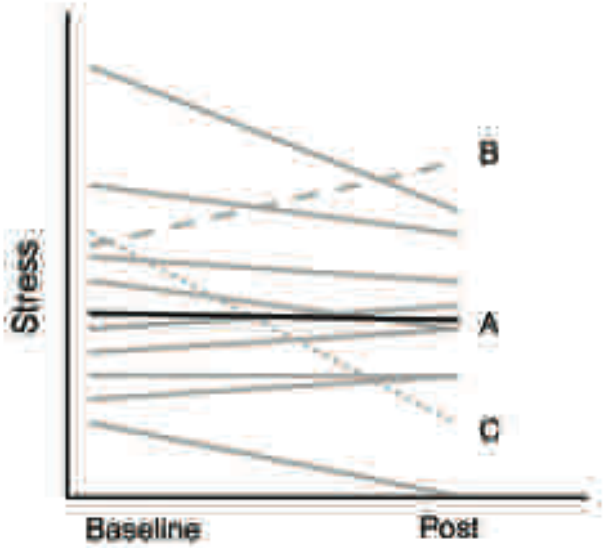

Figure 2. Levels of stress at baseline and after an 8-week mindfulness-based stress reduction program. The mean change is indicated with A (solid black line). Using other methods to look at the individual trajectories could give insight into the working ingredients of the intervention and for whom it may work. For example, qualitative research could give insight into why participant B (dashed line) and C (dotted line) show opposite effects. Moreover, if experience sampling method was used to measure stress at several timepoints, the differences between the participants might disappear; if they do not it is likely that the differences are not due to recall bias.

Qualitative research, while labor intensive, is more likely to provide greater insight into psychological mechanisms, and the effects of the interventions. Interviews can provide valuable information that is not captured by questionnaires. Therefore, even when a large scale RCT is conducted to show effectiveness of the intervention on particular outcome measures, a qualitative evaluation (in a subset) would be a valuable addition. This can also provide insight in mechanisms of effect and generate new hypotheses that could be tested in future research. Furthermore, areas of change that arise from the qualitative data can be incorporated in a new questionnaire designed to try to capture these changes quantitatively.

ESM, used in **Chapter 5**, is another method that is recommended for future research to get better insight into the trajectories of change in individuals. ESM measures experiences and behavior in daily life[31]. Real-time data is collected several times a day at random during consecutive days. In particular, getting insight into how a caregiver deals with everyday difficulties ESM can give much more information than retrospective questionnaires. Recall bias that can be a problem in retrospective questionnaires can be avoided, and associations between different variables can be assessed. Moreover, (multiple) n=1 studies could give us insight into individual processes. For example,

many participants seem to experience a tipping point: a moment when it all comes together. ESM could give insight into whether and when this occurs. Getting insight into the working mechanisms of the intervention could inform possible adaptation of the training. Perhaps with long term experience sampling, the positive spiral can be captured as described in the mindfulness-to-meaning theory. **Figure 3** shows an example of the positive emotion regulatory process of a cancer survivor. ESM might be able to capture this kind of process by showing these fluctuations in positive affect.

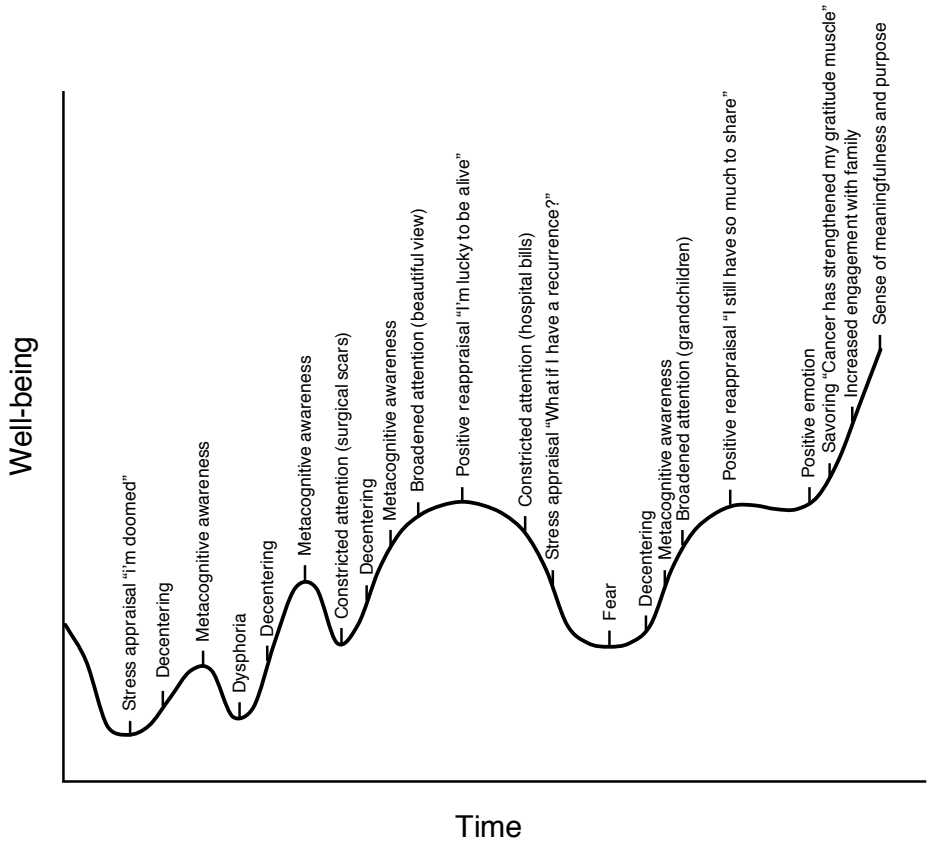

Figure 3. A case example from a cancer survivor showing the mindful positive emotion regulatory process over time. From: Garland et al., 2015[32]

Challenges for future research

One of the major challenges in the field of mindfulness research is the need for more methodologically rigorous studies. Even when an RCT is not possible, an active control group is particularly important given the strong evidence of the Dodo bird verdict (**Box**

1). This states that all psychotherapies are equally effective[33,34]. However, when something is effective for the group as a whole, it does not mean that the therapy is effective for every individual. Different therapies might suit different individuals. Moreover, equally effective does not necessarily mean that the same mechanisms underlie the changes. Also, there are other factors that should be considered. For example, one study showed that the time to relapse recurrence of depression was similar for those who were assigned to maintain their use of antidepressants compared to those assigned to MBCT[35]. While one could focus on the result that they are equally effective, one could also consider the side effects of the medication that people suffer from. Therefore, an equally effective therapy could still be a valuable alternative. Moreover, often research involves only pre and post measurements, and not much is known about the long-term effects. Follow-up is necessary to make a better evaluation and could potentially differentiate between interventions. This is of particular interest with MBI, since what is learned during the training is carried forward. Future research should also investigate the potential importance of refresher sessions. Some studies with long follow-up use refresher sessions[35]. Although these kinds of sessions seem to be an important aspect of the sustainability of interventions[36], it is unclear if and how many are necessary. This is particularly relevant in a progressive disease such as dementia, because people will have to deal with changing circumstances and capacities.

Box 1. The Dodo bird verdict

In 1936, psychologist Saul Rosenzweig coined the term *the Dodo bird verdict* to describe the notion that all therapies are equally effective.

The Dodo bird is a character from the book Alice in Wonderland.

Alice and other characters are wet, and in order to dry themselves the Dodo has them run around until they are all dry. When they asked who had won, the Dodo thought for a while and then said "*Everybody* has won, and all must have prizes."

Rosenzweig argued that similarly with psychotherapies, the common factors are more important than the specific differences, so that all therapies are winners. That is, they all have equally effective outcomes.

Certain components of the interventions require further investigation to assess the magnitude of influence on the beneficial effects. First, future research could clarify the influence of the trainer of the MBI. Several questions remain unanswered such as: are there certain qualities of the trainer that facilitate the benefits for the participants? In both **Chapter 6** and **8**, all participants felt positive about the trainer. Even though these results are from different groups with three different trainers, similar aspects were mentioned such as liking the voice and the way the trainer interacted with the group. It is likely that the trainer is a crucial element in the training by facilitating the group process and providing a safe environment. Although elaborate teacher training and

meditation experience is considered essential to ensure that the mindfulness training is done properly and effectively[37], little research has been done on the importance of trainer experience and competence. Recently, one study showed that trainer competence of MBCT was not associated with treatment outcome for depression[38], whereas another study showed that higher training levels of teachers were associated with positive outcomes in MBSR[39]. Attempts are being made to create quality control of the trainers. In the Netherlands, mindfulness trainers can get certified by an association, which maintains specific requirements regarding their education and experience. However, the question remains whether someone seeking a training is aware of these qualifications. Although more research is needed, a trainer with in-depth teacher training and experience is recommended particularly for vulnerable groups such as caregivers and people with dementia.

Second, the influence of practice on the outcome requires more research. Recently, a meta-analysis showed a small association between home practice and positive intervention outcomes, but there was no evidence for a linear impact of home practice[40]. Another systematic review found that four out of seven studies showed that home practice predicted positive intervention outcomes, and suggested that variability on the guidance on the length of home practice across studies may suppress the relationship between home practice and effect[41]. Sustained engagement with skills practice may be more important than the overall dose or volume of practice over time.

Third, the group effect of the intervention should be taken into consideration when investigating the effects of MBI. Few studies use an active control condition when investigating the effects of MBI. One study showed that MBSRI is not more effective than an active control for improving measures of well-being in a non-clinical population[42]. Another study showed that MBCT was only more effective than active treatment for patients with recurrent depression who have an increase vulnerability[43]. These results emphasize the need for rigorous active control such as the Health Enhancement Program[42]. This program matches the activities in MBSR as closely as possible while not including mindfulness.

Fourth, there are many different kinds of training formats. This variety in training formats is problematic for research because it makes it hard to combine research for meta analyses, and to draw conclusions about effectiveness. Research reviews sometimes include anything that includes any kind of meditation, whether they're programs with short meditation exercises or 2-year long programs. Others focus only on those that are MBSR or MBCT with minor adjustments. Recently, an effort has been made to describe what the important ingredients are for MBI, including trainers (**Table**

3). Crane and colleagues describe the essential and flexible ingredients for MBI. Future studies should use this as a guideline. Moreover, future meta-analyses and reviews can use this as a selection for the studies to evaluate.

Table 3. The essential and flexible ingredients of mindfulness-based programs. From: Crane et al. 2017.

Essential	Flexible
Mindfulness-Based Programs	
• Is informed by theories and practices that draw from a confluence of contemplative traditions, science, and the major disciplines of medicine, psychology and education • Is underpinned by a model of human experience which addresses the causes of human distress and the pathways to relieving it • Develops a new relationship with experience characterized by present moment focus, decentering and an approach orientation • Supports the development of greater attentional, emotional and behavioral self-regulation, as well as positive qualities such as compassion, wisdom, equanimity. • Engages the participant in a sustained intensive training in mindfulness meditation practice, in an experiential inquiry-based learning process and in exercises to develop insight and understanding	• The core essential curriculum elements are integrated with adapted curriculum elements, and tailored to specific contexts and populations • Variations in program structure, length and delivery are formatted
Mindfulness-Based Program Teacher	
• Has particular competencies which enable the effective delivery of the MBP • Has the capacity to embody the qualities and attitudes of mindfulness within the process of the teaching • Has engaged in appropriate training and commits to ongoing good practice • Is part of a participatory learning process with their students, clients or patients	• Has knowledge, experience and professional training related to the specialist populations that the mindfulness-based course will be delivered to • Has knowledge of relevant underlying theoretical processes which underpin the teaching for particular contexts or populations

To conclude, further studies with larger cohorts of older adult expert meditators and longitudinal studies assessing the effects of meditation on meditation-naïve older individuals in randomized controlled trials are warranted. Moreover, future research is needed to investigate the mechanisms underlying the effects of meditation, especially in the context of aging and AD. The Silver Santé Study[44], funded by the European Commission, will investigate the determinants of mental health and well-being in the aging population of Europe. One RCT will include patients with subjective cognitive decline randomized to an MBI or health education program, while another RCT will include cognitively normal older adults. In addition, long-term older meditators are included to provide insight into the mechanisms. These studies will provide greater insight into the role of mindfulness in the aging process.

Conclusion

Mindfulness is sometimes portrayed as a universal panacea for many aspects of human life, aging included. Particularly in the field of aging, mindfulness research is in its infancy and more rigorously sound methods are necessary. Some are tempted to believe that if mindfulness is good for one thing, it will be good for all things. However, since there are many issues with the definition of mindfulness and methodological issues, these parallels are not reliably supported. Moreover, there is a risk of overlooking possible adverse effects. Keeping this in mind, mindfulness is associated with mechanisms related to healthy aging, and interventions seem promising to support the well-being of people with subjective memory problems, as well as people with dementia and their caregivers.

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A

Addendum

Summary

Recently, there has been a growing interest in applying mindfulness-based interventions (MBIs) to postpone age-related cognitive decline and increase well-being. Mindfulness can be described as awareness that emerges through paying attention to the present moment, on purpose, and in an open and nonjudgmental way. A growing body of literature supports the use of MBIs for health benefits and psychological well-being for both healthy and clinical populations. The main aim of this thesis was to gain insight into the mechanisms of mindfulness on aging, to assess how mindfulness fluctuates in daily life, and if it can be boosted with brief exercises. Moreover, this thesis explored a mindfulness-based intervention to support people with dementia and their caregivers. **Chapter 1** provides a general introduction.

The first part of this thesis describes potential mechanisms of mindfulness and aging.

Chapter 2 provides an overview of existing research on whether MBIs can influence cognitive functioning in older adults. Previous studies indicate that MBIs are feasible, however, support for cognitive improvement is inconclusive. Most of the studies had a high risk of bias and small sample sizes. The one study with a large sample size and low risk of bias reported no significant findings on several cognitive measures between participants in the MBIs and active control group. This finding highlights the need for studies that use a standardized intervention format, an active control group, a large sample size, and an extensive neuropsychological test battery.

Chapter 3 examines the association between positive affect and cognitive decline. Previous research shows that mindfulness and positive affect can enhance each other in an upward spiral which improves psychological well-being. Positive affect might influence cognitive aging. Mindfulness could potentially improve cognitive aging by influencing positive affect. In this study, only data on positive affect and cognitive decline were available. Memory, executive function, and information processing speed were assessed over a twelve-year period in participants from the Maastricht Aging Study. No significant association was found between positive affect and decline in memory, executive functions, and information processing speed at the 6- and 12-year follow up. These results bring the protective effects of positive affect on cognitive aging into question.

In **Chapter 4** the association between dispositional mindfulness and low-grade inflammation was examined in participants from the population-based Maastricht Study. Mindfulness can be seen as a trait (dispositional mindfulness) that occurs at varying levels within the population. Higher levels of mindfulness were associated with

lower levels of inflammation, both in participants with and without type 2 diabetes. This association was independent of several lifestyle variables. Diabetes-related stress was assessed in participants with type 2 diabetes. In this group, higher levels of mindfulness were associated with lower levels of diabetes-related distress. These results encourage future research to examine the causality of the association between mindfulness and inflammation and the role of lifestyle in this association.

Chapter 5 describes an experience sampling method (ESM) study in which participants were asked to complete short questionnaires and brief meditation exercises prompted by a smartphone application. Most participants had a positive experience doing the brief meditation exercises several times a day for a week. Half of the participants indicated that, if available, they would use the application to support their meditation practice. Additionally, higher momentary mindfulness predicted higher positive affect at the next moment (i.e., the next time they got a notification) and vice versa. This association was found both during the intervention week (ESM with the brief meditation prompts) and during the control week (ESM only). However, daily mindfulness, which was assessed by an evening questionnaire, did not predict positive affect. Exploring the mindfulness items separately showed that the item *non-judging* predicted positive affect, independent of the level of positive affect at the previous moment. The ESM data showed individual differences in variability of mindfulness and positive affect levels.

The second part of the thesis focuses on mindfulness-based interventions.

In **Chapter 6,** the results of a mixed-method study showed that the 8-week mindfulness-based stress reduction is feasible and acceptable in older adults with subjective memory problems. Participants reported less depressive and stress symptoms, and showed an increase in quality of life and mindfulness in the questionnaires. In their interviews, participants reported positive effects of the training such as increased awareness, serenity, and less worries about memory complaints. However, some participants also indicated that sometimes it was difficult to fit the exercises into their busy lives.

Chapter 7 gives an overview of research on the use of mindfulness-based interventions in people with dementia and caregivers. The literature shows that it is feasible to have a mindfulness-based intervention with dyads consisting of a person with dementia and their caregiver. However, most studies investigate the effects of MBIs with caregivers separately or people with mild-cognitive impairment and not dementia. Studies show preliminary support for improvement in well-being after a training. More research is recommended to investigate both the effects and whether adjustments to the program are beneficial and necessary.

Chapter 8 describes a mixed-methods study on an adjusted mindfulness-based stress reduction training, called TANDEM. Dyads, consisting of a person with early-stage dementia and their informal caregiver (i.e., partner), participated in this group training. Questionnaires showed a small effect for the increase in quality of life in caregivers, and a decrease in quality of life for the people with dementia. A large effect was found for increased levels of mindfulness in caregivers but not for people with dementia. In the interviews conducted after the training was completed, participants reported increased calmness, awareness, acceptance, and resilience. Both caregivers and people with dementia considered both participation in a group and participation with their partner valuable. This study shows that the TANDEM training can provide tools for both the person with dementia and the caregiver to cope with dementia and to support each other.

Chapter 9 describes the main findings of this thesis and provides a general discussion, including methodological considerations as well as implications for future research.

Nederlandse Samenvatting

Er bestaat een groeiende interesse in het toepassen van op mindfulness gebaseerde interventies (MBI's), onder meer om leeftijd gerelateerde cognitieve achteruitgang uit te stellen en het welbevinden te vergroten. Mindfulness zou vertaald kunnen worden met 'opmerkzaamheid'. Het is een bewustzijn dat ontstaat door met aandacht aanwezig te zijn in het huidige moment, opzettelijk en met een niet-oordelende houding. Een toenemend aantal wetenschappelijke publicaties laat zien dat het gebruik van MBI's voor gezondheidsvoordelen en psychologisch welzijn voor zowel gezonde als klinische populaties kan zorgen. Het doel van dit proefschrift was om meer inzicht te krijgen in de mechanismen van mindfulness bij veroudering, te onderzoeken of en hoe mindfulness fluctueert in het dagelijks leven en of het kan worden beïnvloed met korte oefeningen. Bovendien werd in dit proefschrift de toepassing van een MBI onderzocht om mensen met dementie en hun mantelzorgers te ondersteunen. **Hoofdstuk 1** geeft een algemene introductie, bestaande uit de rationale, onderzoeksvragen en de opzet van dit proefschrift.

Het eerste deel van dit proefschrift beschrijft de mogelijke mechanismen van mindfulness en veroudering.

Hoofdstuk 2 geeft een overzicht van het huidige wetenschappelijk onderzoek naar de vraag of MBI's het cognitief functioneren bij ouderen kunnen beïnvloeden. Eerder onderzoek liet zien dat MBI's geschikt zijn voor ouderen, maar het bewijs voor cognitieve verbetering door mindfulnessbeoefening is niet doorslaggevend. De meeste onderzoeken waren mogelijk vertekend ('bias'), oftewel een afwijking in de resultaten door de manier waarop het onderzoek was uitgevoerd en daardoor minder betrouwbaar is, of een kleine steekproefomvang. Het enige onderzoek met een grote steekproefomvang en een laag biasrisico liet geen significante resultaten zien op verschillende cognitieve uitkomstmaten tussen deelnemers in de MBI en de actieve controlegroep. Deze conclusie benadrukt de behoefte aan onderzoek met een gestandaardiseerde interventie, een actieve controlegroep, een grote steekproefomvang en een voldoende uitgebreide neuropsychologische testbatterij.

In **Hoofdstuk 3** werd het verband tussen positief affect en cognitieve achteruitgang onderzocht. Uit eerder onderzoek blijkt dat mindfulness en positief affect elkaar in een opwaartste spiraal te kunnen versterken waardoor het psychologisch welbevinden verbeterd kan worden. Ook lijkt er een verband te bestaan tussen positief affect en cognitieve veroudering. Mindfulness zou mogelijk via positief affect een gunstige invloed op cognitieve veroudering kunnen zorgen. In deze studie waren alleen gegevens over positief affect en cognitie beschikbaar. Verbaal geheugen, executieve functies en snelheid van informatieverwerking werden gemeten over een periode van twaalf jaar in deelnemers aan de Maastricht Aging Study (MAAS). Er werd geen significant verband gevonden tussen positief affect en achteruitgang in het geheugen, executieve functies

en snelheid van informatieverwerking bij de follow-up na 6 en 12 jaar. Deze resultaten zetten vraagtekens bij de beschermende effecten van een positief effect op cognitieve veroudering.

In **Hoofdstuk 4** werd het verband tussen dispositionele mindfulness en laaggradige ontsteking bij deelnemers in het bevolkingsonderzoek van De Maastricht Studie onderzocht. Dispositionele mindfulness is een karaktereigenschap met een hoge mate van variatie in de algemene bevolking. Hogere niveaus van mindfulness bleken geassocieerd met lagere niveaus van ontsteking, zowel bij deelnemers met als zonder type 2 diabetes. Dit verband was onafhankelijk van verschillende leefstijlvariabelen. Een lager niveau van diabetes-gerelateerde stress in deelnemers met type 2 diabetes hield verband met hogere niveaus van mindfulness. Deze resultaten onderstrepen de noodzaak van toekomstig onderzoek om causaliteit in het verband tussen mindfulness en ontsteking en de rol van levensstijl in deze associatie nader te onderzoeken.

Hoofdstuk 5 beschrijft onderzoek naar mindfulness en positief affect gedurende dag met de Experience Sampling Methode (ESM). Met behulp van deze online dagboekmethode werd aan deelnemers gevraagd om korte vragenlijsten in te vullen en korte meditatieoefeningen te doen met behulp van een smartphone-applicatie. De meeste deelnemers hadden een positieve ervaring door de korte meditatieoefeningen meerdere keren per dag gedurende een week uit te voeren. De helft van de deelnemers gaven aan dat zij, indien beschikbaar, de smartphone applicatie zouden gebruiken om hun meditatiebeoefening te ondersteunen. Bovendien voorspelde hogere mindfulness op het ene moment, hoger positief affect op het volgende en omgekeerd. Dit verband werd zowel tijdens de interventieweek (ESM met de korte meditatieoefeningen) als tijdens de controleweek (alleen ESM) gevonden. Het niveau van mindfulness op de dag, die werd gemeten aan de hand van een avondvragenlijst, voorspelde geen positief affect van die dag. Post-hoc analyse van mindfulness items toonde aan dat het item 'niet-oordelen' positieve affect voorspelde onafhankelijk van het niveau van positief affect op het vorige moment. De ESM-gegevens toonden individuele verschillen in variabiliteit van niveaus van mindfulness en positieve affect.

Het tweede deel van het proefschrift richt zich op mindfulness gebaseerde interventies (MBI's).

In **Hoofdstuk 6** laten de resultaten van een onderzoek met kwantitatieve en kwalitatieve methoden zien dat de MBI van 8 weken haalbaar en acceptabel is bij oudere volwassenen met subjectieve geheugenproblemen. Deelnemers rapporteerden minder depressieve en stressklachten en vertoonden een toename in kwaliteit van leven en opmerkzaamheid in de vragenlijsten. In hun interviews rapporteerden de deelnemers positieve effecten van de training, zoals verhoogd bewustzijn, meer rust en

minder zorgen over geheugenklachten. Sommige deelnemers gaven echter ook aan dat het soms moeilijk was om de oefeningen in hun drukke leven in te passen.

Hoofdstuk 7 geeft een overzicht van onderzoek naar het gebruik van op MBI's bij mensen met dementie en mantelzorgers. De literatuur laat zien dat het mogelijk is om een MBI te toe te passen bij dyades bestaande uit een persoon met dementie en hun mantelzorger. De meeste onderzoeken richten zich echter op de effecten van MBI's op mantelzorgers of mensen met milde cognitieve stoornissen, en niet op mensen met dementie. In deze onderzoeken werden aanwijzingen gevonden voor verbetering van het welzijn na een training. Meer onderzoek wordt aanbevolen om zowel de effecten te onderzoeken en of aanpassingen aan het programma nuttig en noodzakelijk zijn.

Hoofdstuk 8 beschrijft een onderzoek, met kwalitatieve en kwantitatieve methodes, over de Training AaNdacht voor mensen met DEmentie en Mantelzorgers (TANDEM). Het TANDEM project had als doel om een training te ontwikkelen en te evalueren voor mensen met dementie (in een vroege fase) en hun mantelzorgers. Deze training werd gebaseerd op de mindfulness-gebaseerde training voor stressvermindering (Mindfulness-based Stress Reduction, MBSR). De deelnemers volgden deze groepstraining in dyades: de persoon met dementie samen met zijn of haar partner. Vragenlijsten toonden een klein effect voor de toename van de kwaliteit van leven bij mantelzorgers en een afname van de kwaliteit van leven voor mensen met dementie. Er werden hogere niveaus van mindfulness bij mantelzorgers gevonden, maar niet bij de mensen met dementie. In de interviews die werden afgenomen nadat de training was voltooid, gaven deelnemers aan dat de training had geholpen met ontspanning, aandacht, acceptatie en het omgaan met moeilijke situaties. Zowel mantelzorgers als mensen met dementie beschouwden zowel deelname in een groep als deelname samen met hun partner als waardevol. Dit onderzoek laat zien dat de TANDEM-training handvaten kan bieden voor zowel de persoon met dementie als diens mantelzorger, om beter met dementie om te kunnen gaan en om elkaar hierin te blijven ondersteunen.

Hoofdstuk 9 beschrijft de belangrijkste bevindingen van dit proefschrift, samen met een algemene discussie, voorzien van een aantal methodologische overwegingen en implicaties voor toekomstig onderzoek.

Zusammenfassung

Es besteht ein wachsendes Interesse daran, auf Mindfulness basierende Interventionen (MBIs) anzuwenden, unter anderem, um den altersbedingten kognitiven Rückgang hinauszuzögern und das Wohlbefinden zu steigern. Mindfulness kann mit „Aufmerksamkeit“ oder “Achtsamkeit” übersetzt werden und beschreibt einen Bewusstseinszustand, der entsteht, wenn man im gegenwärtigen Moment präsent und mit einer nicht wertenden Haltung anwesend ist. Immer mehr wissenschaftliche Publikationen zeigen, dass die Verwendung von MBIs sowohl für gesunde als auch für klinische Bevölkerungsgruppen gesundheitliche Vorteile bieten und das psychische Wohlbefinde fördern kann. Das Ziel dieser Doktorarbeit war es, Einblick in die Mechanismen der Mindfulness im Alter zu gewinnen, um zu untersuchen, ob und wie Mindfulness im täglichen Leben schwankt und ob Mindfulness durch kurze Übungen gesteigert werden kann. Darüber hinaus wurde in dieser Doktorarbeit die Anwendung einer MBI untersucht, um Menschen mit Demenz und ihre informellen Betreuer zu unterstützen. **Kapitel 1** enthält eine allgemeine Einführung, bestehend aus rationalen Forschungsfragen und dem Aufbau dieser Doktorarbeit.

Der erste Teil dieser Doktorarbeit beschreibt die möglichen Mechanismen der Mindfulness und des Alterns.

Kapitel 2 gibt einen Überblick über aktuelle wissenschaftliche Studien, die untersuchen, ob MBIs die kognitive Funktion älterer Menschen beeinflussen können. Frühere Untersuchungen haben gezeigt, dass MBIs für ältere Menschen geeignet sind, jedoch ist der Nachweis einer kognitiven Verbesserung durch Mindfulness nicht eindeutig. Die meisten Studien waren möglicherweise voreingenommen („biased“) oder hatten eine sehr kleine und daher nicht repräsentative Anzahl an Teilnehmern. Die einzige Studie mit einer angemessenen Stichprobengröße und einem niedrigen Verzerrungsrisiko zeigte keinen signifikanten Unterschied in den verschiedenen kognitiven Fähigkeiten zwischen den Teilnehmern der MBI und der aktiven Kontrollgruppe. Diese Erkenntnis unterstreicht den Forschungsbedarf nach einer standardisierten Intervention inklusive einer aktiven Kontrollgruppe, einer großen Stichprobengröße und einer umfangreichen neuropsychologischen Testbatterie.

In **Kapitel 3** wurde der Zusammenhang zwischen positivem Affekt („Gemütszustand“) und kognitivem Rückgang untersucht. Frühere Forschungen zeigen, dass Mindfulness und positiver Affekt sich in einer Aufwärtsspirale gegenseitig verstärken können, sodass sich das psychische Wohlbefinden verbessert. Es scheint auch einen Zusammenhang zwischen positivem Affekt und kognitivem Alter zu geben. Mindfulness kann sich möglicherweise durch positiven Affekt positiv auf das kognitive Altern auswirken. In dieser Studie waren

nur Daten zu positivem Affekt und kognitiver Verschlechterung verfügbar. Das Gedächtnis, die exekutive Gehirnfunktionen und die Informationsverarbeitungsgeschwindigkeit wurden über einen Zeitraum von zwölf Jahren bei Teilnehmern der Maastricht Aging Study (MAAS) gemessen. Kein signifikanter Zusammenhang zwischen positivem Affekt und einer Verschlechterung des Gedächtnisses, der exekutiven Gehirnfunktionen und der Informationsverarbeitungsgeschwindigkeit wurde bei den Nachuntersuchungen nach 6 und 12 Jahren festgestellt. Diese Ergebnisse haben die potentielle Wirkung von positivem Affekt auf das kognitive Altern erneut in Frage gestellten.

In **Kapitel 4** wurde der Zusammenhang zwischen dispositioneller Mindfulness und geringfügigen Entzündungen in Teilnehmern der Bevölkerungsstudie der Maastricht-Studie (DMS) untersucht. Dispositionelle Mindfulness ist ein Charakterzug, der in der allgemeinen Bevölkerung stark variiert. Ein höheres Maß an Mindfulness war sowohl bei Teilnehmern mit als auch ohne Typ-2-Diabetes mit einer geringeren Entzündungsrate verbunden. Diese Beziehung war unabhängig von verschiedenen Lebensstilvariablen. Ein niedrigerer Diabetes-Stress bei Teilnehmern mit Typ-2-Diabetes war mit einem höheren Grad an Mindfulness verbunden. Diese Ergebnisse unterstreichen die Notwendigkeit zukünftiger Forschung, die Kausalität zwischen Mindfulness und Entzündungen sowie die Rolle des Lebensstils in diesem Zusammenhang weiter zu untersuchen.

Kapitel 5 beschreibt die Erforschung von Mindfulness und positivem Affekt in Alltag gemessen mit der Experience Sampling-Methode (ESM). Mit dieser Online-Tagebuchmethode wurden die Teilnehmer gebeten, kurze Fragebögen auszufüllen und eine dreiminütige Meditation mit einer Smartphone-App durchzuführen. Die meisten Teilnehmer empfanden es als positiv, die kurzen Meditationsübungen mehrmals täglich für eine Woche durchzuführen. Die Hälfte der Teilnehmer gab an, dass sie, falls verfügbar, die Smartphone-App zur Unterstützung ihrer Meditation verwenden würden. Darüber hinaus sagte ein höheres Level an momentaner Mindfulness ein höheres Level an positivem Affekt im nächsten Moment (im nächsten Moment der App-Benachrichtigung) vorher und umgekehrt. Diese Verbindung war sowohl während der Interventionswoche (ESM mit den kurzen Meditationsübungen), als auch während der Kontrollwoche (nur ESM) vorhanden. Der tägliche Grad an Mindfulness, der anhand eines abendlichen Fragebogens gemessen wurde, war kein Anzeichen für positiven Affekt. Die Post-hoc-Analyse der Elemente der Mindfulness zeigte, dass die Einheit „nicht urteilend" positiven Affekt vorhersagte, unabhängig vom Level an positiven Affekt im vorhergegangenen Moment. Generell zeigten ESM-Daten individuelle Unterschiede in der Variabilität der Mindfulness und des positiven Affekts.

Der zweite Teil der Arbeit konzentriert nimmt auf Mindfulness basierte Interventionen (MBIs) in den Fokus.

In **Kapitel 6** zeigen die Ergebnisse einer Studie basierend auf quantitativen und qualitativen Methoden, dass eine achtwöchige MBI für ältere Erwachsene mit subjektiven Gedächtnisproblen durchführbar und akzeptabel ist. Die Teilnehmer berichteten über weniger depressive und stressbedingte Beschwerden und die Fragebögen zeigten eine Steigerung der Lebensqualität und Mindfulness. In ihren Interviews berichteten die Teilnehmer über positive Auswirkungen des Trainings, wie zum Beispiel ein gesteigertes Bewusstsein, mehr Ruhe und weniger Bedenken hinsichtlich Gedächtnisstörungen. Einige Teilnehmer gaben jedoch auch an, dass es manchmal schwierig war, die Übungen in ihr hektisches Leben zu integrieren.

Kapitel 7 bietet einen Überblick über die Erforschung von MBIs bei Menschen mit Demenz und informellen Pflegekräften (z.B. Angehörige). Die Literatur zeigt, dass es möglich ist, einen MBI für Dyaden, bestehend aus einer Person mit Demenz und ihrer informellen Bezugsperson, durchzuführen. Die meisten Studien konzentrieren sich jedoch auf die Auswirkungen von MBIs auf informelle Pflegekräfte oder Menschen mit leichter kognitiver Beeinträchtigung und nicht direkt auf Menschen mit Demenz. Diese Studien geben erste Hinweise auf eine Verbesserung des Wohlbefindens nach dem Mindfulness Training. Weitere Untersuchungen werden jedoch empfohlen, um sowohl die Auswirkungen, als auch die Frage zu prüfen, ob Anpassungen des Programms sinnvoll und notwendig sind.

Kapitel 8 beschreibt ein auf Mindfulness basierendes Training zur Stressreduktion, genannt TANDEM, präsentiert in einer Studie mit qualitativen und quantitativen Methoden. Das TANDEM-Projekt zielte darauf ab, ein Programm für Demenzkranke im Anfangsstadium und deren Betreuer zu entwickeln und bewerten. Dieses Training beinhaltet Übungen des Mindfulness-basierten Stressabbaus (MBSR). Die Teilnehmer folgten dem Gruppentraining in Dyaden: die Person mit Demenz zusammen mit ihrem/ihrer Partner/in. Fragebögen zeigten einen kleinen Effekt des Trainings auf den Anstieg der Lebensqualität unter den informellen Pflegekräften und eine Abnahme der Lebensqualität in Menschen mit Demenz. Einen größeren Effekt hatte das Training auf das Level an Mindfulness bei den informellen Betreuern, welches anstiegt. Dies traf jedoch nicht auf die Menschen mit Demenz zu. In den Interviews, die nach Abschluss des Trainings durchgeführt wurden, gaben die Teilnehmer an, dass das Training positiv zur Entspannung, Mindfulness, Akzeptanz und zum Umgang mit schwierigen Situationen beigetragen habe. Sowohl informelle Pfleger als auch Menschen mit Demenz erachten die Teilnahme an einer Gruppe und die Teilnahme mit ihrem Partner als wertvoll. Diese

Forschung zeigt, dass das TANDEM-Training sowohl für den Demenzkranken als auch für die Bezugspersonen von Nutzen sein kann, um besser mit Demenz umzugehen und sich gegenseitig zu unterstützen.

Kapitel 9 beschreibt die Hauptergebnisse dieser Doktorarbeit und leitet zu einer allgemeinen Diskussion über, die eine Reihe methodologischer Überlegungen und Implikationen für die zukünftige Forschung beinhaltet.

Knowledge valorization

The general aim of this thesis was to gain insight into the mechanisms of mindfulness on aging and to explore the applicability of a mindfulness-based intervention (MBI) to support people with dementia and their caregivers. This valorization addendum describes the societal relevance of the obtained knowledge based on the research described in this thesis.

Relevance

Dementia is a global health challenge. Worldwide, approximately 50 million people are currently living with dementia. This number is expected to reach 115 million in 2050. Dementia has an enormous impact both on the people with dementia and their families. People with dementia often feel isolated and marginalized. Those who care for someone with dementia often feel exhausted and strained. The impact of dementia is also a social and economic one; in 2015, the global societal cost was estimated to be more than 800 billion US dollars. According to the World Health Organization, dementia should be regarded as a global public health priority. Despite significant resources spent on finding a pharmacological treatment, there is no cure for this neurodegenerative condition. Therefore, other avenues to face dementia should be explored, such as prevention as well as improvement of the support of those currently living with dementia. This thesis investigated the role of mindfulness as a possible link with age-related cognitive decline and whether mindfulness could delay the onset of such decline. For example, mindfulness-based interventions (MBIs) might influence risk factors of dementia such as depression, diabetes, obesity, physical inactivity, hypertension, and smoking. Mindfulness could modify these risk factors and prevent or delay the neuropathological cascade leading to cognitive decline. The studies described in this thesis provide insight into these mechanisms, but the cross-sectional nature precludes causal statements. Moreover, this thesis looked into the use of mindfulness-based intervention to support people with dementia and their caregivers. People with dementia and caregiver have expressed a clear need for positive support that goes beyond the diagnosis itself. Questions such as 'How do you live with the diagnosis?' and 'How do you find a new balance together?' play an important role. MBIs might be the intervention that can effectively help dyades cope with dementia.

Target audience

The findings described in this thesis are relevant for people with dementia, caregivers, dementia health care professionals, and health insurance companies.

Informal caregivers fulfill an important role in the care for people with dementia. Unfortunately, most caregivers experience caregiving as stressful. In comparison with caregivers of physically frail elderly people and non-caregivers, caregivers of people

with dementia show higher levels of psychological distress. Caregivers often struggle with acceptance, although they have reported that this is very important to be able to adapt to the situation. Difficulty to acknowledge changes interferes with acceptance. MBIs are able to work on the one hand to reduce stress, and on the other hand to learn how to deal with changes and therefore stimulate acceptance. Moreover, caregivers that have participate in an MBI will learn how to take better care of themselves; a process that is often overlooked because of a focus of care on their partner. Our research also indicates that participating with their partner together could have added benefits for their relationship such as improved communication and increased connectedness.

Similarly, people with dementia might benefit from participating in MBIs. In particular, a program as described in this thesis in which people with dementia participate together with their caregiver. It gives them the tools to learn how to live with the diagnosis and deal with difficult situations. Our research shows that people with early-stage dementia are capable to participate in MBIs. Because the materials of the TANDEM project are made available to certified trainers throughout the Netherlands, more people might be reached.

Results from this thesis could be of interest for health insurance companies and policy makers. In particular, it can be part of a prevention strategy for both general health. More specifically, it can support people with dementia and their caregivers. When people with dementia and their caregivers can participate in an MBI shortly after the diagnosis, it is expected that they will experience less distress. Moreover, it seems reasonable to assume that by investing in the ability to cope with the life changing diagnosis, the caregiver will be able to maintain their supporting role longer. Also other categories of older individuals might benefit from MBIs. People with diabetes that have higher levels of mindfulness show lower levels of diabetes related distress. Perhaps MBIs can reduce distress in people with diabetes. Although more research is needed, it is a relatively low-cost intervention that could prevent or slow down diseases such as diabetes.

Dementia health care professionals should consider MBIs as an option for both caregivers and people with early stage dementia. On the project's website www.tandemproject.nl certified trainers can be found who may provide the TANDEM training. The results of this thesis indicate that MBIs can help people cope with the diagnosis.

Activities and products

With the input of dementia experts and mindfulness trainers, the TANDEM training was developed. The program was based on a standard Mindfulness-Based Stress Reduction program and consists of an 8-week group training of 2,5 hours each week. It was adapted to better suit people with dementia and their caregivers. A manual for the trainer and the accompanying workbook were developed and distributed among certified mindfulness trainers in the Netherlands.

Results of the research in this thesis were presented at several conferences, symposia and Alzheimer Café's. Moreover, the TANDEM project has been visible through both specific websites (e.g. www.alzheimer-nederland.nl) as well as mainstream media (Psychology Magazine and the local newspaper De Limburger).

Innovation and implementation

The TANDEM project was one of the first projects that included people with dementia and their caregivers together in a single mindfulness training. Certified trainers in the Netherlands can request the materials of the training free of cost. Almost 200 trainers have done this so far, with the majority having the intention to start a TANDEM group. The study has contributed to a wider acceptance of MBIs in the care for people with dementia and their caregivers.

Our study involving Experience Sampling Method is one of the few that have investigated state mindfulness and the association with positive affect. This in combination of short meditation exercises provides new possibilities for people to maintain their practice after a training. It also contributed to the understanding of different facets of mindfulness in daily life. The ESM technique may help us in the future to elucidate the underlying mechanism of mindfulness intervention programs by enabling insight into moment-to-moment causal pathways.

In addition, the link between inflammation and mindfulness opens a new avenue for early intervention. Future research can further investigate whether MBIs can influence inflammation.

List of publications

This thesis

Berk, L., Miranda Schram, M., Jim van Os, J., Marjolein de Vugt, M., Casper Schalkwijk C., Coen Stehouwer, C., Nicolaas Schaper, N., Martin van Boxtel, M. (*in preparation*). Associations of low-grade inflammation with mindfulness in individuals with and without type 2 diabetes

Berk, L., Warmenhoven, F., Stiekema, A., van Oorsouw, K., van Os, J., de Vugt, M., & van Boxtel, M. (*under review: Frontiers in Aging Neuroscience*). Mindfulness-based Intervention for People with Dementia and their Partners: Results of a Mixed-Methods Study.

Berk, L., van Boxtel, M., & van Os, J. (*under review: Mindfulness*) Do short meditation exercises boost mindfulness state and positive affect in daily life? An experience sampling study.

Berk, L., Warmenhoven, F., van Os, J., & van Boxtel, M. (2018). Mindfulness Training for People with Dementia and their Caregivers: Rationale, Current Research, and Future Directions. *Frontiers in Psychology,* 9, 982.

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Author Information

Lotte Berk was born on September 7th, 1985 in Almelo, the Netherlands. In 2003 she graduated high school (Erasmus, Almelo). After spending a couple of years working, including a year in Spain, she started University College Utrecht and obtained her Bachelor of Arts degree in Liberal Arts & Sciences in 2008 (Magna Cum Laude). At the University of Amsterdam she started the Research Master Psychology. During this program, she went to the University of California - San Diego (UCSD) to write her Master thesis. After obtaining her Master of Science degree in 2011 (Cum Laude), she moved to San Diego. At the UCSD Department of Psychiatry, she worked as a research associate on projects investigating brain functioning in adolescents with substance use disorders. In October 2014 she moved back to the Netherlands to start her PhD at the department of Psychiatry & Neuropsychology and Maastricht University under supervision of Dr. Martin van Boxtel, Prof. dr. Jim van Os, and Prof. dr. Marjolein de Vugt. During this time, Lotte became a certified mindfulness trainer and illustrated a book on Acceptance and Commitment Therapy. Lotte currently works as a Psychology Lecturer at University College Utrecht.

Lotte Berk werd geboren op 7 september 1985 in Almelo, Nederland. In 2003 behaalde zij haar VWO-diploma (Erasmus, Almelo). Na een aantal jaar te hebben gewerkt, waaronder een jaar in Spanje, bepaalde ze in 2008 bij University College Utrecht haar bachelor in Liberal Arts & Sciences (Magna Cum Laude). Aan de Universiteit van Amsterdam startte zij de Research Master Psychology. Tijdens dit programma ging ze naar de University of California - San Diego (UCSD) om haar masterscriptie te schrijven. Na het behalen van haar master in 2011 (Cum Laude) verhuisde ze naar San Diego. Bij de UCSD afdeling Psychiatrie werkte ze als onderzoeksmedewerker aan projecten die hersenfuncties onderzoeken bij adolescenten met verslavingsstoornissen. In oktober 2014 verhuisde ze terug naar Nederland om te werken als promovenda op de afdeling Psychiatrie en Neuropsychologie van de Universiteit Maastricht onder supervisie van Dr. Martin van Boxtel, Prof. dr. Jim van Os en Prof. dr. Marjolein de Vugt. Gedurende deze tijd werd Lotte een gecertificeerde mindfulness-trainer en illustreerde zij een boek over Acceptance and Commitment Therapy. Lotte werkt momenteel als docent Psychologie aan University College Utrecht.

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geworden van de crazy cat ladies app zonder een kat te hebben :D Bedankt voor het delen van jullie leuke filmpjes en foto's die me altijd weer vrolijk maken! Astrid, bedankt voor het afnemen van TANDEM interviews en wat leuk dat we ooit ook een tandem toch gedaan hebben :) Nico, en Ron, heel erg bedankt voor jullie onmisbare ondersteuning! Danielle, wat was het leuk om samen het dagje uit te mogen organiseren en wat fijn dat ik met alle hulpvragen bij jou terecht kan. Rafke, bedankt dat je zo enthousiast en zelfstandig te werk bent gegaan aan het MiM project. Charlotte en Marloes, wat heb ik een geluk gehad dat jullie mij hebben geholpen met het ESM project. Door jullie harde werk en enthousiasme hebben we straks een mooie publicatie. Anneloes, bedankt voor het transcriberen voor het TANDEM project.

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Gijs, wat ben je geweldig! Door jou voelt dit proefschrift niet als mijn eerste boek want How 2 ACT was dat natuurlijk eigenlijk al. Jouw enthousiasme werkt aanstekelijk en bedankt dat ik mijn droom (om een boek te illustreren) door jou kon verwezenlijken!

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Hola familia! Lieve Martijn, Anna, en vati. Wat is het fijn om jullie onvoorwaardelijke liefde te hebben. Samen eten, huttentochten maken, wandelen aan het strand in Breskens, op familiebezoek in Duitsland, herinneringen aan mama ophalen. Elke keer wanneer we samen zijn, zijn dat momenten waar ik weer helemaal kan opladen. Wat ben ik blij dat ik nu in Nederland woon zodat ik dichter bij jullie ben (ook al is Maastricht toch een beetje buitenland).

Dearest Peter, my dogsitter, my best friend. Thank you so much for your love and support in whatever I want to do. Most important: you make sure I have fun. You know when to put me on the couch with Kafka to watch Star Trek, and you always make me laugh. I'm so excited that we get to share our lives together. Every year with you is the best year ever.

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Thesis defenses from MHeNs - School for Mental Health and Neuroscience

2013

Rob Havermans: Bipolar disorder in daily life; Mood and cortisol responses to naturally occurring events. Supervisor: Prof.dr. M. de Vries; Co-Supervisor: Dr. N. Nicolson.

Véronique Moers-Hornikx: Deep brain stimulation and the cerebellum. Supervisors: Prof.dr. J. Vles / Prof.dr. Y. Temel; Co-Supervisor: Dr. G. Hoogland.

Nicole Veldhorst-Janssen: Intranasal delivery of rapid acting drugs. Supervisors: Prof.dr. M. Marcus / Prof.dr. C. Neef; Co-Supervisor: Dr. P.H. van der Kuy.

Stéphanie Knippenberg: Vitamin D and Multiple Sclerosis: immunological and clinical outcome. Supervisor: Prof.dr. J. Cohen-Tervaert; Co-Supervisors: Dr. J. Damoiseaux / Dr. Y.Bols.

Erik D. Gommer: Dynamic Cerebral Autoregulation: from methodology towards clinical application. Supervisors: Prof.dr. W.H. Mess / Prof.dr. R.B. Panerai, UK; Co-Supervisor: Dr.ir. J.P.H. Reulen.

Olga A.H. Reneerkens: Can PDE inhibition improve cognition ? Translational insights. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. J. Prickaerts;.

Lyzel S. Elias-Sonnenschein: Clinical and biomarker correlates of genetic risk factors for Alzheimer's disease. Supervisor: Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. P.J. Visser.

Diego F. Mastroeni: Epigenetic Dysregulation and the Pathophysiology of of Alzheimer's Disease. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. P.D. Coleman, Sun City, Arizona; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van denHove.

Leonidas Chouliaras: Epigenetic Regulation in Aging and Alzheimer's disease: A translational perspective. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Liesbeth Knaepen: Perinatal events and altered pain sensitivity in later life. Supervisors: Prof.dr. E.A.J. Joosten / Prof.dr. D. Tibboel, EUR; Co-Supervisor: Dr. J. Patijn.

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Hilde Braakman: Imaging the brain; neuronal correlates of cognitive impairment in children with frontal lobe epilepsy. Supervisors: Prof.dr. A.P. Aldenkamp /Prof. dr. J.S.H. Vles; Co-Supervisors: Dr.ir. W.H. Backes / Dr. P.A.M. Hofman.

Willem H. van Zwam: Aneurysmal subarachnoid hemorrhage: imaging strategies and cost-effectiveness aspects in diagnostic work-up and post-therapeutic follow-up. Supervisors: Prof.dr. J.T. Wilmink / Prof.dr. J.E. Wildberger; Co-Supervisor: Dr. P.A.M. Hofman.

Klara De Cort: The Pathogenesis of Panic Disorder. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. E.J.L. Griez; Co-Supervisors: Dr. K.R.J. Schruers / Dr. I. Van Diest, Leuven.

Kim van Wijck: Mind the Gap; experimental studies on splanchnic hyperfusion and gastrointestinal integrity loss in man. Supervisors: Prof.dr. W.A. Buurman /Prof.dr. C.H.C. Dejong; Co-Supervisor: Dr. K. Lenaerts.

Yvette Roke: Antipsychotic-induced hyperprolactinemia in children and adolescents with mainly autism spectrum disorders. Prevalence, symptoms, clinical consequences and genetic risk factors. Supervisors: Prof.dr. P.N. van Harten / Prof.dr. J.K. Buitelaar (RUN); Co-Supervisor: Dr. A. Boot (UMCG).

Fleur Goezinne: Retinal detachment surgery: pre and postoperative prognostic factors. Supervisors: Prof.dr. F. Hendrikse / Prof.dr. C.A.B. Webers; Co-Supervisor: Dr. E.C. La Heij (Amsterdam).

Ralph L.J.G. Maassen: The Merits of Videolaryngoscopy during Glottic Visualisation for Endotracheal Intubation. Supervisors: Prof.dr. M. Marcus / Prof.dr. A. van Zundert (University of Queensland).

Maria J. de Sousa Guerreiro: The role of sensory modality in age-related distraction. Supervisor: Prof.dr. C.M. van Heugten; Co-Supervisor: Dr. P.W.M. van Gerven.

Ine Rayen: Effects of developmental fluoxetine exposure on neurobehavioral outcomes. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski / Dr. T.D. Charlier (Ohio University, USA).

Nynke M.G. Bodde: Psychogenic non-epileptic seizures; a separate disorder or part of a continuum? Supervisors: Prof.dr. R. van Oostenbrugge / Prof.dr. K. Vonck (UZ Gent); Co-Supervisors: Dr. R. Lazeron / Dr. A. de Louw (Epilepsiecentrum Kempenhaeghe, Heeze).

Alejandro M. Gomez: Novel strategies for making myasthenia less gravis: targeting plasma cells and the neuromuscular junction. Supervisor: Prof.dr. M.H. De Baets; Co-Supervisors: Dr. M. Losen / Dr. P. Martinez-Martinez.

Mohammad S. Rahnama'i: Prostaglandins and Phosphodiesterases in the Urinary Bladder Wall. Supervisors: Prof.dr. Ph. Van Kerrebroeck / Prof.dr. S. de Wachter (Universiteit Antwerpen); Co-Supervisor: Dr. G. van Koeveringe.

Mariken B. de Koning: Studying biomarkers in populations at genetic and clinical high risk for psychosis. Supervisors: Prof.dr. T. Amelsvoort / Prof.dr. J. Booij (AMC).

Fabien Boulle: Epigenetic regulation of BDNF/TrkB signaling in the pathophysiology and treatment of mood disorders. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof. dr. L. Lanfumey (Universiteit Parijs); Co-Supervisors: Dr. D. van den Hove / Dr. G. Kenis.

2014

Iris Nowak-Maes: Tinnitus; assessment of quality of life & cost-effectiveness. Supervisors: Prof.dr. M. Peters / Prof.dr. B. Kremer; Co-Supervisors: Dr. M. Joore / Dr. L. Anteunis.

Marjolein Huijts: Cognitive function in patients with cerebral small vessel disease. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. A.A. Duits / Dr. J. Staals.

Markus Gantert: Fetal inflammatory injury as origin of long term disease: Lessonsfrom animal models. Supervisors: Prof.dr. B. Kramer / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A.Gavilanes.

Elke Kuypers: Fetal development after antenatal exposures: Chorioamnionitis and maternal glucocorticoids. Supervisors: Prof.dr. B.W. Kramer / Prof.dr. H.W. Steinbusch / Prof.dr. Suhas G. Kallapur (University of Cincinnati, Ohio, USA).

Pieter Kubben: Ultra low-field strength intraoperative MRI for Glioblastoma Surgery. Supervisor: Prof.dr. J.J. van Overbeeke; Co-Supervisor: Dr. H. van Santbrink.

Laura Baijens: Surface electrical stimulation of the neck for oropharyngeal dysphagia in Parkinson's disease: therapeutic aspects and reliability of measurement. Supervisor: Prof.dr. B. Kremer; Co-Supervisor: Dr. R. Speyer, Townsville.

Janneke Hoeijmakers: Small fiber neuropathy and sodium channels; a paradigm shift. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. C.G. Faber / Dr. I.S.J. Merkies.

Stephanie Vos: The Role of biomarkers in preclinical and prodromal Alzheimer's disease. Supervisor: Prof.dr. F.R. Verhey; Co-Supervisor: Dr. P.J. Visser.

Muriël Doors: The Value of Optical Coherence Tomography in Anterior Segment Surgery. Supervisors: Prof.dr. R.M. Nuijts / Prof.dr. C.A. Webers; Co-Supervisor: Dr. T.T.J.M. Berendschot.

Anneke Maas: Sleep problems in individuals with genetic disorders associated with intellectual disability. Supervisors: Prof.dr. I. Curfs / Prof.dr. R. Didden.

Sebastiaan van Gorp: Translational research on spinal cord injury and cell-based therapies; a focus on pain and sensorimotor disturbances. Supervisors: Prof.dr. B. Joosten / Prof.dr. M. van Kleef; Co-Supervisors: Dr. J. Patijn /Dr. R. Deumens, KU Leuven.

Andrea Sannia: High risk newborns and brain biochemical monitoring. Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Alessandria, Italy / Dr. A.W.D. Gavilanes.

Julie A.D.A. Dela Cruz: Dopamine mechanisms in learning and memory: Evidence from rodent studies. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R.J. Bodnar, New York; Co-Supervisor: Dr. B.P.F. Rutten.

René Besseling: Brain wiring and neuronal dynamics; advances in MR imaging of focal epilepsy. Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr.ir. W.H. Backes; Co-Supervisor: dr. J.F.A. Jansen.

Maria Quint-Fens: Long-term care after stroke; development and evaluation of a long- term intervention in primary care. Supervisors: Prof.dr. J.F.M. Metsemakers /Prof.dr. C.M. van Heugten / Prof.dr. M. Limburg, Almere; Co-Supervisor: dr. G.H.M.I. Beusmans.

Veronique Moulaert: Life after survival of a cardiac arrest; the heart of the matter. Supervisors: Prof.dr. J.A. Verbunt / Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford, UK.

Feikje Smeets: The hallucinatory-delusional state: a crucial connection in the psychosis symptom network. Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. T. Lataster.

Lies Clerx: Alzheimer's disease through the MR-eye; novel diagnostic markers and the road to clinical implementation". Supervisor: Prof.dr. F. Verhey; Co-Supervisors: Dr. P.J. Visser / P. Aalten.

Sonny Tan: The subthalamic nucleus in Parkinson's disease. Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch / Prof.dr. T. Sharp, Oxford, UK / Prof.dr. V. Visser-Vandewalle, Koln.

Koen van Boxem: The use of pulsed radiofrequency in the management of chronic lumbosacral radicular pain. Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A.J. Joosten; Co-Supervisor: Assoc. Prof.dr. J. van Zundert.

Jérôme Waterval: Hyperostosis cranialis interna. Supervisors: Prof.dr. J.J. Manni / Prof.dr. R.J. Stokroos.

Sylvie Kolfschoten-van der Kruijs: Psychogenic non-epileptic seizures; the identification of neurophysiological correlates. Supervisors: Prof.dr. A.P. Aldenkamp /Prof.dr. K.E.J. Vonck, Universiteit Gent; Co-Supervisors: Dr. J.F.A. Jansen / Dr. R.H.C. Lazeron, Kempenhaeghe.

Wouter Pluijms: Spinal cord stimulation and pain relief in painful diabetic: polyneuropathy, a translational approach. Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A. Joosten; Co-supervisor: Dr. C.G. Faber.

Ron Handels: Health technology assessment of diagnostic strategies for Alzheimer's disease. Supervisors: Prof.dr. F.R.J. Verhey / Prof.dr. J.L. Severens (EUR); Co-Supervisor: Dr. M.A. Joore / Dr. C.A.G. Wolfs.

Evelyn Peelen: Regulatory T cells in the pathogenesis of Multiple Sclerosis: potential targets for vitamin D therapy. Supervisors: Prof.dr. R.M.M. Hupperts / Prof.dr. J.W. Cohen Tervaert; Co-Supervisor: Dr. J.G.M.C. Damoiseaux / Dr. M.M.G.L.Thewissen, Diepenbeek.

Reint Jellema: Cell-based therapy for hypoxic-ischemic injury in the preterm brain. Supervisors: Prof.dr. B.W.W. Kramer / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. W.T.V. Germeraad / Dr. P. Andriessen,Veldhoven.

Maria Wertli: Prognosis of Chronic Clinical Pain Conditions: The Example of Complex Regional Pain Syndrome 1 and Low Back Pain. Supervisors: Prof.dr. M. van Kleef; Co-Supervisor: Dr. F. Brunner, Zürich / Dr. R. Perez, VUmc.

Dagmar Zeef: An experimental model of Huntington's disease: Validation & Stimulation. Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. A. Jahanshahi.

Jeroen Decoster: Breaking Down Schizophrenia into phenes, genes and environment. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. M. De Hert, KU Leuven; Co-Supervisor: Dr. R. van Winkel.

Eaja Anindya Sekhar Mukherjee: Fetal Alcohol Spectrum Disorders: exploring prevention and management. Supervisor: Prof.dr. L.M.G. Curfs; Co-Supervisor: Prof. S. Hollins, St. George's University of London, UK.

Catherine van Zelst: Inside out; On stereotype awareness, childhood trauma and stigma in psychosis. Supervisors: Prof.dr. Ph. Delespaul / Prof.dr. J. van Os.

Ibrahim Tolga Binbay: Extended Psychosis Phenotype in the Wider Social Environment Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. M. Drukker.

Frank Van Dael: OCD matters in psychosis. Supervisors: Prof.dr. J. van Os / Prof.dr. I. Myin-Germeys.

Pamela Kleikers: NOXious oxidative stress: from head toe too and back. Supervisors: Prof.dr. H.H.H.W. Schmidt / Prof. dr. H.W.M. Steinbusch; Co-Supervisor: Dr. B. Janssen.

José Luis Gerardo Nava: In vitro assay systems in the development of therapeutic interventions strategies for neuroprotection and repair. Supervisors: Prof.dr.med. J. Weis / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. G.A. Brook, RWTH Aachen.

Eva Bollen: Cyclic nucleotide signaling and plasticity. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R. D'Hooge, KU Leuven; Co-Supervisor: Dr. J. Prickaerts.

2015

Jessica A. Hartmann: A good laugh and a long sleep; Insights from prospective and ambulatory assessments about the importance of positive affect and sleep in mental health. Supervisor: Prof.dr. J. van Os; Co-Supervisors: C.J.P. Simons / Dr. M. Wichers.

Bart Ament: Frailty in old age; conceptualization and care innovations. Supervisors: Prof.dr. G.I.J.M. Kempen / Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. M.E. deVugt.

Mayke Janssens: Exploring course and outcome across thepsychosis-continuum. Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. T. Lataster.

Dennis M.J. Hernau: Dopayours is not dopamine: genetic, environmental and pathological variations in dopaminergic stress processing. Supervisor: Prof.dr. I. Myin- Germeys; Co-Supervisors: Prof.dr. F.M. Mottaghy / Dr. D. Collip.

Ingrid M.H. Brands: The adaptation process after acquired brain injury Pieces of the puzzle. Supervisors: Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford UK; Co-Supervisors: Dr. S.Z. Stapert / Dr. S. Köhler.

Francesco Risso: Urinary and salivary S100B monitoring in high risk infants. Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Alessandro Borghesi: Stem and Progenitor Cells in Preterm Infants: Role in the Pathogenesis and Potential for Therapy. Supervisor: Prof.dr. L. Zimmermann; Prof.dr. B. Kramer; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Claudia Menne-Lothmann: Affect dynamics; A focus on genes, stress, and an opportunity for change. Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers / Dr. N. Jacobs.

Martine van Nierop: Surviving childhood new perspectives on the link between childhood trauma and psychosis. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. J. van Os; Co-Supervisor: Dr. R. van Winkel.

Sylvia Klinkenberg: VNS in children; more than just seizure reduction. Supervisors: Prof.dr. J. Vles / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie.

Anouk Linssen: Considerations in designing an adult hearing screening programme. Supervisor: Prof.dr. B. Kremer; Co-Supervisors: Dr. L. Anteunis / Dr. M. Joore.

Janny Hof: Hearing loss in young children; challenges in assessment and intervention. Supervisors: Prof.dr. B. Kremer / Prof.dr. R. Stokroos / Prof.dr. P. van Dijk, RUG; Co-Supervisor: Dr. L. Antheunis.

Kimberly Cox-Limpens: Mechanisms of endogenous brain protection; Clues from the transcriptome. Supervisors: Prof.dr. J. Vles / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Els Vanhoutte: Peripheral Neuropathy outcome measures; Standardisation (PeriNomS) study part 2: Getting consensus. Supervisors: Prof.dr. C. Faber / Prof. dr. P. van Doorn; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Mayienne Bakkers: Small fibers, big troubles; diagnosis and implications of small fiber neuropathy. Supervisors: Prof.dr. C. Faber / Prof.dr. M. de Baets; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Ingrid Kramer: Zooming into the micro-level of experience: An approach for understanding and treating psychopathology. Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers, UMC Groningen / Dr. C. Simons.

Esther Bouman: Risks and Benefits of Regional Anesthesia in the Perioperative Setting. Supervisors: Prof.dr. M. van Kleef / Prof.dr. M. Marcus, HMC, Qatar / Prof.dr. E. Joosten; Co-Supervisor: Dr. H. Gramke.

Mark Janssen: Selective stimulation of the subthalamic nucleus in Parkinson's disease; dream or near future. Supervisors: Prof.dr. Y. Temel / Prof.dr. V. Visser-Vandewalle, Keulen / Prof.dr. A. Benazzouz, Bordeax, France.

Reina de Kinderen: Health Technology Assessment in Epilepsy; economic evaluations and preference studies. Supervisors: Prof.dr. S. Evers / Prof.dr. A. Aldenkamp;Co-Supervisor: Dr. H. Majoie / Dr. D. Postulart, GGZ O-Brabant.

Saskia Ebus: Interictal epileptiform activity as a marker for clinical outcome. Supervisors: Prof.dr. A. Aldenkamp / Prof.dr. J. Arends, TUE / Prof.dr. P. Boon, Universiteit Gent, België.

Inge Knuts: Experimental and clinical studies into determinants of panic severity.Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. K. Schruers; Influencing panic.

Nienke Tielemans: Proactive coping post stroke: The Restored4Stroke Self-Management study. Supervisors: Prof.dr. C. van Heugten / Prof.dr. J. Visser-Meily, UMC Utrecht;Co-Supervisor: Dr. V. Schepers, UMC Utrecht.

Tom van Zundert: Improvements Towards Safer Extraglottic Airway Devices. Supervisors: Prof.dr. A.E.M. Marcus / Prof.dr. W. Buhre / Prof.dr. J.R. Brimacombe, Queensland, Australia / Prof.dr. C.A. Hagberg.

Tijmen van Assen: Anterior Cutaneous Nerve Entrapment Syndrome Epidemiology and surgical management. Supervisors: Prof.dr. G.L. Beets / Prof.dr. M. van Kleef / Dr. R.M.H. Roumen / Dr. M.R.M. Scheltinga, MMC Veldhoven.

Rohit Shetty: Understanding the Clinical, Immunological and Genetic Molecular Mechanisms of Keratoconus. Supervisors: Prof.dr. R.M.M.A. Nuijts / Prof.dr. C.A.B. Webers.

Christine van der Leeuw: Blood, bones and brains; peripheral biological endophenotypes and their structural cerebral correlates in psychotic disorder. Supervisor: Prof.dr. J. van Os; Co-supervisor: Dr. M. Marcelis.

Sanne Peeters: The Idle Mind Never Rests; functional brain connectivity across the psychosis continuum. Supervisor: Prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Nick van Goethem: α7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. J. Prickaerts.

Nicole Leibold: A Breath of fear; a translational approach into the mechanisms of panic. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K.R.J. Schruers / Dr. D.L.A. van den Hove.

Renske Hamel: The course of mild cognitive impairment and the role of comorbidity.Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisors: Dr. I.H.G.B. Ramakers / Dr. P.J. Visser.

Lucia Speth: Effects of botulinum toxin A injections and bimanual task-oriented therapy on hand functions and bimanual activities in unilateral Cerebral Palsy. Supervisors: Prof.dr. J. Vles; Prof.dr. R. Smeets; Co-supervisor: Dr. Y. Janssen-Potten, Adelante Hoensbroek.

Yuan Tian: The effects of Lutein on the inflammatory pathways in age-related macular degeneration (AMD). Supervisors: Prof.dr. C. Webers; Prof.dr. A. Kijlstra, WUR; Co- supervisor: Dr. M. Spreeuwenberg; Dr. H. Tange.

Peggy Spauwen: Cognition and Type 2 diabetes; the interplay of risk factors.Supervisors: Prof.dr. F. Verhey; Prof.dr. C. Stehouwer; Co-supervisor: Dr. M. van Boxtel

Marc Hilhorst: Crescentic glomerulonephritis in ANCA associated vasculitis.Supervisors: Prof.dr. J. Cohen-Tervaert; Co-supervisor: Dr. P. van Paassen

Martin Gevonden: The odd one out: exploring the nature of the association between minority status and psychosis. Supervisors: Prof.dr. J-P. Selten; Prof.dr. J. Booij, Uva; Prof.dr. I. Myin-Germeys

Bart Biallosterski: Structural and functional aspects of sensory-motor Interaction in the urinary bladder. Supervisors: Prof.dr. Ph. Van Kerrebroeck; Prof.dr. S. De Wachter, UvAntwerpen; Co-supervisors: Dr. G. van Koeveringe; Dr. M. Rahnama'i.

Alexandra König: The use of information and communication technologies (ICT) for the assessment of patients with Alzheimer's Disease and related disorders. Supervisors: prof.dr. F. Verhey; prof.dr. Ph. Robert, Nice, Fr; Co-supervisors: dr. P. Aalten; dr. R. David, Nice. Fr.

Michelene Chenault: Assessing Readiness for Hearing Rehabilitation. Supervisors: prof.dr.M.P.F. Berger; prof.dr. B. Kremer; Co-supervisor: dr. L.J.C. Anteunis.

Anand Vinekar: Retinopathy of Prematurity. Recent advances in tele-medicine screening, risk factors and spectral domain optical coherence tomography imaging. Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. N.J. Bauer

Fleur van Dooren: Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors. Supervisors: prof.dr. F.R.J. Verhey; prof.dr.J.K.L. Denollet, UvT; prof.dr. F. Pouwer, UvT; Co-supervisor: dr. M.T. Schram.

Gabriëlla Pons van Dijk: Taekwondo and physical fitness components in middle-aged healthy volunteers; the Sekwondo study. Supervisors: prof.dr. J. Lodder; prof.dr. H. Kingma; Co-supervisor: dr. A.F. Lenssen.

Yara Pujol López: Development and psychoneuroimmunological mechanisms in depression. Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove; Dr. Aye Mu Myint, München.

Romina Gentier: UBB+1; an important switch in the onset of Alzheimer's disease. Supervisors: Prof. H. Steinbusch; Prof. D. Hopkins; Co-supervisor: Dr. F. van Leeuwen.

Sanne Smeets: Insights into insight: studies on awareness of deficits after acquired brain injury. Supervisor: Prof. C. van Heugten; Prof. R. Ponds; Co-supervisor: Dr. I. Winkens

Kim Beerhorst: Bone disease in chronic epilepsy: fit for a fracture. Supervisor: Prof. A. Aldenkamp; Prof. R. van Oostenbrugge; Co-supervisor: Dr. P. Verschuure.

Alex Zwanenburg: Cerebral and cardiac signal monitoring in fetal sheep with hypoxic- ischemic encephalopathy. Supervisor: Prof. T. Delhaas; Prof. B. Kramer; Co-supervisors: Dr. T. Wolfs; Dr. P. Andriessen, MMC.

Ismail Sinan Guloksuz: Biological mechanisms of environmental stressors in psychiatry. Supervisor: Prof. J. van Os; Co-supervisors: Dr. B. Rutten; Dr. M. Drukker.

Seyed Ehsan Pishva MD: Environmental Epigenetics in mental health and illness. Supervisor: Prof.dr. J. van Os; Co-supervisors: Dr. B.P.F. Rutten; Dr. G. Kenis.

Ankie Hamaekers: Rescue ventilation using expiratory ventilation assistance; innovating while clutching at straws. Supervisors: Prof.dr. W.F. Buhre; Prof.dr. M. van Kleef.

Rens Evers. 22q11.2 deletion syndrome: intelligence, psychopathology and neurochemistry at adult age. Supervisors: Prof.dr. L.M.G. Curfs; Prof.dr. T. v. Amelsvoort.

Sarah-Anna Hescham. Novel insights towards memory restoration. Supervisor: Prof.dr. Y. Temel; Co-supervisor: Dr. A. Blokland; Dr. A. Jahanshahi.

João P. da Costa Alvares Viegas Nunes. Insulin receptor sensitization improves affective pathology in various mouse models. Supervisor: Prof.dr. H.W.M. Steinbusch; Co- supervisors: Dr. K-P. Lesch; Dr. T. Strekalova; Dr.B.H. Cline, Oxford.

Yanny Ying-Yee Cheng. Clinical Outcomes After Innovative Lamellar Corneal Transplantation Surgery. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. J.S.A.G. Schouten.

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Oliver Gerlach. Parkinson's disease, deterioration during hospitalization. Supervisor: Prof.dr. R. van Oostenbrugge; Co-supervisor: Dr. W. Weber.

Remo Arts. Intracochlear electrical stimulation to suppress tinnitus. Supervisor: Prof.dr. R.J. Stokroos; Co-supervisor: Dr. E.L.J. Georg.

Mitchel van Eeden. The €- Restore4stroke study: Economic evaluation of stroke care in the Netherlands. Supervisors: Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. v. Heugten; Co-supervisor: dr. G.A.P. van Mastrigt.

Pim Klarenbeek. Blood pressure and cerebral small vessel disease. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisor: Dr. J. Staals.

Ramona Hohnen. Peripheral pharmacological targets to modify bladder contractility. Supervisor: Prof.dr. Ph.E.V. van Kerrebroeck; Co-supervisors: Dr. G.A. van Koeveringe; Dr. M.A. Sahnama'i; Dr. C. Meriaux.

Ersoy Kocabicak. Deep brain stimulation of the subthalamic nucleus: Clinical and scientific aspects. Supervisors: Prof. dr. Y. Temel; Prof.dr. K. van Overbeeke; Co-supervisor: Dr. A. Jahanshahi.

Sven Akkerman. Temporal aspects of cyclic messenger signaling in object recognition memory; a pharmalogical approach. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: dr. J. Prickaerts; dr. A. Blokland.

Anja Moonen. Emotion and Cognition in Parkinson's disease; etiology and neurobiological mechanisms. Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisor: dr. A.F.G. Leentjens.Anna Schüth. Three-dimensional bladder tissue morphology. Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. M. v. Zandvoort, Aachen; Prof.dr. Ph. V. Kerrebroeck.

Elisabeth van der Ven. Ethnic minority position as risk indicator for autism- Spectrum and psychotic disorders. Supervisors: Prof.dr. J.P. Selten; Prof.dr. J. van Os.

Zuzana Kasanova. Environmental reactivity for better or worse; The impact of stress and reward on neurochemistry, affect and behavior across the psychosis continuum. Supervisor: Prof.dr. I. Myin-Germeys, KU Leuven/UM; Co-supervisor: dr. D. Collip.

Danielle Lambrechts. Ketogenic diet therapies; treatment for children and adults with refractory epilepsy. Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisor: dr. A.J.A. de Louw, Kempenhaghe, Heeze.

Frank van Bussel. Advanced MRI in diabetes; cerebral biomarkers of cognitive decrements. Supervisors: Prof. dr.ir. W.H. Backes; Prof.dr. P.A.M. Hofman; Co-supervisor: dr. J.F.A. Jansen.

Lisa Schönfeldt. Neurostimulation to treat brain injury? Supervisors: Prof.dr. Y. Temel; Prof.dr. S. Hendrikx, Hasselt; Co-supervisor: dr. A. Jahanshahi.

Rianne Geerlings. Transition in patients with childhood-onset epilepsy; a long way to adulthood. Supervisor: Prof.dr. A.P. Aldenkamp; Co-supervisors:dr. A.J.A. de Louw, dr. L.M.C. Gottmer, Kempenhaeghe.

Nele Claes. B cells as multifactorial players in multiple sclerosis pathogenesis: insights from therapeutics. Supervisors: Prof.dr. V. Somers, Hasselt; Prof.dr. R. Hupperts Co-supervisors: Prof.dr. P. Stinissen, dr. J. Fraussen, Hasselt.

Olaf Schijns. Epilepsy surgery and biomarkers from history to molecular imaging. Supervisors: Prof.dr. J.J. van Overbeeke; Prof.dr. H. Clustermann, Aachen; Co-supervisors: dr. G. Hoogland; dr. M.J.P. v. Kroonenburgh.

Lizzy Boots. Balanced and Prepared; development and evaluation of a supportive e- health intervention for caregivers of people with early-stage dementia. Supervisors: Prof.dr. F.R.J. Verhey; Prof.dr. G.I.J.M. Kempen; Co-supervisor: dr. M.E. de Vugt.

Wouter Donders. Towards patient-specific (cerebro-) vascular model applications. Supervisors: Prof. dr. T. Delhaas; Prof.dr.ir. F.N. van de Vosse, TUE; Co-supervisor: dr.ir. W. Huberts.

Sizzle Vanterpool. The implications of intrauterine invasion by microbes for placental Pathology and the occurrence of adverse pregnancy outcomes. Supervisor: Prof.dr. B.W. Kramer. Co-supervisors: dr. J.V. Been, Erasmus MC Rotterdam, dr. U von Rango.

Manuela Heins. The Relationship between Social Adversity, Psychosis, and Depression across an Individual's Life Span. Supervisor: Prof.dr. I. Myin-Germeys.Christianus van Ganzewinkel. NEONATAL PAIN; Out of Sight, Out of Mind?Supervisor: Prof.dr. B.W.W. Kramer; Co-supervisor: dr. P. Andriessen, MMC Veldhoven.

Anne-Hilde Muris. Hype or hope? Vitamin D in multiple sclerosis; A clinical and immunological perspective. Supervisor: Prof.dr. R.M.M. Hupperts; Co-supervisor: dr. J.G.M.C. Damoiseaux.

Gerard Bode. The link between ceramide transporters, innate Immunity and Alzheimer's disease. Supervisor: Prof.dr. M.H.V. de Baets; Co-supervisors: dr. P. Martinez, dr. M. Losen.

Jo Stevens. Advanced diagnostics and therapeutics for Alzheimer's disease. Supervisor: Prof.dr. M. de Baets; Co-supervisors: dr. M. Losen, dr. P. Martinez-Martinez.

Rosan Luijcks. Stress and pain in muscles and brain; developing psychophysiological paradigms to examine stress and pain interactions. Supervisors: Prof.dr. J.J. van Os; Prof.dr.ir. H.J. Hermens, UT; Co-supervisor: dr. R. Lousberg.

M.C. Haanschoten. Towards efficient cardiac surgery – the integrating role of anesthesiology and intensive care. Supervisors: Prof. dr. W. Buhre; Prof. dr. A. van Zundert (Queensland); Co-supervisors: Dr. M.A. Soliman Hamad; Dr. A. van Straten (Catharina zkhs.)

Harmen Jan van de Haar. Microvascular and blood-brain barrier dysfunction in Alzheimer's disease. Supervisor: Prof.dr.ir. W. Backes; Prof.dr. F. Verhey; Co-supervisor: Dr. J. Jansen; Dr.ir. M. v. Osch, LUMC.

Coenraad Itz. Chronic low back pain, considerations about: Natural Course, Diagnosis, Interventional Treatment and Costs. Supervisor: Prof.dr. M. van Kleef; Prof.dr. F. Huygen, EUR; Co- supervisor: Dr. B. Ramaekers.

Willemijn Jansen. The Path of Alzheimer's disease: from neuropathology to clinic. Supervisor: Prof.dr. F. Verhey; Co-supervisors: Dr. P.J. Visser; Dr. I. Ramakers.

Ligia dos Santos Mendes Lemes Soares. Phosphodiesterase inhibitors: a potential therapeutic approach for ischemic cerebral injury. Supervisor: Prof. dr. H.W.M. Steinbusch; Co-supervisors: Dr. R.M. Weffort de Oliveira, Brazil; Dr. J. Prickaerts

Martijn Broen. Anxiety and depression in Parkinson's disease. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisors: Dr. A.F.G. Leentjens; Dr. M.L. Kuijf.

Sandra Schipper. Extrasynaptic receptors as a treatment target in epilepsy. Supervisor: Prof.dr. J.H.S. Vles; Co-supervisors: Dr. G. Hoogland; Dr. S. Klinkenberg; Dr. M.W. Aalbers, RUG.

João Casaca Carreira. Making sense of Antisense Oligonucleotides Therapy in Experimental Huntington's disease. Supervisor: Prof.dr. Y. Temel; Co-supervisors: Dr. A. Jahanshahi; Dr. W. van Roon-Mom, LUMC. Dominique IJff. Trick or Treat? Cognitive side-effects of antiepileptic treatment. Supervisors: Prof.dr. A.P. Aldenkamp; Prof.dr. M. Majoie; Co-supervisors: Dr. J. Jansen; Dr. R. Lazeron, Kempenhaeghe.

Alfredo Ramirez. Neurogenetic approach in neurodegenerative disorders. Supervisors: Prof.dr. B.P.F. Rutten; Prof.dr. H.W.M. Steinbusch; Prof.dr. M.M. Nöthen, University of Bonn.

Nienke Visser. Toric Intraocular lenses in cataract surgery. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. N.J.C. Bauer.

Jakob Burgstaller. Prognostic indicators for patients with degenerative lumbar spinal stenosis. Supervisor: Prof.dr. M. van Kleef; Co-supervisors: Dr. M.M. Wertli, University of Zurich; Dr. H.F. Gramke.

Mark van den Hurk. Neuronal Identity and Maturation: Insights from the Single-Cell Transcriptome. Supervisors: Prof.dr. H.W.M. Steinbusch; Prof.dr. B.P.F. Rutten; Co-supervisors: Dr. G. Kenis; Dr. C. Bardy, Adelaide.

Maria Nikiforou. Prenatal stress and the fetal gut. Potential interventions to prevent adverse outcomes. Supervisors: Prof.dr. B.W. Kramer; Prof.dr. H.W. Steinbusch; Co-supervisor: Dr. T.G. Wolfs.

Janneke Peijnenborgh. Assessment of cognition, time perception, and motivation in children. Supervisors: Prof. dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisors: Dr. J. Hendriksen; Dr. P. Hurks.

Joany Millenaar. Young onset dementia; towards a better understanding of care needs and experiences. Supervisors: Prof.dr. F. Verhey; Prof.dr. R. Koopmans, RUN; Co- supervisors: Dr. M. de Vugt; Dr. C. Bakker, RUN.

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Adriana Smits. Perinatal factors and hearing outcome. Supervisors: Prof.dr. R.J. Stokroos; Prof.dr. B.W. Kramer; Prof.dr. B. Kremer.

Angela Bouwmans. Transcranial sonography in parkinsonian disorders: clear window or blurred vision. Supervisor: Prof.dr. W.H. Mess; Co-promotores: Dr. W.E.J. Weber; Dr. A.F.G. Leentjens.

Björn K. Stessel. Patient centred care after day surgery: scope for improvement. Supervisors: Prof.dr. W. Buhre; Prof.dr. B. Joosten. Co-supervisor: Dr. A.H. Gramke.

Jan Guy Bogaarts. Quantitative EEG and machine learning methods for the detection of epileptic seizures and cerebral asymmetry. Supervisor: Prof.dr. W.M. Mess; Co-supervisor: Dr.ir. J.P.H. Reulen; Dr.ir. E.D. Gommer.

Martin M. Müller. Pregnancy derived products for treatment of perinatal brain injuries. Supervisors: Prof.dr. B.W.W. Kramer; Prof.dr. D. Surbek, Bern; Co-supervisors: Dr. T. Wolfs; Dr. G. Gavilanes.

Daan Ophelders. Novel treatment strategies for the protection of the preterm brain; Re- balancing inflammation and regeneration. Supervisor: Prof.dr. B. Kramer; Co-supervisor: Dr. T. Wolfs; Dr. R. Jellema.

Rosalie van Knippenberg. Experience sampling in dementia care; an innovative intervention to support caregivers in daily life. Supervisors: Prof.dr. F. Verhey; Prof. dr. R. Ponds; Prof.dr. I. Myin-Germeys, KU Leuven; Co-supervisor: Dr. M. de Vugt.

Claudia Vingerhoets. Investigating neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA; Co-supervisor: Dr. O. Bloemen

Dennis Oerlemans. Evolution of Neuromodulation for Lower Urinary Tract Dysfunction; Past, Present and Future. Supervisors: Prof.dr. Ph. van Kerrebroeck; Prof.dr. G. van Koeveringe. Co-supervisors: Dr. E. Weil; Dr. T. Marcelissen.

Marion Levy. Evaluation of BDNF/TrkB signaling as a common target in the treatment of major depression and Alzheimer's disease. Supervisors: Prof.dr. H. Steinbusch; Prof. L. Lanfumey, Université Paris Descartes, France. Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove.

Patrick Domen. Stay connected: a family-based diffusion imaging study in psychotic disorder. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Marcelis

Geor Bakker. Innovative Approaches to Understanding the Neurobiology of Psychosis. Supervisors: Prof.dr. T. van Amelsfoort; Prof.dr. J. Booij, UvA. Co-supervisor: dr. M. Caan, UvA; dr. O. Bloemen.

Wilma Boevink. HEE! Over Herstel, Empowerment en Ervaringsdeskundigheid in de psychiatrie. Supervisors: Prof.dr. J. van Os; Prof.dr. Ph. Delespaul. Co-supervisor: dr. H. Kroon.

Nataliia Markova . Modified swim test as a mouse depression paradigm of enhanced Cognitive processing: the role of GSK3β. Supervisor: Prof.dr. H. Steinbusch; Prof. dr. K-P. Lesch, University of Wuerzburg. Co-supervisor: Dr. T. Strekalova.

Merijn van de Laar. Individual differences in insomnia; implications of Psychological factors for diagnosis and treatment. Supervisor: Prof.dr. A. Aldenkamp; Prof.dr. D. Pevernagie, Universiteit Gent. Co-supervisor: Dr. S. Overeem, TUE.

Willem Buskermolen. If only I could tell …; Measuring predictors for challenging behaviour in people with both intellectual disability and hearing impairment Supervisor: Prof.dr. A. Aldenkamp. Co-supervisor: Dr. J. Hoekman, UL.

Kay Deckers. The role of lifestyle factors in primary prevention of dementia; an epidemiological perspective. Supervisor: Prof.dr. F. Verhey. Co-supervisor: Dr. M. van Boxtel; Dr. S. Köhler.Brechje Dandachi-FitzGerald. Symptom validity in clinical assessments. Supervisors: Prof.dr. R. Ponds; Prof.dr. F. Verhey.

Maurice Theunissen. Understanding factors affecting postoperative Quality of Life. Supervisors: Prof.dr. M. Peters, Prof.dr. M. Marcus. Co-supervisor: Dr. H. Gramke.

Anna Cleutjens. COgnitive-Pulmonary Disease? Neuropsychological functioning in patients with COPD. Supervisors: Prof.dr. E. Wouters, Prof.dr. R. Ponds. Co-supervisors: Dr. D. Janssen, Horn, Dr. J. Dijkstra.

Laura Serpero. Next Generaton Biomarkers in Perinatal Medicine: S100B Protein. Supervisors: Prof.dr. D. Gazzalo, Alessandria, Italy; Prof.dr. B..W.W. Kramer. Co-supervisor: Dr. A.W.D. Gavilanes.

Alessandro Varrica. S100B Protein and Congential Heart Diseases: Brain Aspects. Supervisors: Prof.dr. D. Gazzalo, Alessandria, Italy; Prof.dr. J.S.H. Vles; Prof.dr. L.J.I. Zimmermann. Co-supervisor: Dr. A.W.D. Gavilanes.

Pim R.A. Heckman. Targeting phosphodiesterase type 4 for improving cognitive fronto- striatal function: a translational approach. Supervisor: Prof.dr. J.G. Ramaekers. Co- supervisors: Dr. J.H.H.J.. Prickaerts; Dr. A. Blokland.

Sven van Poucke. Platelets, form sample to big data; exploring granularity in platelet research. Supervisors: Prof.dr. M.A.E. Marcus; Prof.dr. W. Buhre. Co-supervisor: Dr. M. Lancé.

Désirée M.J. Vrijens. Dysfunctions of the Lower Urinary Tract and Affective Symptoms. Supervisors: Prof.dr. Ph.E.V. van Kerrebroeck; Prof.dr. G.A. van Koeveringe. Co- supervisors: Dr. C. Leue.

Tamar van Veenendaal. Neurotransmitters & Networks. An MR view on epilepsy and antiepileptic drugs. Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. A.P. Aldenkamp. Co- supervisor: Dr. J.F.A. Jansen.

Evelien M. Barendse. Autism Spectrum Disorders in High functioning Adolescents; Diagnostic considerations (AHA). Supervisors: Prof.dr. A.P. Aldenkamp; Prof.dr. R.P.C. Kessels, Radboud University.

Roy Lardenoije. A venture into the epigenetics of aging and Alzheimer's Disease. Supervisors: Prof.dr. B.P.F. Rutten; Prof.dr. H.W.M. Steinbusch. Co-supervisors: Dr. D. van den Hove; Dr. C.A. Lemere, USA.

Charlotte L. Mentzel. The course recognition and treatment of movement disorders in severe mental illness. Supervisors: Prof.dr. P.N. van Harten; Prof.dr. M.A.J. de Koning- Tijssen, UMCG. Co-supervisor: Dr. P.R. Bakker.

Tim Batink. Third Wave Behaviour Therapy: Process Measures and Contextual Interventions. Supervisors: Prof.dr. F.P.M.L. Peeters; Prof.dr. J.J. van Os; Prof.dr. M.C. Wichers, UMC Groningen.Kevin L.J. Rademakers. Detrusor Underactivity: From Theory To Clinical Assessment. Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. Ph.E.V. van Kerrebroeck. Co-supervisor: Dr. M. Oelke.

Iris M.J. Lange. Should I stay or should I go ? Brain mechanisms underlying fear and safety learning, and explosure therapy outcome. Supervisors: Prof.dr. K.R.J. Schruers; Prof.dr. T.A.M.J. van Amelsfoort. Co-supervisor: Dr. L. Goossens.

Ruben G.F. Hendriksen. Evidence for a dystrophin-associated encephalopathy in Duchenne Muscular Dystrophy. Supervisor: Prof.dr. J.S.H. Vles. Co-supervisors: Dr. G. Hoogland; Dr. M.W. Aalbers, UMC Groningen.

Michael Gofeld. Strengths and limitations of the lumbar spine ultrasound-guided interventions. Supervisor: Prof. dr. M. van Kleef. Co-supervisor: Dr. M. Sommer.

Willem A.R. Zwaans. Strategies for chronic inguinal pain. Supervisor: Prof.dr. M. van Kleef. Co-supervisors: Dr. R.H.M. Roumen; Dr. M.R.M. Scheltinga, MMC Veldhoven.

Linda M. Rolf. Mapping the effects of vitamin D in multiple sclerosis A 3D Perspective. Supervisor: Prof.dr. R.M.M. Hupperts. Co-supervisors: Dr. J.G.M.C. Damoiseaux; Dr. J.J.F.M. Smolders, CWZ Nijmegen.

Maarten van Beek. Spinal Cord Stimulation in Clinical and Experimental Painful Diabetic Polyneuropathy. Supervisors: Prof.dr. E.A. Joosten; Prof.dr. M. van Kleef. Co- supervisor: Dr. S.M.J. van Kuijk.

Melina Barkhuizen. Genetic and perinatal risk factors for movement disorders. Supervisors: prof.dr. B.W.W. Kramer, prof.dr. H.W.M. Steinbusch, Prof.dr. A.F. Grobler. Co- supervisor: dr. A.W.D.Gavilanes-Jimenez.

Renske Uiterwijk. Cognitive function and cerebral small vessel disease in hypertension. Supervisor: prof.dr. R.J. van Oostenbrugge. Co-supervisor: Dr. J.E.A. Staals.

Elles Douven. Depression and apathy after stroke. Supervisor: prof.dr. F.R.J. Verhey. Co- supervisors: Dr. P. Aalten, dr. J. Staals.

Mauro Pessia. Brain K+ Channels: from molecular and physiological features to autism spectrum disorder and intellectual disability. Supervisors: prof.dr. H.W.M. Steinbusch, prof.dr. M.B. Donati, It.

Carsten Leue. Hyperarousal in the Hospital and what to do about it: the MED-PSYCH- NET - a transitional network approach fostering personalized care in psychosomatic medicine. Supervisors: Prof.dr. J. van Os, Prof.dr. A. Masclee. Co-supervisors: Dr. J. Strik, Dr. J. Kruimel

Andrea S. Herrera Soto. Aminochrome, an endotoxin for inducing a new rat model of Parkinson's Disease. Supervisor: prof.dr. H.W.M. Steinbusch. Co-supervisors: Prof.dr. Juan Segura-Aquilar; prof. G. Diaz-Veliz, Santiago of ChileEline E.B. de Clerck. Ocular neurodegenerative changes and macular cysts in prediabetes and type 2 diabetes. Supervisors: Prof.dr. C.A.B. Webers, Prof.dr. C.D.A. Stehouwer. Co-supervisor: Dr. J.S.A.G. Schouten

Steven T.H. Honings. Exploring psychosis and multidirectional violence: a prospective study in the general population. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Drukker

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Sau May Wong. Advances in Microvasculair MRI Techniques: Breaking the Pathophysiological Barriers in Cerebral Small Vessel Disease. Supervisor: Prof.drir. W.H. Backes, Porf.dr. R.J. van Oostenbrugge. Co-supervisor: Dr. J.F.A. Jansen

Mark B.N. van Winkel. Lonely at heart and stressed in company of Others; the influence of daily life social experiences and emotions on depression. Supervisors: prof.dr. F. Peeters; prof.dr. I. Myin-Germeys, KU Leuven/UM; prof.dr. M. Wichers, UMC Groningen

Harsha Birur Laxmana Rao. Revisiting the vascular theory of glaucoma using optical coherence tomography angiography. Supervisors: prof.dr. C.A.B. Webers; prof.dr. R.N. Weinreb, University of California, San Diego

Babette L.R. Reijs. Cognitive correlates of cerebrospinal fluid biomarkers for Alzheimer's disease. Supervisor: prof. dr. F.R.J. Verhey. Co-supervisors: Dr. P.J. Visser; dr. I.H.G.B. Ramakers

Rachel Slangen. Spinal cord stimulation in painful diabetic peripheral Neuropathy. Clinical- and cost-effectiveness. Supervisors: prof.dr. M. van Kleef; Prof.dr. C. Dirksen; prof. dr. C. Faber

Ganne Chaitanya. Epilepsy: A network disorder. Supervisors: prof.dr. A.P. Aldenkamp; prof. P. Satishchandra, NIMHANS, Bangalore, India. Co-supervisors: Dr. J.F.A. Jansen; Dr. S. Zinger, TUE

Sumitha Rajendrarao. New Insight into the Multifaceted Pathogenic Mechanisms of Sporadic Amyotrophic Lateral Sclerosis. Supervisors: prof.dr. B.W. Kamer; prof.dr. H.W. Steinbusch. Co-supervisor: prof. T.R. Raju, NIMHANS, Bangalore, India

Suzanne Roggeveen. Interference of mobile phone with electrophysiology and emotions; results from short-term experimental studies. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. R. Lousberg.

Matthias Walter. Multi-methodological approaches to investigate lower urinary tract function in health and disease. Supervisors: Prof.dr. Ph.E.V.A. van Kerrebroek; Prof.dr. G.A. van Koeveringe; Prof.dr. A. Curt, Zürich, CH.

Lalit Gupta. Inhomogeneities in spontaneous brain fluctuations. Supervisors: Prof.dr.ir. WH. Backes; Prof. dr. P.A.M. Hofman. Co-supervisor: Dr. J.F.A. Jansen. Chaitra Jayadev. Impact of imaging the pediatric retina. Supervisor: Prof.dr. C.A.B. Webers. Co-supervisor: Dr. N.J.C. Bauer; Dr. A. Vinekar.

Annelie Klippel. Navigating through complexity; processes and mechanisms underlying the development of psychosis. Supervisors: Prof.dr. I. Myin-Germeys, KU-Leuven; Prof.dr. M.C. Wichers, UMC Groningen. Co-supervisor: Dr. U. Reininghaus.

Kürşat Altinbaş. Reconstructing The Diagnostic Framework of Bipolarity. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. I.S. Gülöksüz.

Andrea J.R. Balthasar. Eyes of the needle; Spectral tissue sensing, an innovative technology for detecting various tissue types during percutaneous needle-based procedures in locoregional anesthesia and pain medicine. Supervisor: Prof.dr. M. van Kleef. Co-supervisor: Dr. G-J. van Geffen, Radboud UMC Nijmegen.

Walmari Pilz. Shedding light on oropharyngeal dysphagia in myotonic dystrophy type 1. Supervisor: Prof.dr. B. Kremer. Co-supervisors: Dr. L.W.J. Baijens; Dr. V. Lima Passos.

Nynke J. van den Hoogen. Repetitive painful procedures in the neonate: Treatment and adult pain sensitivity. Supervisors: Prof.dr. E.A.J. Joosten, Prof.dr. D. Tibboel, Erasmus MC-Sophia, Rotterdam. Co-supervisor: Dr. J. Patijn.

Carlota Mestres Gonzalvo. Medication optimisation; Methodological aspects and new strategies. Supervisors: Prof.dr. F.R.J. Verhey, Prof.dr. P.H.M. van der Kuy, Erasmus MC Rotterdam. Co-supervisors: Dr. R. Janknegt, Zuyderland MC.

Carolin Hoffmann. The Brain under Attack: Autoantibodies in Psychotic Disorders. Supervisors: Prof.dr. P. Martinez, Prof.dr. B. Rutten, Prof.dr. J. van Os, UU/UM.

Jindra M. Bakker. On the bumpy road of happiness: Mechanisms of daily life reward processing and how it can be changed. Supervisors: Prof.dr. M. Wichers, UMC Groningen, Prof.dr. I. Myin-Germeys, KU Leuven/UM. Co-supervisor: Dr. L. Goossens.

Marasha-Fiona de Jong. Between mood and matter; studies on the interface between mood disorders and physical conditions. Supervisor: Prof.dr. F.P.M.L. Peeters. Co- supervisors: Prof.dr. Mischoulon.

Anouk Smeets. New insights in deep brain stimulation for Tourette syndrome. Supervisor: Prof.dr. Y. Temel. Co-supervisors: Dr. L. Ackermans, Dr. A.A. Duits, de. A.F.G. Leentjens.

Margaretha Skowron. Cisplatin resistance in urothelial carcinoma; Understanding and targeting inherent and acquired mechanisms. Supervisors: Prof.dr. G.A. van Koeveringe, Prof.dr. P. Albers, Heinrich-Heine Univ. Düsseldorf. Co-supervisors: Dr. J.G.H. van Roermund, Dr. A. Romano.

Thierry Mentzel. Capturing the cacophony of movement. Supervisors: Prof.dr. P.N. van Harten, Prof.dr. H.A.M. Daanen, VUA. Co-supervisor: Dr.mr. O.J.N. Bloemen, GGZ Hilversum/UM.Petronella de Meij. Quality indicators for the assessment of pain clinic care: A step forward? Quality from professionals and pain patients' perspective (QiPPP). Supervisors: Prof.dr. G.D.E.M. van der Weijden, Prof.dr. M. v. Kleef. Co-supervisor: Dr.A.J.A. Köke.

Thomas Vaessen. Stress sensitivity in psychosis: assessment, mechanism & intervention. Supervisor: Prof. dr. I. Myin-Germeys, KU Leuven/UM.

Yori van der Steen. Dissecting the psychosis continuum; risk factors along the pathway from experiences to disorder. Supervisor: Prof.dr. I. Myin-Germeys, KU Leuven/UM, Prof.dr. R. van Winkel, KU Leuven.

Aryo Zare. Unveiling the sensory connections between the bladder and the brain that involve the periaqueductal gray matter. Supervisor: Prof.dr. G.A. van Koeveringe; Co- supervisor: Dr. A. Jahanshahi.

Magdalena Weidner. Brain serotonin throughout development – for better and for worse. Supervisors: Prof.dr. H.W.M. Steinbusch, Prof.dr. K.P. Lesch, JM.Univ. Würzburg. Co- supervisor: Dr. D.L.A. van den Hove.

Catherine Vossen. Cortical processing of pain; the role of habituation. Supervisors: Prof.dr. E.A. Joosten, Prof. dr. J. van Os, UU/UM. Co-supervisor: Dr. R. Lousberg.

Whitney Freeze. Microvascular contributions to dementia; Exploring the role of blood- brain barrier leakage in cerebral small vessel disease and Alzheimer disease. Supervisors: Prof.dr. F.R.J. Verhey, Prof.dr.ir. W.H. Backes. Co-supervisor: Dr. H.I.L. Jacobs.

Simone Schüller. Characterization of Stem and Immune Cell Ontogeny to Inform Prevention and Treatment of Infections in Preterm Newborns. Supervisors: Prof. dr. B.W.W. Kramer, Prof.dr.med. A. Berger, Wien. Co-supervisor: Dr. E. Villamor.

Michael J. Kemna. Predicting relapses in ANCA associated vasculitis. Supervisor: Prof.dr. J.W. Cohen Tervaert. Co-supervisors: Dr. J. Damoiseaux, Dr. P. van Paassen.

Artemis Iatrou. Epigenetics in mental and neurodegenerative disorders. Supervisor: Prof.dr. B.P.F. Rutten. Co-supervisors: Dr. D.L.A. van den Hove, Dr. G. Kenis.

Laura Wielders. Prevention & Treatment of Cystoid Macular Edema after Cataract Surgery. Supervisor: Prof. dr. R.M.M. Nuijts. Co-supervisors: Dr. J.S.A.G. Schouten, CWZ Nijmegen, Dr. B. Winkens.

Daisy Hoofwijk. The way to understanding Chronic Postsurgical Pain; From clinical and psychological predictors to incorporating genetics. Supervisor: Prof. dr. W.F.F.A. Buhre; Prof.dr. E.A.J. Joosten; Co-Supervisor: dr. H.-F. Gramke; dr. A.A.A. Fiddelers.

Loes Leenen. Self-management in Epilepsy; The Goal is: "Live with a Z(s)mile. Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. van Heugten.

Chiara Peila. 'Effects of Pasteurization and Refrigerated Storage on Human Milk Neurobiomarkers Concentrations. Supervisors: Prof.dr. D. Gazzallo, Alessandria, It./MUMC+; Prof.dr. G. Visser, UU; Prof.dr. E. Bertino, Alessandria, It.

Raymond van de Berg. The Vestibular Implant: Feasibility in humans. Supervisor: Prof.dr. H. Kingma; Co-supervisor: dr. J.-P. Guyot, Université de Genève, CH.

Nils Guinand. The Vestibular Implant: a more stable horizon for patients with a bilateral vestibular deficit? Supervisors: prof.dr. H. Kingma; Prof.dr. J.-P. Guyot, Université de Genève, CH.

Jasper Smit. Exploring deep brain stimulation as a treatment for tinnitus. Supervisors: Prof.dr. R.J. Stokroos; Prof.dr. Y. Temel; Co-supervisor: dr. Jahanshahianvar.

Bindu Paravil Sankaran. Brain MRI in Mitochondrial Disorders: Correlating the Phenotype with Genotype. Supervisor: Prof.dr. H. Smeets; Prof.dr. A. Taly, NIMHANS, Bangalore, India.

Syenna Schievink. Vascular cognitive impairment; at the heart of the matter. Supervisor: Prof.dr. F.R.J. Verhey; Prof.dr. R.J. van Oostenbrugge; Co-supervisor: dr. S. Köhler.

Isabelle Bos. Biomarkers of Alzheimer's disease; relations with vascular factors and cognition in the pre-dementia stages. Supervisor: Dr. P.J. Visser; Prof.dr. F.R.J. Verhey; Co-supervisor: dr. S.J.B. Vos.

Stijn Michielse. Road work ahead; cerebral pathways mediating Psychological mechanisms underlying the psychosis spectrum. Supervisor: Prof.dr. J.J. van Os; Co- supervisor: dr. M.C. Marcelis.

Georgios Schoretsanitis. Risperidone-based therapeutic regimens; Drug interactions and adverse drug reactions. Supervisor: prof.dr. K.R.J. Schruers; Co-supervisor: dr. M. Bak .

Alieske Dam. INLIFE; An innovative online social support intervention for caregivers of persons with dementia. Supervisor: Prof.dr. M.E. de Vugt; Prof.dr. F.R.J. Verhey; Co- supervisor: Dr. M.P.J. van Boxtel.

Roel Haeren. Vascular ventures; Analysis of vascular structures and function in epilepsy. Supervisor: Prof.dr. Y Temel; Co-supervisor: dr. K. Rijkers; Dr. G. Hoogland.

Chiara Fabbri. Pharmacogenomics of antidepressant drugs: perspectives for the personalization of treatment in depression. Supervisors: Prof.dr. K. Schruers; Prof.dr. A. Serretti, Bologna.

Esther van Duin. Dancing in the (B)rain'; neurobiology of reward, stress & Information processing in 22q11.2 deletion syndrome. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA. Co-supervisor: dr. D. Hernaus.Rob Verdonschot. Oropharyngeal dysphagia and its psychiatric Comorbidities; The prevalence of affective symptoms and the unmet clinical need for integrated care in medically unexplained symptoms. Supervisor: Prof.dr. B. Kremer; Co-supervisors; Dr. L. Baijens; dr. S. Vanbelle.

Lisanne Breuer. Accelerated Cognitive Ageing in Epilepsy' Does it Exists? Supervisors: Prof.dr. A. Aldenkamp; Prof.dr. P. Boon, UZ Gent; Co-supervisors: dr. A. de Louw, Kempenhaeghe, Heeze; dr.ir. S. Zinger, TUE.

Liselot Kerpershoek. Access to formal dementia care; A European perspective. Supervisors: Prof.dr. F. Verhey; Prof.dr. M. de Vugt; Prof. B. Woods, Bangor University, UK Co-supervisor: Dr. C. Wolfs.

Henrietta Steinhart. Same Same but Different; Psychological Interventions and how to Mind the Knowledge Practice Gap. Supervisor: Prof.dr. I. Myin-Germeys. Co-supervisor: Dr. U. Reininghaus.

Ulrich Mehnert. The management of urine storage dysfunction in the neurological patient. Supervisors: Prof.dr. G. van Koeveringe; Prof.dr. Ph.van Kerrebroeck; Prof.dr. S. Wachter, Antwerpen; Prof.dr E. Chartier-Kastler, Sorbonne, Paris.

Giovanne B. Diniz. Weaning-induced alterations on neuropeptidergic populations of the rat hypothalamus. Supervisors: Prof.dr. H. Steinbusch; Prof.dr. J. Bittencourt, ICB/USP, Brasil.

Rajani Ravindra Battu. Inherited Retinal Diseases: New Imaging and Molecular Genetics. Supervisor: Prof.dr. C.A.B. Webers. Co-supervisors:Dr. J.S.A.G. Schouten, CWZ; dr. T.T.J.M. Berendschot.

Jans van Ool. Diagnostic and neuropsychiatric considerations in epilepsy and intellectual disability; Psychological perspectives. Supervisor: Prof.dr. A. Aldenkamp. Co-supervisors: Dr. J. Hendriksen; Dr. H. Schelhaas, Kempenhaeghe.

Eveline Janssen. Depression in the elderly: focus on high risk groups. Supervisors: Prof.dr. F. Verhey; Prof.dr. M. de Vugt. Co-supervisor: Dr. M. Schram.

Cécile Kicken. Extreme blood coagulation; investigating the influence of physiological extremes on thrombin generation and platelet activation. Supervisor: Prof.dr. W. Buhre Co-supervisors; Dr. B. de Laat; Dr. M. Lancé, Qatar.

Martinus van Eerd. Diagnosis and Interventional Pain Treatment of Cervical Facet Joint Pain. Supervisor: Prof. dr. M. van Kleef. Co-supervisor; Dr. J. Patijn, Eindhoven; Dr. M. Sommer