Memory Functioning in Depression: Empirical Evidence for Episodic Memory Impairments, possible Causes, and suggested Risk Factors

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Abstract

Depressive disorders are amongst the most widespread mental health issues that can lead to a reduced quality of life. Even though depression is commonly known to be a disorder of affect, it is often accompanied by various difficulties with cognitive functions such as memory-related impairments as well. However, inconsistent empirical findings of previous investigations still lead to a lack of clarity regarding cognitive functioning in depression. Therefore, the major aim of the present doctoral thesis was to assess and explore memory-related functioning in clinically depressed patients compared to healthy individuals using the Wechsler Memory Scale in its recent edition (WMS-IV). Particularly, the main purpose was to clarify whether depression is associated with severe episodic memory impairments and if certain characteristics of depressed individuals might explain such cognitive deficits. In Study I, age and gender could be shown to exert a general effect on certain components of episodic memory. As a major prerequisite for all subsequent analyses, Study II confirmed that the WMS-IV test battery for the most part provides suitable neuropsychological measures for the purpose of comparing test performances of depressed patients with those of healthy controls. In line with preliminary expectations, episodic memory performances turned out to be significantly lower for depressed patients than for healthy controls in Study III. The findings additionally supported the assumption that depression-related impairments in episodic memory might be partially explained by certain executive dysfunctions in depression. Study IV further emphasized the role of disorder subtypes for explaining cognitive dysfunctions as patients with recurrent depressive episodes were found to feature even lower WMS-IV test performances than patients with their first depressive episode. Finally, these findings were extended by examining certain factors that might possibly contribute to the development of episodic memory impairments in depression. Besides the general effects of age, gender, and education, the findings of Study V further suggested that especially those patients that are affected by higher levels of depression severity, longer illness durations, or by more depressive episodes than other depressed patients are at greater risk to develop more severe memory-related impairments in the course of the disorder. In due consideration of several methodological strengths and limitations, the findings of the present research studies and their implications for future research and clinical practice are discussed at the end of this thesis.

Zusammenfassung

Depressive Störungsbilder zählen heute zu den weit verbreiteten psychischen Erkrankungen, die die allgemeine Lebensqualität der Betroffenen stark herabsetzen können. Obwohl sie vorwiegend als affektive Störungen bezeichnet werden, so gehören häufig auch kognitive Symptome wie Gedächtnisdefizite zu den Begleiterscheinungen einer Depression. Empirische Befunde zur Gedächtnisleistung von depressiven Patienten liefern bislang jedoch kein einheitliches Bild darüber, ob und inwiefern kognitive Fähigkeiten durch die Erkrankung beeinflusst werden. Das Ziel der vorliegenden Arbeit war es deshalb, Gedächtnisleistungen von klinisch depressiven Patienten mittels der Wechsler Gedächtnisskala in der aktuellen Fassung (WMS-IV) zu erheben und mit den Gedächtnisleistungen einer Gruppe gesunder Probanden zu vergleichen. Auf Grundlage der so gewonnen neuropsychologischen Daten sollte geklärt werden, ob die depressive Symptomatik insbesondere mit Beeinträchtigungen im episodischen Langzeitgedächtnis in Verbindung stehen könnte und ob sich die Ausprägung bestimmter störungsspezifischer Charakteristika für die Vorhersage dieser Defizite eignet. In Studie I konnten zunächst generelle Alters- und Geschlechtereffekte auf bestimmte Komponenten des episodischen Gedächtnisses in einer Stichprobe gesunder Probanden aufgedeckt werden. Des Weiteren erbrachten die Ergebnisse in Studie II den für alle nachfolgenden Analysen erforderlichen Nachweis, dass sich die WMS-IV als neuropsychologisches Instrument für den Vergleich der Gedächtnisleistungen von depressiven Patienten und gesunden Probanden eignet. Erwartungsgemäß zeigte dieser Vergleich in Studie III, dass depressive Patienten ein signifikant geringeres Leistungsniveau als gesunde Probanden in Aufgaben des episodischen Gedächtnisses aufwiesen. Zusätzlich unterstützten weitere Befunde aus Studie III die Annahme, dass sich Beeinträchtigungen des episodischen Gedächtnisses bei depressiven Patienten zumindest teilweise durch ihre Defizite in exekutiven Funktionen erklären lassen. Darüber hinaus unterstreichen die Ergebnisse aus Studie IV auch die Rolle der Störungsform, da hier gezeigt werden konnte, dass Patienten mit einer rezidivierenden Depression in bestimmten Komponenten des episodischen Gedächtnisses stärkere Leistungseinbußen aufwiesen als Patienten, die erstmaliger an einer depressiven Episode erkrankt waren. Schließlich wurden diese Befunde durch zusätzliche Analysen möglicher Einflussfaktoren für die episodischen Gedächtnisdefizite depressiver

Patienten in der letzten Studie der vorliegenden Arbeit ergänzt. Neben den Einflüssen des Alters, Geschlechts und der Bildung, lassen die Ergebnisse in Studie V vermuten, dass insbesondere Patienten, die einen höheren Schweregrad der Depression, eine längere Erkrankungsdauer oder wiederholt auftretende depressive Episoden aufweisen, einem höheren Risiko ausgesetzt sind, stärkere episodische Gedächtnisdefizite im Verlauf der Krankheit zu entwickeln als andere depressive Patienten. Unter Berücksichtigung diverser methodischer Stärken und Limitationen werden die Befunde der vorliegenden Arbeit sowie ihre Implikationen für zukünftige Forschung und für die klinische Praxis abschließend diskutiert.

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance (univariate)
BCSE	Brief Cognitive Status Exam
CRH	Corticotrophin releasing hormone
CFA	Confirmatory factor analysis
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition
EF	Executive functioning
HPA	Hypothalamic-pituitary-adrenal axis
IC	Inhibitory control
ICD-10	International Classification of Disease – Tenth Edition
LTM	Long-term memory
LTD	Long-term depression
LTP	Long-term potentiation
MANOVA	Analyses of variance (multivariate)
MC	Mental control
MGCFA	Multigroup confirmatory factor analysis
MDD	Major depressive disorder
RAM	Resource allocation model
RD	Recurrent depression
SEM	Structure equation model
WHO	World Health Organization
WM	Working memory
WMS-IV	Wechsler Memory Scale – Fourth Edition
WMH	White matter hyperintensities
ZKPR	Center of Clinical Psychology and Rehabilitation (Zentrum für Klinische Psychologie und Rehabilitation)

List of Publications

Study I **(see Appendix A)**

Pauls, F., Petermann, F., & Lepach, A. C. (2013). Gender differences in episodic memory and visual working memory including the effects of age. *Memory, 21*, 857-874.

Study II **(see Appendix B)**

Pauls, F., Petermann, F., & Lepach, A. C. (2013). Memory assessment and depression: Testing for factor structure and measurement invariance of the Wechsler Memory Scale – Forth Edition across a clinical and matched control sample. *Journal of Clinical and Experimental Neuropsychology, 35*, 702-717.

Study III **(see Appendix C)**

Pauls, F., Petermann, F., & Lepach, A. C. (2014). Episodic memory and executive functioning in currently depressed patients compared to healthy controls. *Cognition and Emotion*. Advance online publication. doi: 10.1080/02699931.2014.915208

Study IV **(see Appendix D)**

Pauls, F., Lepach, A. C., & Petermann, F. (2013). Depression und Gedächtnis: Gedächtnisleistungen im Vergleich zwischen Depressiven und Gesunden. [Depression and memory: Comparison of memory performances in depressive and healthy adults]. *Gesundheitswesen, 75*, 754-760.

Study V **(see Appendix E)**

Pauls, F., Lepach, A. C., & Petermann, F. (2014). *The role of patient characteristics for explaining episodic memory and executive functioning in depression: A path-analytical approach.* Manuscript submitted for publication.

Introduction

"That's the thing I want to make clear about depression: It's got nothing at all to do with life. In the course of life, there is sadness and pain and sorrow, all of which, in their right time and season, are normal - unpleasant, but normal. Depression is in an altogether different zone because it involves a complete absence: absence of affect, absence of feeling, absence of response, absence of interest. The pain you feel in the course of a major clinical depression is an attempt on nature's part (nature, after all, abhors a vacuum) to feel up the empty space. But for all intents and purposes, the deeply depressed are just the walking, waking dead."

Elizabeth Wurtzel (1994, p. 22)

Like for all other basic emotions, deep sadness and despondency are experienced by every human being at one time or another, but accompanying feelings of depression that last only a few days are usually not an enduring problem for most people affected. In the case of a clinical depression, however, the situation is quite different. In contrast to subclinical manifestations, a clinical depression in terms of a major depressive disorder (MDD) is marked by considerable symptom severity and describes a disabling condition which may persistently affect and deteriorate a person's social functioning, physical condition, and health status in general (Andrade et al., 2003; Austin, Mitchell, & Goodwin, 2001; McCall & Dunn, 2003). Moreover, depression is said to be a highly relapsing and recurrent mental disorder common in the healthy and medically ill population as well as among psychiatric patients (Dickens et al., 2006; Kessler et al., 2003). Since it can be conceptualized in part as a brain disease in which genetic and environmental factors may contribute to its pathogenesis and etiology (Johnston-Wilson et al., 2000), those individuals affected often complain about diverse cognitive impairments. Neuropsychological research in the domain of cognitive functioning has rapidly accelerated over the past decades and helped to increase our general understanding of the link between depression and cognition. In addition to executive dysfunctions (e.g. Braw, Aviram, Bloch, & Levkovitz, 2011; Gohier et al., 2009; Stordal et al., 2004), for example, cognitive impairments in depression have often been associated with further memory-related

dysfunctions (Matthews, Coghill, & Rhodes, 2008; Neu, Kiesslinger, Schlattmann, & Reischies, 2001; Vythilingam et al., 2004). Episodic memory as one part of the declarative subsystem of long-term memory (LTM) requires a sense of the self in the past that often involves emotional contexts. Therefore, it is the type of memory that is suggested to be affected the most by depressive symptomatology (e.g. Lemogne, Piolino, Jouvent, Allilaire, & Fossati, 2006). That is because emotional states are generally known to be a major prerequisite for episodic memory formation and represent an integral part of it (McIntyre, Power, Roozendaal, & McGaugh, 2003; Roozendaal, McEwen, & Chattarji, 2009; Strange & Dolan, 2004). Findings from structural and functional neuroimaging studies emphasizing abnormalities in memory-related cortical and subcortical brain regions have additionally substantiated the high probability of occurrence of episodic memory impairments in depression (Ahdidan et al., 2011; Campbell, Marriott, Nahmias, & MacQueen, 2004; Cheng et al., 2010; Pu et al., 2011; Tae et al., 2011). While the majority of studies using neuropsychological assessments could also demonstrate significantly low levels of episodic memory performance in depressed individuals (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Williams et al., 2007), other investigations failed to find any comparable deficits (e.g. Fossati et al., 2004; Grant, Thase, & Sweeney, 2001). Although episodic memory is known to be marked by a multifaceted and complex nature, the effects of individual variables such as age and gender as well as those describing which psychometric tasks were used to assess which episodic memory components have not yet been taken into sufficient account. Therefore, the considerable variability of empirical findings regarding episodic memory and other memory-related functions in depression might at least reflect general differences in crucial sample characteristics (see Hammar & Årdal, 2009; McClintock, Husain, Greer, & Cullum, 2010, for reviews) and in the tasks used to assess certain memory components (Hammar & Årdal, 2012; Jermann, Van der Linden, Adam, Ceschi, & Perroud, 2005).

In conclusion, a major challenge in understanding the role of memory-related impairments in depression is the obvious lack of consensus on a conclusive cognitive profile characterizing depressed individuals. Therefore, further research defining more precisely those variables associated with memory-related dysfunctioning in depression is indispensable in order to clarify the most critical among unresolved issues. In this regard, the present work aims to go some way towards answering the following questions in order to obtain a more comprehensive understanding of the complex nature of episodic memory and its link to depression:

- What are the most prominent variables that are suggested to affect episodic memory functioning in general?
- Can we suggest episodic memory to be impaired in depression even after controlling for sample and task characteristics?
- Are there further memory-related dysfunctions in depression that may explain possible episodic memory impairments?
- Can we consider certain characteristics in depressed individuals to predict different levels of episodic memory functioning?

Considering that such cognitive dysfunctions may significantly reduce adaptive functioning such as treatment compliance, response to treatments, and rehabilitation (Greer, Kurian, & Trivedi, 2010), the role of standardized assessment measures becomes increasingly more relevant to improve clinical decision making in therapeutic treatment programs.

Project description and field of research

The present doctoral thesis and all research studies included were accomplished in the period from 2011 to 2014 at the Center of Clinical Psychology and Rehabilitation, University of Bremen. Data used in this thesis were collected on the basis of a follow-up validation project as part of the German standardization and adaptation of the Wechsler Memory Scale – Forth Edition (WMS-IV). The research studies presented in the thesis (Appendix A to E) originated during this period but before the according norm values were finally developed. Based on the German Census data, the standardization sample for the WMS-IV comprised of 696 healthy adults aged between 16 and 69 years who were selected to form a representative sample of the German adult population. Within a total of nine age groups, the standardization sample was stratified based on age, sex, ethnicity, educational background, and geographic region.

Taken together, the present research was conducted in order to extend the currently available knowledge on cognitive functioning in depression. Investigating memory-related impairments in a clinically depressed population was accomplished by comparing neuropsychological assessment data between a clinical and healthy control sample. Besides using parts of the standardization data for the healthy control sample, the present research additionally focused on a cohort of 215 clinically depressed patients who were recruited from three different inpatient and outpatient centers in Bremen. All neuropsychological

examinations took place in clinical units and within the premises of the Center of Clinical Psychology and Rehabilitation. The inpatient and outpatient centers that participated on a voluntary basis were the "Ameos Klinikum Dr. Heines", "Klinikum Bremen-Nord", and "Klinikum Bremen-Ost" psychiatric clinics.

Structure of the present doctoral thesis

The present doctoral thesis can be subdivided into two major parts, starting with the theoretical framework to present and outline the general research topic. For this purpose, the concept of human memory is introduced in Chapter 1, especially focusing on episodic memory as the main subject of the present thesis. A further review is conducted on how episodic memory functioning is generally affected by age, gender, and chronic stress that might be caused by depression. Following this, Chapter 2 gives an overview of the main aspects of the depressive symptomatology and reviews different frameworks that have been proposed over time to conceptualize depression from cognitive, behavioral, biological, and biopsychosocial perspectives. Connecting the contents of the first two chapters, the current state of research on memory-related impairments in depression is then summarized in Chapter 3. Further on, consideration is given to relevant theoretical models that provide possible cognitive explanations including the contribution of executive dysfunctioning and cognitive effort as well as neuropsychological explanations describing the role of anatomical and functional changes to specific brain regions for cognitive deficits in depressed individuals.

Following the aforementioned theoretical considerations, the second major part of the thesis addresses the present empirical research by emphasizing its rationale and methodological approaches in Chapter 4. Since this research comprises a total of five empirical studies which more or less depend on each other, the subsequent chapters portray the main sample characteristics and results of each single study in a strictly hierarchical order. Based on the findings of Study I, Chapter 5 first aims to clarify whether gender and age have a considerable effect on episodic memory functioning and if so, what it might mean for all subsequent research studies included in the present thesis. Since the clinical utility of the Wechsler Memory Scale in its recent version had not been made subject to an assessment before, Chapter 6 first addresses the important issue of construct validity. That is, before proceeding with further analyses, it was deemed necessary to demonstrate that the WMS-IV represents a comprehensive neuropsychological test battery allowing for comparisons between the test performances of depressed and healthy individuals (Study II). Subsequently, Chapter 6 summarizes the findings of Study III and Study IV in order to answer the main questions of

the present doctoral thesis concerning the link between depression and memory-related functioning. Finally, possible risk factors for certain episodic memory impairments are discussed on the basis of the according study findings in Chapter 7 by clarifying the role of specific patient characteristics for episodic memory functioning in depression (Study V). After providing an overview of all study findings presented and discussed in Chapter 4 to Chapter 7, the final part of this thesis (Chapter 8) discloses the strength and limitations of the present research. Having regard to the latter, main conclusions are then drawn from the present research by offering recommendations and advice for future research in order to further enhance the understanding of the link between depression and memory. Important implications for clinical practice are finally outlined in the closing part of the thesis which additionally offers advice to clinical care to consider the advantages of using neuropsychological assessment instruments for diagnostic and further treatment purposes.

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Theoretical Framework

Chapter 1

Memory

The human memory is understood to comprise a set of complex and interactive systems that differ in the way of storing information and how they become available to consciousness and behavior. Among these memory systems, short-term memory is characterized by a temporal storage of a limited amount of information whose maintenance highly depends on attentional processes. Another memory system with quite different characteristics and processes is addressed the following section.

1.1 The concept of long-term memory

After being translated from short-term memory, personally relevant information is finally stored in long-term memory (LTM) which represents the second and final stage of the classic dual memory model proposed by Atkinson and Shiffrin (1968). LTM can be understood as a memory system that allows one to recall information encoded in the recent or distant past, thus enabling the storage of memories over a long period of time. Despite one's everyday impressions of forgetting, it is commonly suggested that LTM can store a seemingly unlimited amount of information that decays very little over time (see Klimesch, 2013, for an overview). From a physiological perspective, the most prominent theories indicate that the acquisition of long-term memories involves neural changes in the brain (Cooke & Bliss, 2006), a process known as long-term potentiation (LTP). In simple terms, LTP describes a long-lasting enhancement in signal transmission between neurons that mainly results from an increase in synaptic efficacy due to continuous stimulation (Bliss & Lømo, 1973). LTP enables neural circuits in the brain to create networks that are continuously altered and strengthened due to synaptic plasticity (Bliss & Collingridge, 1993). Accordingly, forgetting occurs when the formerly strengthened connections among the neurons in a neural network become weaker over time, a process known as long-term depression (LTD), or when the activation of a new network is superimposed over an older one, thus causing interference in the older memory (Purves, 2008). Finally, the prevailing idea is that the interaction between LTP and LTD at

least facilitates the generation of complex cognitive maps including stronger and weaker neural connections (Kemp & Manahan-Vaughan, 2007).

Since several different subsystems of memory have been distinguished over the past decades, contemporary theories do not view LTM as a unitary system but rather subdivide it into hierarchical taxonomic modules based on the type of information that is being encoded or retrieved.

Non-declarative and declarative memory

According to Atkinson and Shiffrin's (1968) early model of human memory, there are two conceptually different but overlapping components of LTM coexisting. One of these components is the non-declarative memory that comprises motor procedures and cognitive skills as well as simple conditioning, priming, and non-associative learning. Retrieval of such types of memories is considered implicit and includes behavioral procedures such as appropriate movements of the body. These are typically acquired through elaborative processing strategies including repetition and practice. The resultant motor actions are so deeply embedded that they are running automatically and unconsciously, thus requiring only little cognitive resources. As this LTM component has been found to be located in the striatum and in some parts of the basal ganglia, non-declarative memory is suggested to be largely independent of the hippocampus (Foerde & Poldrack, 2006). In contrast, declarative or explicit memory as the second component of LTM refers to all memories that are consciously available. There are several cortical and subcortical brain areas where declarative memory could likely be located. Although the precise location of storage is mostly unknown, the medial temporal lobe of the brain was found to be involved in explicit but not implicit memory (Aggleton, 2008; Meulemans & Van der Linden, 2003). Declarative memory can be further subdivided into two subsystems known as semantic and episodic memory. While the latter relates to specific situations and personal experiences in the past, semantic memory involves information of a factual nature such as knowledge about the general meaning of objects and concepts. Unlike episodic memory, semantic memory is responsible for the recollection of knowledge without providing any context information about the knowledge acquisition itself (Wood, Baxter, & Belpaeme, 2012). As will be described in the following subsection, the essence of episodic memory lies in the conjunction of self-awareness and subjectively sensed time, thus requiring context-dependent information (Spaniol, Madden, & Voss, 2006).

Episodic memory

Mentally travelling from the present back to the past is said to be unique to humans. First and foremost, it requires the ability to keep temporal-spatial information of events in mind, thus enabling one to re-experience critical life events (Ranganath, Michael, & Craig, 2005; Wood et al., 2012). Following the common conceptualization of LTM, episodic memory represents one of two declarative memory components with the other being semantic memory. While the latter functions as a mental dictionary for organized knowledge about verbal concepts, episodic memory provides information about certain events in the past for recollecting personal experiences in terms of their location and temporal occurrence (Tulving, 2001). This is accomplished through a widely distributed network of cortical and subcortical brain regions that overlap with but also extend beyond the neural networks subserving other memory systems.

The medial temporal lobe and the hippocampus being bilaterally located within it have been identified as critical parts of forming episodic memories (Meulemans & Van der Linden, 2003). The hippocampus is especially important for retaining episodic memories, identifying commonalities between different episodes, and linking these episodes into specific memory spaces (Nadel, Ryan, Hayes, Gilboa, & Moscovitch, 2003). The other important area of the brain indirectly associated with memory is the prefrontal cortex. Despite the traditional idea that prefrontal brain regions are more likely associated with numerous memory processes other than LTM, research in neuropsychology has highlighted the importance of the prefrontal cortex in promoting successful episodic memory formation (Fletcher & Henson, 2001). Thus, individuals suffering from lesions in prefrontal brain regions could be shown to often feature episodic memory impairments as well (Duarte, Ranganath, & Knight, 2005). Following those findings, it was argued that such memory impairments are likely to arise as a consequence of deficits in executive functions located in the prefrontal cortex. Concerning executive functioning, some theories emphasize the role of the prefrontal cortex in directing attention toward goal-relevant information and inhibiting irrelevant information during encoding and retrieval of episodic memories (e.g. E. K. Miller & Cohen, 2001). Such theories mostly suggest that this region implements executive processes including attentional selection, the organization of goal-directed behaviors, inhibition, and working memory that may influence episodic memory functioning. Nevertheless, episodic memory is considered as being a recently evolved, late-developing, and early-deteriorating past-oriented memory system probably

unique to humans. Since it is suggested to be strongly influenced by internal or external factors and more vulnerable than other memory systems to neuronal dysfunctioning, it is important to describe in detail those variables that affect episodic memory functioning the most.

1.2 Effects on episodic memory functioning

Besides other sociocultural influences (e.g. Herlitz & Kabir, 2006), educational background has already been shown to yield robust associations with various cognitive functions (McCarthy et al., 2003). These have often been attributed to the positive effects of education on the overall ability to control for cognitive processes (Le Carret, Lafont, Mayo, & Fabrigoule, 2003), on strategy implementation while performing on cognitive tasks (Brucki & Nitrini, 2008), and on structural changes in the formation of subcortical brain regions with age (Piras, Cherubini, Caltagirone, & Spalletta, 2011). Moreover, longer durations of education have been found to be positively associated with higher levels of memory-related functioning (Angel, Fay, Bouazzaoui, Baudouin, & Isingrini, 2010; Springer, McIntosh, Winocur, & Grady, 2005). Apart from education, further demographic variables, including age and gender, have also been identified to affect the ability to remember past events even in the absence of clinical disease. Cognitive impairments, especially those related to episodic memory, have also been considered as a result of chronic stress.

Cognitive aging

Since ageing is related to the deterioration of various cognitive functions, age-related declines are said to be most pronounced for a variety of processes involved in declarative memory functioning (Bucur et al., 2008). Unlike semantic memory, episodic memory appears to decline considerably with age. That is, older adults often have more difficulty recalling what they have experienced in the past than their younger counterparts. On the one hand, there are several competing theories postulating the potential mechanisms for age-related declines in episodic memory, including a more shallow depth of initial encoding (Glisky, Rubin, & Davidson, 2001), decreasing processing resources with age (Brickman & Stern, 2009), or a failure in retrieving memories (Spaniol et al., 2006). On the other hand, however, there is also some evidence that such declines in episodic memory functioning are not unique to cognitive changes but instead could be attributed to age-related declines of more elementary perceptual-

motor abilities such as processing speed (Park et al., 2002; Veiel & Storandt, 2003). Moreover, several explanations for the link between episodic memory and aging have emerged from the recent literature indicating quite different patterns of age-related declines in episodic memory across several modalities and domains. Whether the extent of interindividual variability systematically increases as a function of age is still somewhat unclear and should thus be clarified by further research.

Gender specificity in episodic memory

In addition to age, previous investigations also indicated that gender is responsible for varying levels of episodic memory performances. It has been suggested that such differences vary in magnitude as a function of the type of material to be remembered. It has also been argued that the magnitude of gender-specific differences in episodic memory may vary depending on whether memories rely predominantly on verbal or visual processing (Lewin, Wolgers, & Herlitz, 2001). Accordingly, women are generally thought to excel in verbally recalling specific events from their past simply because of their superior verbal abilities (e.g. Sommer, Aleman, Bouma, & Kahn, 2004). Analogous to this, encoding and retrieval of episodic memories requiring visual processing are suggested to result in gender-specific differences favoring men due to their advantages in visuospatial abilities. In real life situations, however, encoding or retrieving episodic memories often requires both verbal and visual processing rather than a single modality. Since a female advantage has been observed on several memory measures which were neither explicitly verbal nor visual, it has been argued that women might have a slight advantage over men in basic episodic memory functioning irrespective of the type of material to be remembered (Bloise & Johnson, 2007; Herlitz & Rehnman, 2008; Herlitz & Yonker, 2002; Öberg, Larsson, & Bäckman, 2002). Thus, even when prompted to remember an object's location for example, which at first glance clearly requires visual processing, women might profit from their verbal advantage if verbalizing strategies can be employed on such tasks (Voyer, Postma, Brake, & Imperator-McGinley, 2007).

In research on age and gender-related specificity in episodic memory functioning, explanations of gender differences also depend on whether the magnitude of such differences varies across different stages in life. Given that salient hormonal changes take place in puberty, for example, a change in the magnitude or direction of gender-linked effects around that time would suggest biological components to be the main cause of gender-related specificity (see

Andreano & Cahill, 2009, for an overview). In addition to hormonal effects, some brain imaging studies have also found that men might be more affected by age-related declines in brain volume than women (Sowell et al., 2007; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004). Accordingly, gender differences in episodic memory functioning favoring women could then be expected to considerably increase with age. However, it has to be taken into account that other study findings have also indicated a decreasing female advantage in memory-related functioning with age (e.g. Maitland, Herlitz, Nyberg, Bäckman, & Nilsson, 2004). Due to the inconsistency of current findings, it still remains unclear how gender-specificity in episodic memory is related to age. Moreover, relatively few investigations on this topic have even attempted to statistically separate the influence of verbal and visual processing from episodic memory performance (e.g. Öberg et al., 2002). In conclusion, more comprehensive analyses are necessary in order to clarify how memory-related functioning is really affected by the interaction between age and gender.

Effects of stress on episodic memory functioning

As part of a critical life experience or in response to disease, stress is broadly defined as a condition that more or less perturbs physiological and psychological homeostasis (McEwen, 2000). Since a permanent exposure to stressful situations is often accompanied by cognitive impairments, stress has been suggested to negatively impact basic neurological structures and metabolic processes involved in learning and context-dependent memory functioning (Nater et al., 2007; Schoofs, Preuss, & Wolf, 2008; Schwabe, Bohringer, & Wolf, 2009; Schwabe et al., 2007).

Chronic stress has been shown to likely increase the risk of brain atrophy of the hippocampus and prefrontal cortex which are both associated with memory-related functioning (Lupien & Lepage, 2001). From a cognitive perspective, worry, anxiety, and other cognitive activities associated with stress are suggested to impede the allocation of processing resources in memory-related functioning (e.g. Conway & Pleydell-Pearce, 2000). Clinical investigations have provided empirical evidence for this thesis. Some studies have even suggested long-term effects of stress on memory processes, reporting decrements in recalling episodic memories as a function of stress in response to disease (e.g. Golier et al., 2002). Together the majority of findings suggest that stress in a very intrusive way can disrupt encoding and retrieval processes, and might even have long lasting effects on memory-related functioning. Noting that memory involves several processes, some of which are relatively

stable and others that change with increasing age, stress in response to disease may further exacerbate normal age-related declines in memory-related functioning. Since the predisposing role of chronic stress for the development or maintenance of various types of psychological disorders is well-documented (Pittenger & Duman, 2008; Swaab, Bao, & Lucassen, 2005), stress is also considered as a significant risk factor for disordered affective states (Freedland et al., 2003; Grippo, Beltz, & Johnson, 2003). One type of affective disorder which is commonly associated with chronic stress is therefore closely addressed in the following chapter.

Chapter 2

The Nature of Depression

In the broadest sense, the term depression includes a number of meanings ranging from everyday moods of feeling down to more serious manifestations including psychotic symptoms and an increased risk of suicide. In a more clinical sense, depression is defined as a type of affective disorder comprising emotional (e.g. depressed mood), motivational (e.g. anhedonia), cognitive (e.g. negative thoughts, feelings of hopelessness), and somatic (e.g. loss of energy, sleep disturbances) symptoms. Just like everyone experiences happiness, interest and motivation, most people will experience some of these negative symptoms in varying degrees, and some will suffer from severe depressive disorders. Thus, the following sections aim to clarify how to define, classify, and explain the clinical manifestation of a depression.

2.1 Classification and psychopathology

In research and clinical practice, an important question is whether a clinically relevant depression is qualitatively different from the experience of temporarily feeling depressed, or whether there are just quantitative differences in symptoms, which distinguish these two conditions. Clarifying this question could not only enhance the understanding of affective disorders in general, but might also have important implications for planning clinical interventions to prevent relapse or recurrence in individual cases. As a basic prerequisite for this, it is necessary to clearly distinguish between subjective feelings of dysphoria which are commonly referred to as a form of subclinical depression and clinical depression which is commonly defined by objective diagnostic criteria. If depressive symptoms have been too frequent, intense, and long-lasting to the extent that they interfere with social life, it is likely that subclinical depression has changed into clinical depression which then requires professional treatment. Whenever it is necessary to confirm or exclude the presence of clinical depression, two different diagnostic systems are available to researchers and clinicians. The 'Diagnostic and Statistical Manual of Mental Disorders' in its fourth edition (DSM-IV-TR; American Psychiatry Association, 2000) and the 'International Classification of Disease' in its

tenth edition (ICD-10; World Health Organization, 1993) are both operational diagnostic systems that attempt to classify affective disorders and other psychological disorders according to the number of critical symptoms that are simultaneously present in a certain period of time as well as their adverse effects on social functioning. The DSM-IV-TR primarily distinguishes between different diagnostic categories. For affective disorders, these categories include unipolar depressive disorders (major depressive episode, dysthymic disorder, and depressive disorders being not otherwise specified) and bipolar depressive disorders (bipolar I disorder with at least one manic episode, bipolar II disorder with at least one hypomanic and one depressive episode, cyclothymic disorder, and bipolar disorders being not otherwise specified). Furthermore, the DSM-IV-TR allows depressive disorders to be defined according to the severity of the last episode, the recurrence of episodes and whether the disorder has become chronic. Depressive disorders are additionally judged to be a direct effect of a general medical condition or a result of substance intoxication. In contrast to the DSM-IV-TR, the description of affective disorders in the ICD-10 involves a narrative paragraph with less specific criteria for diagnosis. Here affective disorders include mild, moderate, and severe depressive episodes, dysthymia, recurrent depressive episodes, recurrent brief depressive episodes, manic episodes, bipolar affective disorder, cyclothymia, and mixed-affective episodes. Moreover, depression severity represents a distinct syndrome as opposed to a modifier of an episode.

Major depressive disorder

According to the diagnostic systems previously described, a major depressive disorder (MDD) is defined as a complex clinical syndrome that includes more than just a feeling or an emotional state. It is said to last at least four months if left untreated, and while most people will make a full recovery from a depressive episode, subclinical features may remain for months to years after the MDD has resolved in under a third of those being affected (American Psychiatry Association, 2000). In general, there are many variations of symptoms and symptom patterns seen in an MDD. A common framework used to explore these symptoms is to categorize them into emotional, cognitive, behavioral, and physical domains. Thus, an MDD is characterized by a constellation of some, but not necessarily all, of those symptoms which in turn have to be present for the same two week period. Typical symptoms of an MDD are addressed next followed by a description of epidemiological aspects of depression.

Emotional symptoms

Above all else, an MDD is popularly known as a disorder of mood. The feeling of depression is often characterized by feelings of low mood and dysphoria (Carr & McNulty, 2006), but, as with all emotions, depressive feelings can also range in severity. In its mild form, it can be marked by a sense of vague unhappiness that fluctuates throughout the day. In more severe cases of depression it can be experienced as a smothering and constant sense of desolation and despair. However, these manifestations are not essential and the affective components of depression can be further experienced as irritability, anhedonia or a sense of emptiness (American Psychiatry Association, 2000). Often a combination of such emotional symptoms is common.

Behavioral symptoms

Depressive behavior is often understood to be withdrawing from social contact and from previously enjoyable activities. This phenomenon is thought to be partially explainable by the loss in motivation and the reduced sense of enjoyment that is experienced by many depressed individuals (Hammen & Watkins, 2008). When suffering from a severe MDD, reduced motivation can not only cause social isolation and the resulting loss of social feedback, but might also extend to a lack of impetus to carry out daily living. In mild cases, however, a person experiencing depression may still be able to carry out such activities but likely receives little sense of reward from them.

Physical symptoms

There are various physical symptoms that are often experienced by those suffering from an MDD including rapid changes in appetite or weight, fatigue or disrupted sleep, and loss of interest in sexual activities. Furthermore, depressed individuals often report a chronic sense of tiredness and exhaustion whereas sleeping problems often vary between those affected. While some may experience early morning waking and have great difficulty going back to sleep again, others may have sleeping patterns that are disrupted throughout the night (Sadock & Sadock, 2007). Some depressed individuals may suffer from hypersomnia so that they sleep considerably more than they used to. Despite such sleep disorders, further physical symptoms may

also include diurnal variation in mood. Thus, depressed individuals can feel worse in the morning and notice improvement in their mood across the day (Carr & McNulty, 2006). Finally, those individuals may also be affected by psychomotor retardation involving a sense of being slowed or weighed down in action or activities. In contrast, others may experience psychomotor agitation thus feeling restless and nervous (Sadock & Sadock, 2007).

Cognitive symptoms

Depressed people often tend to attach less importance to their own self-worth which may then result in reduced feelings of self-esteem (Carr & McNulty, 2006). Accompanying this can be a sense of guilt and internal blame as depressed individuals assume disproportional responsibility for negative events (Beck & Alford, 2009). Another cognitive symptom is a pervasive sense of pessimism and cynicism expressed by low expectations for the future and an overwhelming feeling of hopelessness (Young, Rygh, Weinberger, & Beck, 2008). As well as negative thoughts being characteristic of an MDD, there are also further cognitive features of depression such as reduced attention and concentration as well as impairments in memory-related functioning.

In contemporary society, depression is among the most prevalent of all psychiatric disorders. Recent estimates indicate that up to 20% of the world population will experience a clinically significant episode of depression at some point in their lives (Kessler & Wang, 2009; Petermann et al., 2012; Petermann & Petermann, 2012). Based on the results of the Global Burden of Disease Study, the risk for developing an MDD appears to be so high that the World Health Organization (WHO) decided to rank depression as the single most burdensome disease in the world in terms of total disability-adjusted years among people in the middle years of life (Murray & Lopez, 1997). Moreover, MDD is frequently found to be comorbid with other mental illnesses such as anxiety disorders and physical difficulties such as cardiac problems (e.g. Carney & Freedland, 2009). As a result, MDD is said to not only cause substantial economic costs and costs in the healthcare system but also to negatively impact social functioning (Kessler et al., 2006). Regarding the latter, there is mounting evidence that MDD may reduce the quality of interpersonal relationships, in particular, those between married couples and children. On the one hand, the rate of divorce has been found to be higher among depressed than among non-depressed spouses (e.g. Wade & Cairney, 2000). On the

other hand, children of depressed parents have been found to be at higher risk of psychopathology (Joormann & Gotlib, 2008). Importantly, depression in general is a highly recurrent disorder. More than 75% of depressed patients have experienced more than one depressive episode, often relapsing within two years of recovery from the first lifetime MDD (Boland & Keller, 2009). In conclusion, this high recurrence rate in depression suggests that there are specific factors that increase people's risk of developing repeated depressive episodes.

2.2 Cognitive and behavioral models of depression

Since the early 1960's, there has been a growing interest in developing psychological concepts to describe the origin and the nature of depression. It has been suggested that certain cognitive symptoms such as rumination on negative thoughts and mind wandering may have a considerable impact on memory-related functioning in depression. According to this, the most influential cognitive theories of depression will be discussed in the following subsection.

Cognitive theory of depression

Aaron T. Beck and his colleagues originally designed their cognitive model in an attempt to provide a conceptualization of depression that could then be used to inform treatment (Beck, 2005). Beck thus expressed dissatisfaction with the ideas of the time in which conceptualizations of depression tried to assign functions to depressive symptoms and psychopathology as a whole, without specifying different forms of depression (Beck & Alford, 2009). In response to this, he built on the work of cognitive theorists of the time in order to create his own theory of depression. Moreover, Beck aimed to create a model that had empirical support for its construction of psychopathology as well as for efficacy in its therapeutic strategies (Beck, 2005). Generally, there are two central components to this cognitive model of depression comprising the cognitive triad and the negative information processing bias.

The cognitive triad

The cognitive triad primarily refers to how depressed individuals perceive their world, their future, and themselves. Beck and his colleagues proposed the theory that people suffering from depression most likely see their world in a negative shade and

that they expect it to be full of obstacles. They often feel as if they are surrounded by ongoing losses and neutral events are expected to be unfavorable or disparaging (Beck, 2005). The future is seen as hopeless and bleak and negative emotions are expected to last forever. The same negative filter is applied to the self which is judged as inadequate, unlikeable, and as a failure in general. All of these depressive thoughts are accompanied by the strong belief that their negative experiences are due to innate flaws within themselves (Young et al., 2008).

A strength of the cognitive triad is that this theory tries to connect the aforementioned groups of emotional, behavioral, physical, and cognitive symptoms that characterize the psychopathology of depression. That is, depressive thoughts contribute to the emotional as well as to the behavioral symptoms of depression. Becoming withdrawn and disinterested could thus be thought of as protection from further negative experience and failure whenever having negative expectations about the world, the future, and one's own capacity to cope with problems (Beck & Alford, 2009). Accordingly, today's cognitive therapy for depression aims to address these distorted cognitions and is based on the belief that emotional, behavioral, and physical symptoms can be reduced by altering the underlying thoughts in depression.

The negative information processing bias

Another basic hypothesis of Beck's cognitive theory of depression is that cognitive disturbances precede the change in mood and are responsible for the maintenance of depression. Prior to the onset of dysphoria, the affected person is considered to misinterpret reality due to several biased information processing strategies applied. Based on this idea, the second central component of Beck's cognitive model suggests that depressed individuals perceive reality through a negative cognitive screen. Information processing in depression is thought of as being spontaneously biased because negative information is attended more readily than positive or neutral information (Hammen & Watkins, 2008). It is exactly this information processing bias that lies beyond some of the common cognitive distortions often observed in depression. These distortions include ignoring positive experiences or attributing this to nothing but luck (selective thinking), seeing things in a black and white manner, drawing global conclusions from a single incident (overgeneralization), exaggerating a setback until it becomes a complete disaster (catastrophizing), and easily jumping to unconstructive conclusions based on insufficient evidence (arbitrary inferences).

Theory of learned helplessness and hopelessness

While Beck's model of depression is among the most prominent theories, other researchers such as Seligman and Abraham have proposed alternative cognitive and behavioral models of depression. On the basis of his studies on dogs' responses to electric shocks across several conditions, Seligman (1972) developed his theory of learned helplessness. Initially, he observed that dogs attempt to escape the unavoidable aversive stimulus until, after a while, they learnt that escape was not possible. In conclusion, dogs resigned themselves to the aversive stimulus without making any further attempts to escape. Seligman transferred these findings to depression by proposing that when humans go through uncontrollable stressors and situations they eventually give up trying to find proper solutions (Beck & Alford, 2009). As the dogs resign themselves to getting shocked, depressed individuals can resign themselves to ongoing negative experiences.

Abramson and his colleagues further extended the original theory of learned helplessness by including the attributional styles model. Generally, people are suggested to make attributions about the causes of either positive or negative experiences in their lives across three different continuums connecting the poles global vs. specific, stable vs. unstable, and internal vs. external attributions (Abramson, Seligman, & Teasdale, 1978). Accordingly, people who continually attribute their negative experiences to nothing but global, stable, and internal characteristics, are described as having a negative explanatory style. Those people affected may then become apathetic, pessimistic, and develop hopelessness (Sanjuán & Magallares, 2009), which is a proximal and sufficient cause of hopelessness depression[1]. In general, this hopelessness theory tends to underscore the importance of cognitive processes in the etiology, maintenance, and treatment of depression. It posits that people are vulnerable to depression because they tend to generate interpretations of stressful life events that have negative implications for their future and for their self-worth.

As in the case of Beck's cognitive theory of depression, Seligman and Abramson developed a psychological model of depression without, however, taking into consideration that the development and persistence of depression could also be explained by biological factors.

[1] A theoretically derived subtype of depression characterized by symptoms such as retarded initiation of responses, lack of energy, sad affect, and apathy (see Abramson, Metalsky, & Alloy, 1989, for a detailed description).

2.3 Biological models of depression

Although cognitive-behavioral models of depression attempt to unify the domains of symptomatology by integrating thoughts, behaviors, and emotions, neither Beck's nor Seligman's theory considers biological aspects to the same extent. In particular, the role of neurotransmitters and stress hormones needs to be taken into account when trying to fully understand why some people are more likely to develop affective disorders while others are less vulnerable to depression.

Neurotransmitter system

The three main neurotransmitters associated with depression are the monoamines serotonin, dopamine, and norepinephrine, which are all vital to efficient running of the limbic system. The latter in turn is responsible for drives, emotions, and several memory-related processes (Hammen & Watkins, 2008). Once inhibiting the reuptake of monoamines was found to be useful in the medical treatment of depressive disorders, monoamines became an area of great interest in the biological causes of depression (Dunlop & Nihalani, 2006; S. Lee, Jeong, Kwak, & Park, 2010). Researchers supporting the monoamine hypothesis claim that a lack of monoamines, predominantly low levels of norepinephrine and serotonin, could be seen as the general cause of depression. However, challenging investigations and medical developments began to identify flaws in this hypothesis. Firstly, it has been argued that a considerable number of depressed patients does not respond to antidepressant medication (aan het Rot, Mathew, & Charney, 2009; S. Lee et al., 2010). Secondly, taking monoamine precursor chemicals does not necessarily alleviate depressive symptoms and a reduction in the concentration of monoamines does not automatically cause depression (Krishan & Nestler, 2008). Thirdly, it has been argued that some, but not all antidepressant medications, directly affect the relevant monoamine systems. While most antidepressant medications affect the availability of neurotransmitters within hours of administration, the alleviation of depressive symptoms does not occur for several weeks (Duman & Monteggia, 2006; Krishan & Nestler, 2008). Therefore, it is suggested that monoamines are likely to have an indirect effect rather than a direct effect on the psychopathogenesis of depression. In particular, monoamines are thought of as indirectly affecting certain depressive symptoms by increasing neurogenesis in certain areas of the brain such as the hippocampus (Warner Schmidt & Duman, 2006). It is

thus conceivable that this increase may be one reason for the time-delay between administration of antidepressants and their effects on depressive symptoms.

Neuroendocrine system

In the face of danger, survival is supported by the gradual activation of a number of physiological systems that focus attention and increase responsiveness. However, a constant activation of these systems as a result of ongoing stressors can have a harmful impact on physiology that is in turn linked to the development of depression. The hypothalamic-pituitary-adrenal axis (HPA) has been found to play a central role in the maintenance of depression. In times of stress the hypothalamus releases the corticotrophin releasing hormone (CRH) which in turn leads to the release of the adrenocorticotropic hormone (ACTH) from the pituitary (Pariante & Lightman, 2008). The latter prompts the release of cortisol and other glucocorticoid hormones from the adrenal glands to stimulate the biological systems which then help to respond adaptively to external stressors (Bao, Meynen, & Swaab, 2008). To maintain this HPA stress response at a normal level, a negative feedback loop normally controls the levels of ACTH and cortisol in the blood. In depression, however, this feedback loop often appears to fail so that the nervous system continues to respond to a stressor in a chronic manner (Bao et al., 2008). Such a dysregulation of stress response has been observed in almost half of all depressed patients (Sapolsky, 2000).

In conclusion, depression seems to be associated with increased cortisol levels and elevated cortisol levels have even been shown to be indicative of a poor prognosis and the likelihood of relapse after treatment (Hammen & Watkins, 2008). It has been suggested that a long-term increase in the cortisol concentration can damage the hippocampus and other emotion regulation systems (A. L. Lee, Ogle, & Sapolsky, 2002; Thomas, Hotsenpiller, & Peterson, 2007). Moreover, cortisol seems to disrupt the serotonin system by interfering with the release of serotonin and reducing the sensitivity of corresponding receptors (Van Praag, 2004). Although cognitive and biological models of depression both aim to explore single cognitive, physiological, and environmental realms, none of them intends to integrate different domains in order to describe the development and maintenance of depression. One of those integrative biopsychosocial models of depression is therefore described next.

2.4 Biopsychsocial models of depression

Not all individuals who experience a stressor become inevitably depressed and not all depressed individuals have previously experienced a stressor. Therefore, biopsychosocial models aim to integrate the cognitive and biological models of depression etiology, along with the social components of experiencing negative life events. The most popular of these models is known as the diathesis-stress model.

Diathesis-stress model

Diathesis-stress models typically suggest that some people have a pathophysiological vulnerability which represents a predisposition to depression. This vulnerability needs to be triggered by the occurrence of a stressful event first in order to result in depression. Since vulnerability levels vary widely across individuals, those with a greater vulnerability are thought of as being more prone to depression from smaller stressors (Ingram & Luxton, 2005). In addition to genetic or neurobiological predispositions, the vulnerability can also be cognitive in nature. While there are still inconsistent research findings, some investigations indicated an interaction between those cognitive styles proposed by Beck (1991) and Abramson (1978) and types of negative life events (Mazure & Maciejewski, 2003). Diathesis-stress models also propose that stressors in early life may have a considerable impact on the development of certain brain structures and functions. This could be seen as one explanation for a disrupted HPA axis feedback loop found in many depressed patients. Depressed individuals with a history of childhood trauma, for example, have thus been found to feature higher levels of cortisol for longer periods of time than healthy controls (Dunlop & Nihalani, 2006; Gunnar & Quevedo, 2007). As a result, a history of childhood trauma may increase the likelihood of developing depression in response to stressors as an adult (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008).

Chapter 3

Memory-Related Impairments in Depression

At present, there is some evidence suggesting that depressive disorders may increase the risk of cognitive dysfunctioning or functional disability (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Charney et al., 2003; Geda et al., 2006; Sáez-Fonseca, Lee, & Walker, 2007). The most common among such dysfunctions are frequently associated with memory-related functioning. Since empirical findings on the association between memory-related impairments and depression still appear to be somewhat heterogeneous, there is a need to thoroughly review the existing literature on this topic.

3.1 Current state of research

Cognitive impairments in depression have already been demonstrated across a wide range of memory-related functioning including executive functions (e.g. Braw et al., 2011; Gohier et al., 2009; Stordal et al., 2004), attention (e.g. Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011), declarative memory (e.g. Matthews et al., 2008; Vythilingam et al., 2004), and processing speed (e.g. Elgamal, Denburg, Marriott, & MacQueen, 2010; Rund et al., 2006; Sheline et al., 2006). Moreover, some of those impairments, albeit in a milder form, have been reported to persist although depressive symptoms decrease (Behnken et al., 2010; Bhalla et al., 2009; Nakano et al., 2008; Reppermund, Ising, Lucae, & Zihl, 2009) and even after clinical recovery (Airaksinen, Wahlin, Larsson, & Forsell, 2006). This phenomenon is usually referred to as pseudodementia which describes the occurrence of reversible memory-related impairments that follow after the onset of depression (see Butters et al., 2004, for a comprehensive review). Despite some contradictory findings indicating little to no declarative memory impairments in remitted depressed patients (e.g. Merens, Booij, & van der Does, 2008), other studies found such cognitive deficits to predate the diagnosis of depression, thus considering memory-related impairments to be premorbid markers of the disorder (Airaksinen, Wahlin, Forsell, & Larsson, 2007). Given that memory-related impairments in depression have often been associated with deficits in recollecting

context-dependent information from the past, episodic memory functioning is said to be more affected by depression than other memory components.

Episodic memory impairments

Along with a number of other memory-related impairments (Braw et al., 2011; Gohier et al., 2009; Nitschke, Heller, Etienne, & Miller, 2004; Wang et al., 2006), depressive disorders have been suggested to negatively impact several components of declarative memory. According to Tulving (2002) the ability to recollect episodic memories in particular is thought to be strongly influenced by the current emotional state. Thus, episodic memory functioning appears as more vulnerable to the negative emotional symptoms of depressive disorders compared to other memory-related functions (Lemogne et al., 2006). However, it is important to note that there are still contradictory findings regarding the association between episodic memory and depression. While some previous investigations could clearly demonstrate lower episodic memory performances of depressed individuals when compared to healthy controls (Airaksinen et al., 2004; Williams et al., 2007), others failed to find similar effects (e.g. Fossati et al., 2004; Grant et al., 2001). Thus, the inconsistency of empirical findings might indicate that although depression is likely to be accompanied by severe episodic memory impairments, this may not necessarily be generalizable to all depressed individuals (McCall & Dunn, 2003). Accordingly, another possible explanation for the inconsistent findings is that there might have been substantial differences across studies regarding the selection of clinically depressed individuals examined. For this reason, certain characteristics of depressed patients, including demographic and disorder-related variables, as well as their possible contribution to episodic memory impairments in depression are addressed in the following subsection.

Effects of patient characteristics

Demographic variables

As already discussed in Chapter 1, it seems to be widely accepted that, irrespective of any disease, aging by itself may cause a decrease in various memory-related functions. And although depressed individuals often complain of such deficits, it is not yet clear whether effects of age on memory-related functioning in depression are different from those in healthy individuals. While some previous studies showed lower levels of episodic memory functioning even in young patients when compared

to healthy controls (Smith, Muir, & Blackwood, 2006), thus being interpreted as early signs of pseudodementia, data on this topic generally seems to be quite controversial (Castaneda, Tuuio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Herrmann, Goodwin, & Ebmeier, 2007). In fact, the most evident memory-related impairments have been reported in older patients (Alexopoulos, Kiosses, Murphy, & Heo, 2005; Baudic, Tzortzis, Dalla Barba, & Traykov, 2004; Dunlosky, Hertzog, & Powell-Moman, 2005; Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2007; Hickie, Naismith, Ward, Scott, & Mitchell, 2005; Maeshima et al., 2013; Morimoto et al., 2011; Sheline et al., 2006; Sneed, Keilp, Brickman, & Roose, 2008). However, there are also studies that have not observed this trend, but instead have demonstrated that even depressed adolescents may be as vulnerable to memory-related impairments as older patients (Fossati, Coyette, Ergis, & Allilaire, 2002; Günther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004; Matthews et al., 2008). Nevertheless, it should be noted that the majority of previous investigations have only been conducted among middle-aged, elderly, or among patients regardless of their age (see Elderkin-Thompson et al., 2004, for a review), while only very few studies explored clear-cut age groups with congruently defined age ranges (e.g. Smith et al., 2006).

In addition to aging effects, some investigations also suggest a gender-related specificity of episodic memory impairments in depression, since female depressed patients have been found to perform significantly worse especially on visual measures of episodic memory when compared to male patients (Sárosi et al., 2008). Women could also be considered to be more cognitively affected by depression than men because they seem to be more vulnerable to affective disorders in general.

Disorder-related variables

In addition to demographic characteristics of depressed patients, previous research also focused on a set of clinical factors that have been suggested to be linked to memory-related impairments in depression. Among those clinical factors, certain disorder-related variables including the number of prior depressive episodes and recurrence, illness duration, depression severity, comorbidity, and medication status have been found to more or less modulate several cognitive deficits in depression.

For example, previous investigations could show that memory-related functioning usually appears to be more susceptible to factors related to past burdens of affective disorders, such as the recurrence of depressive episodes (e.g. MacQueen,

Galway, Hay, Young, & Joffe, 2002). Just as patterns of memory-related impairments have frequently been found to vary as a function of the number of prior depressive episodes, more severe episodic memory impairments have been observed in individuals suffering from recurrent depression (RD) when compared to healthy individuals (Lampe et al., 2003). In some investigations, patients with a history of more than one depressive episode were even found to manifest more and larger impairments on certain memory-related functions such as episodic memory than patients suffering from their first episode (Fossati et al., 2004; Karabekiroğlu, Topçuoğlu, Gimzal Gönentür, & Karabekiroğlu, 2010; Paelecke-Habermann, Pohl, & Leplow, 2005; Smith et al., 2006). Overall, these findings suggest that there could be at least some cognitive deficits accompanying recurrent depressive episodes which might not yet be prominent in first-episode depressed individuals. However, this idea is challenged by other studies indicating that although memory-related dysfunctioning is already evident in depressed patients suffering from the first depressive episode (MacQueen et al., 2003), recurrent episodes do not have any additional effect on memory-related functioning (Lampe, Sitskoorn, & Heeren, 2004; Reischies & Neu, 2000). Regardless of this controversy, it is at least conceivable that prior depressive episodes might contribute to the reinforcement of cognitive impairments in general and boost the development or maintenance of memory-related impairments in particular.

In addition to the recurrence of depression, some previous studies have also reported that the magnitude of cognitive deficits may be closely associated with current depression severity (Egeland et al., 2005; Grant et al., 2001; McDermott & Ebmeier, 2009; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). This has been supported by investigations that found depressed patients with severe forms of depression to feature more memory-related impairments than patients with milder forms (Fossati et al., 2004; Paelecke-Habermann et al., 2005). However, it is worth noting that the majority of such investigations failed to sufficiently examine whether effects of depression severity can be regarded as generalizable across different components of episodic memory, or whether those effects might be mediated by further memory-related impairments such as executive dysfunctions.

A few recent studies have also focused on the effects of illness duration on cognitive declines in depression. Since a long-term depressive disorder is known to likely be accompanied by a structural alteration of the hippocampus (McKinnon, Yucel, Nazarov, MacQueen, & Glenda, 2009; Sheline, Gado, & Kraemer, 2003), the duration

of depressive episodes was found to correlate with several dysfunctions in episodic memory and executive functioning (Elderkin-Thompson, Moody, Knowlton, Hellemann, & Kumar, 2011; Hermens, Naismith, Redoblado Hodge, Scott, & Hickie, 2010). In contrast, other studies failed to find considerable effects accounted for by the duration of depressive episodes on memory-related brain regions and the associated cognitive functions (Lampe et al., 2004; Reischies & Neu, 2000).

In addition to possible effects of those disorder-related variables describing the number, severity, and duration of depressive episodes, patterns of memory-related impairments in depression could also depend on additional comorbid disorders. Although depression is typically known to be highly comorbid with other psychiatric disorders, research has thus far provided very little information regarding the role of psychiatric comorbidity on memory-related functioning in depression. Since comorbidity in depression has not yet been subject to much investigation, only a few studies have provided evidence of pronounced memory-related impairments in depressed patients with versus without comorbid disorders (Basso et al., 2007; Kizilbash, Vanderploeg, & Curtiss, 2002; Tarsia, Power, & Sanavio, 2003). Nevertheless, it should be considered that psychiatric comorbidity is often inadequately reported and controlled for in studies of depression-related cognitive impairments and may accordingly serve as a confounding variable, thus explaining some of the contradictory results.

Furthermore, it should be acknowledged that some psychopharmacological treatments might also exert either negative or positive effects on cognitive functioning whereas others might have no effect (Borkowska, Drozdz, Ziółkowska-Kochan, & Rybakowski, 2007; Culang et al., 2009). Accordingly, previous investigations have demonstrated memory-related functioning to be less impaired in medicated depressed individuals than in un-medicated ones (Gualtieri, Johnson, & Benedict, 2006) or that memory-related functioning in depression could be improved by antidepressant treatment (Vythilingam et al., 2004). Other studies, however, could neither find any improvement nor deterioration in memory-related functioning after antidepressant treatment (MacQueen et al., 2002). Generally, it can be assumed that antidepressants may enhance some cognitive functions while simultaneously diminishing others (Kalb, Dörner, & Kalb, 2006; Kampf-Sherf et al., 2004).

3.2 Cognitive explanations

Recent functional neuroimaging studies suggest abnormal neuronal activity in depressed individuals when performing on cognitive measures (A. J. Holmes & Pizzagalli, 2008; Pizzagalli, 2006). Given that depression is associated with elevated negative cognitions and rumination (Siegle, Moore, & Thase, 2004), an intrinsic processing such as focusing on negative automatic thoughts might engage cognitive resources that would otherwise be allocated to processing of relevant information (Christopher & MacDonald, 2005). Memory-related impairments in depression could thus be explained by executive dysfunctioning in general and by deficits in resource allocation and effortful processing in particular.

Executive dysfunctioning

Since executive functioning (EF) is widely accepted to include numerous cognitive processes, many attempts have been made to find a generally applicable and universal definition of EF. In the broadest sense, EF can be understood as the overall ability to maintain an appropriate set of cognitive behaviors for attainment of a future goal (Welsh, Pennington, & Groisser, 1991). This mainly includes planning strategies such as selecting and initiating actions as well as controlling strategies such as monitoring actions and inhibiting irrelevant impulses (Fossati et al., 2004). Among those impairments that have been observed in depressed individuals across a broad range of cognitive domains, deficits in EF are the most prominent (Stordal et al., 2004). At present, there is strong evidence indicating that EF can be negatively affected by depression as depressive symptoms have been shown to decrease the general abilities of planning and initiating actions (Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2006; P. O. Harvey et al., 2004; Mahurin et al., 2006; Rogers et al., 2004; Tavares et al., 2007) as well as impede more specific processes involved in mental and inhibitory control (Langenecker et al., 2005; Paelecke-Habermann et al., 2005; Reppermund et al., 2009). The most consistent executive dysfunction in depression has been associated with inhibitory control. The latter describes an active process that allows one to restrict access to information that is relevant and to delete information that is no longer relevant (Hasher, Zacks, & May, 1999). Despite some contradictory findings (e.g. P. O. Harvey et al., 2004), research has also indicated that depression severity may also play a role in the degree of executive dysfunctioning (e.g. Taylor, Wagner, & Steffens, 2002). The neural mechanisms by which executive

dysfunctions may occur in depression are a topic of ongoing debate in the field of neuropsychology. And although there is still no consensus on the specific mechanisms underlying executive dysfunctioning in depression, it is believed that depression may cause structural and functional changes of the prefrontal brain regions, which in turn might then lead to executive dysfunctioning (Alvarez & Emory, 2006; Kaiser et al., 2003).

In addition to more specific and narrow executive processes such as mental and inhibitory control, EF is also said to comprise those cognitive processes that are related to working memory[2] (Chan, Shum, Toulopoulou, & Chen, 2008). Accordingly, EF includes certain cognitive processes that control and integrate memory-related activities and possess a definite role on memory-related functioning such as episodic memory as well (Busch et al., 2005). Due to the strong association between EF and other memory-related functions, executive dysfunctions, especially those related to inhibitory control and working memory, seem to be key factors for memory-related impairments in depression (Joormann, 2005). It is therefore conceivable that deficits in encoding or retrieving episodic memories may not only be the result of fundamental impairments in memory functioning but also result indirectly from executive dysfunctioning, or from the complex interaction between both of them. Thus, disturbance in inhibitory control for example, could lead depressed individuals to process irrelevant information and consequently reduce their ability to adequately recollect episodic memories (Fossati et al., 2002).

Cognitive effort and speed hypotheses

The role of executive dysfunctioning in depression is somewhat challenged by the idea that reduced memory-related functioning of depressed individuals may be generally based on a non-specific lack of effort in performance rather than reflect any specific cognitive impairment (Porter, Bourke, & Gallagher, 2007). According to this hypothesis, depressed individuals are often marked by general problems in allocating effort to those memory tasks which demand much effort (e.g. Hammar & Årdal, 2012). Effortful processing, as often required for free recall, relies on elaborate processing activities such as organization and systematic clustering, which demand a high level of attention and cognitive control. This is in

[2] Working memory is a multi-component memory system allowing for the temporal maintenance and manipulation of visual and auditory information required to carry out complex cognitive activities such as learning, reasoning, and comprehension. It is involved in the selection, initiation, and termination of information-processing functions such as encoding, storing, and retrieving information from LTM (see Baddeley, 2000, for a detailed description).

contrast to automatic processing, which is related to skills that have been severely practiced and are mastered in such a degree that they will not improve any further (Hasher & Zacks, 1979). Unlike free recall, recognizing information for the most part involves automatic processing skills that require minimal attention without interfering with other simultaneously ongoing mental processes. In conclusion, the cognitive effort hypothesis states that effortful processing skills are more impaired in depression than those of automatic processing (e.g. Jermann et al., 2005). According to this, depressed individuals are expected to show lower performances on memory tasks due to a lack of motivation and a lower degree of effort than required for free recall (Egeland et al., 2003; Hammar, 2003; Hammar, Lund, & Hugdahl, 2003a, 2003b; Scheurich et al., 2007). Since some studies have demonstrated that memory-related impairments may, at least to some extent, also be apparent in task predominantly requiring automatic processing (Den Hartog, Derix, Van Bemmel, Kremer, & Jolles, 2003; Naismith, Hickie, Ward, Scott, & Little, 2006), current findings still seem to be quite divergent on this topic (e.g. Taconnat et al., 2010).

Besides the cognitive effort hypothesis, the cognitive speed hypothesis states that many of the apparent specific cognitive deficits in depression relate to a more global difficulty in processing and are actually the outcome of a general, task-independent, and non-specific decrease in processing speed (Den Hartog et al., 2003; Egeland et al., 2003). As a result, memory-related impairments are therefore suggested to be not primarily based on deficits in any specific memory domain. However, this point of view is challenged by other studies reporting contradictory findings and arguing that cognitive deficits in depression are for the most part associated with specific cognitive processes involved in memory-related functioning (e.g. Erickson et al., 2005).

Resource allocation model

The underlying premise of the resource allocation model (RAM; Ellis & Ashbrook, 1988) is that the cognitive capacity available is frequently occupied by the ruminative thoughts of depressed individuals. Provided that cognitive capacity is limited, other cognitive functions associated with memory will then have fewer cognitive resources to rely on for adequate memory performance. Consequently, depressed individuals are expected to show deterioration in performance when compared to non-depressed individuals. Since not all memory tasks demand cognitive resources to their full capacity, the RAM indicates that memory tasks requiring more cognitive resources would be affected by depression whereas simple tasks may

remain unaffected. Many different research methodologies have been employed to investigate the RAM hypotheses. Some brain imaging studies used attentional tasks (Meinhardt & Pekrun, 2003), whereas others assessed physiological responses such as pupillary motility in depressed samples as an indicator for attentional allocation (Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010). Most of those studies indicated that depressed individuals tend to allocate more cognitive resources away from the task at hand, which then corresponds to a decline in attentional performance.

3.3 Neuropsychological explanations

In addition to functional changes in the neurotransmitter and neuroendocrine systems, certain structural changes to the brain are also suggested to underlie memory-related functioning in depression. The fields of research in this area that have recently received the most attention focus on abnormalities in the medial temporal lobes and the prefrontal cortex (Ahdidan et al., 2011; Cheng et al., 2010; Pu et al., 2011; Tae et al., 2011). Therefore, these two brain regions should be carefully addressed in the following subsection.

Medial temporal and prefrontal lobe atrophy

The hippocampus, an important subcortical structure of the limbic system, is bilaterally located in the medial temporal lobes and is suggested to play an important role in learning and declarative memory functioning (Kalisch et al., 2006; Rasch, Buechel, Gais, & Born, 2007). Hippocampal atrophy was thus found to have a considerable effect on memory-related functioning (Hickie et al., 2005). Consequently, a compromised hippocampus is strongly associated with a decline in declarative memory performance (Persson et al., 2006). In addition to a significant loss of hippocampal volume which was found in depressed patients when compared with healthy controls, an increasing volume loss was found to be associated with longer illness durations (Colla et al., 2007) and higher frequency of depressive episodes. So far, the causes of hippocampal volume loss are still under intense investigation. As discussed earlier, increased cortisol levels have already been shown to likely occur with depression and a continued exposure to cortisol has also been linked to hippocampal volume loss causing cognitive decline (O'Hara, Coman, & Butters, 2006). At present, it is considered more likely that elevated cortisol levels lead to decreased neurogenesis in the hippocampus rather than to

the death of hippocampal neurons (Henn & Vollmayr, 2004; Sapolsky, 2004). However, studies investigating the effects of cortisol on hippocampal volume and on memory-related functioning revealed mixed results. While corticosteroid treatments could be linked to both smaller hippocampal volume and declarative memory impairments (Brown et al., 2004), other investigations demonstrated a relationship between corticosteroid use and a decline in memory performance without any structural changes in the hippocampus (Hájek, Kopeček, Preiss, Alda, & Höschl, 2006). It has therefore been proposed that some posterior regions of the hippocampus are at least responsible for memory-related impairments in depression while more anterior regions are not (Becker & Wojtowicz, 2007; Neumeister et al., 2005). Nevertheless, this could at least partially explain why depressed individuals often tend to inadequately process and memorize information (Beck & Alford, 2009). At worst, the resulting memory-related impairments could further lower mood in depression.

In addition to medial temporal lobe atrophy, it is widely accepted that changes in the neural activity of prefrontal brain regions may also explain episodic memory impairments in depression. The prefrontal cortex is known to participate in the regulation of behavior and plays an important role in executive functioning including working memory. As increased activation in both the hippocampus and the frontal lobes has often been observed while performing on an episodic memory task (e.g. Martin et al., 2007), changes in the prefrontal cortex are also related to depressive disorders. This is further supported by findings indicating smaller frontal cortex volumes in depressed individuals when compared to healthy controls (Bell-McGinty et al., 2002). In line with observations of impaired cognitive functions in depression (Tavares et al., 2007), several previous investigations have found a pattern of predominantly decreased prefrontal cortex activity in depressed patients when performing on executive functioning tasks. This pattern of activity is considered to be strongly associated with lower levels of task performance (Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003). Moreover, attempts have been made to clarify whether white matter hyperintensities[3] (WMH) in the frontal lobes are caused by memory-related impairments in depression (Teodorczuk et al., 2007). However, clear results on the effects of WMH have not been established yet.

[3] This term is typically used to refer to areas of high intensity observed on particular types of magnetic resonance imaging scans of the human brain. They are usually seen in normal aging but are also used as indicators for various neurological disorders and psychiatric illnesses (see Taylor et al., 2003, for a detailed description).

Neurotransmitter deficits

As already outlined in Chapter 1, monoamines such as serotonin, dopamine, and norepinephrine are suggested to significantly contribute to the maintenance of depressive symptomatology. Since changes to the neurotransmitter levels, such as decreased concentrations of monoamines in temporal and frontal lobes, have been found to occur with depression, lower levels of serotonin have been linked to impairments in LTM and executive functioning (Schmitt, Wingen, Ramaekers, Evers, & Riedel, 2006). Compared to the effects of neurotransmitters on LTM, the role of serotonin on WM is less examined with findings indicating either unclear or no relationships between lower levels of serotonin and decreased WM performances (Barch, 2004; Mendelsohn, Riedel, & Sambeth, 2009).

Empirical Research

Chapter 4

Foundations of the Present Research

As depicted in previous chapters, depression does not only change the way people feel but may also exert an effect on their mental representations about themselves and the world around them. Moreover, cognitive theories of depression posit that people's thoughts, opinions, and interpretations can also increase the risk of developing depressive episodes. More than three decades of research focusing on the link between cognition and emotion has thus far provided support for many aspects of such cognitive theories about depression. The primary goal of a large body of investigations has been to gain a more comprehensive understanding of those memory-related impairments that can be attributed to sustained negative affect, the hallmark feature of depression. However, although depression has already been shown to have a substantial impact on at least some memory components, the link between depression and episodic memory functioning has not yet been fully understood. Despite cognitive and neuropsychological explanations, it is not yet clear whether general impairments in episodic memory could be suggested as simple correlates of depression or why those impairments are present in some but not all depressed individuals. A closer comparison between studies that have provided evidence for memory-related impairments in depression and studies that have not can lead to a more precise characterization of cognitive processes in depressed individuals.

4.1 Rationale and importance of the present research

While early investigations mostly focused on demonstrating that depressed and non-depressed individuals differ in the content of their thoughts and memories, the present research studies aim to go some way toward exploring the nature of those memory-related impairments that characterize depression. Since previous studies failed to provide a coherent pattern of findings regarding memory-related impairments in depression, it was considered imperative to address the most critical shortcomings of the previous research at first before taking the necessary steps to overcome such issues in the present research studies. Therefore,

possible reasons for these inconsistent findings across studies are initially summarized in the following subsection.

Theoretical and methodological issues in previous investigations

The current state of research on episodic memory impairments in depression is for the most part marked by inconsistent or even conflicting findings. Assuming that such inconsistencies could likely be caused by various sources of error, theoretical and methodological issues should be always taken into account when interpreting previous investigations on memory-related functioning in depression. Accordingly, possible reasons for such varying empirical findings can be mostly attributed to either differing sample characteristics or the methods used to assess different episodic memory components across studies.

With regard to sample characteristics, it should be considered that certain demographic factors, among them age, gender, and education, might affect memory-related functioning in certain ways (e.g. Herlitz & Rehnman, 2008; Moore & Johnson, 2008; Quinn & Liben, 2008). However, neither studies on healthy individuals nor those examining clinically depressed patients have sufficiently controlled for interaction effects of these factors on episodic memory performance. Even in a healthy population, it still remains to be clarified whether there are gender differences in episodic memory functioning, and, if so, whether these are stable across different age groups and across different memory measures. Thus, further empirical research should address this issue by clarifying the role of subgroup-specific differences for episodic memory in order to control for possible confounding effects. In addition to such potential error sources, conflicting findings in studies examining depressed individuals could be explained by the use of different inclusion criteria of disorder-related variables such as different depression subtypes, illness durations, and levels of depression severity. Furthermore, previous investigations could have also been potentially confounded by the effects of certain comorbid psychiatric disorders and medication statuses of the depressed patients examined. On the one hand, the detection of differential relationships between disorder-related features and memory performance might support the presence of unique mechanisms in distinct subgroups of depressed individuals. On the other hand, profound evidence for the effects of disorder-related variables on cognitive functioning would also indicate the importance of taking these clinical features into account whenever investigating memory-related impairments in depression. This may also explain the discrepancies between findings in studies where these factors have not

been controlled for. Consequently, studies on the relationship between depression and cognition should carefully control for and explicitly report those demographic and disorder-related characteristics that may serve as possible confounders. In studies comparing episodic memory performances between healthy and depressed individuals, for example, both groups have often been inadequately matched for age, gender, and education. Given the heterogeneous nature of psychiatric conditions, another common methodological shortcoming had been the small sample size in many studies. It is possible that the absence of depression-related effects on episodic memory functioning might be due to the lack of statistical power to identify differences between healthy and depressed individuals.

In addition to possible confounding effects of sample characteristics, the diversity of neuropsychological assessment methods[4] further complicates the comparability and interpretability of previous empirical findings. Although self-reports may provide critically important information, these are often affected and confounded by the presence of neuropsychiatric conditions, thus having less value than standardized psychometric tests (e.g. Bowie et al., 2007). While earlier studies tended to use a variety of such self-report measures, contemporary investigations on memory-related functioning have recently begun to utilize a wide variety of more objective neuropsychological instruments. Although those investigations have generally provided support for the hypothesis that depression is characterized by biases in memory-related functioning (Mathews & MacLeod, 2005), mixed results on episodic memory impairments in depression could still be caused by differences in the materials or measures used to assess episodic memory performance. Since previous investigations often failed to differentiate between specific episodic memory domains such as auditory and visual memory, the application of different task modalities could be suggested as one reason for different findings across the studies. According to the cognitive effort hypothesis, another reason for inconsistent findings could be the fact that the pattern of episodic memory impairments in depressed individuals may depend on whether memory tasks include free recall requiring more cognitive effort or recognition requiring less cognitive effort (Hammar & Årdal, 2012). Although a few studies examining specific task characteristics have already demonstrated that depressed patients are more likely to be impaired on free recall than on recognition tasks (e.g. Jermann et al., 2005), the current state of research is for the most part quite divergent on this matter (e.g. Taconnat et al., 2010).

[4] In clinical settings, neuropsychological assessment methods often include an interview of the patient's background, a behavioral observation, and an administration of intrinsically performance-based neuropsychological tests. The latter aim to objectively assess individual strengths and enable to detect possible deficits in different cognitive domains (P. D. Harvey, Velligan, & Bellack, 2007).

Specific aims of the present research studies

According to the aforementioned lack of consistent findings in previous investigations, the overall objective of this doctoral thesis is to address the most crucial methodological issues in order to extend the present knowledge of memory-related functioning in depression. Since previous studies have partially failed to take crucial sample characteristics into account, it was deemed necessary to initially clarify the general role of cognitive aging and gender specificity for different episodic memory components (Study I). Moreover, this approach was regarded as essential for all subsequent studies because possible effects of age and gender, once identified, could then be taken into account by either controlling for those variables or including them in later analyses.

As a major prerequisite for interpretable between-group comparisons it is indispensable to initially prove whether the neuropsychological instrument used to assess memory-related functioning measures the same memory dimensions across healthy and depressed individuals. Therefore, measurement invariance of the according measures is first tested before proceeding with further analyses (Study II). The core theme of the doctoral thesis is then addressed by clarifying whether depression can be suggested to have a profound impact on episodic memory functioning when possible gender- and age-related effects are taken into account (Study III). This is due to the fact that the currently available literature has not yet clarified whether depression has an effect on episodic memory in general, and if so, which memory components are affected the most. Comparisons between memory performances of healthy and depressed individuals are thus carried out in an attempt to highlight the specific link between depression and episodic memory impairments. Theses impairments are analyzed across different memory components in order to provide evidence for differentiated patterns of episodic memory impairments in depression. In order to detect possible differences between the subtypes of depression, episodic memory impairments, if existing, are separately analyzed for patients with MDD and patients with RD and compared between both groups. The effect of depression on executive functioning is subsequently analyzed in a next step to clarify whether certain executive dysfunctions could be regarded as a key factor in the explanation of possible episodic memory impairments in depression (Study IV).

Besides offering a comprehensive understanding of cognitive deficits in depression, another major aim of the present research is to establish an empirically-based model that reveals the most important associations between demographic or disorder-related variables

and memory-related performances (Study V). The basic consideration underlying this approach is the identification of the cumulative effects of those variables on different episodic memory components to extend the knowledge of possible risk factors for developing memory-related impairments in depression. As described above, the present research is structured in a hierarchical sequence, following the steps needed to accomplish all specific objectives of the doctoral thesis. Accordingly, the present research studies are conducted in order to clarify the following overarching issues:

- Does cognitive aging and gender exert an effect on episodic memory functioning? (Study I)
- Can we suggest certain patterns of episodic memory impairments in depression and if so, does executive dysfunctioning explain such impairments? (Study II, Study III, Study IV)
- Are there certain characteristics of depressed patients that predict individual levels of episodic memory functioning and might thus increase the risk of developing memory-related impairments in depression? (Study V)

4.2 Methodological approach

In order to achieve the objectives of the present doctoral thesis, a total of five studies, all following a quasi-experimental cross-sectional design, were conducted in an orderly scientific approach. Thus, the following subsections outline all relevant research characteristics including information about the procedure for recruitment and the basic characteristics of the study samples, an overview of the sample composition for each of the present research studies, and a description of the neuropsychological assessment and further data collection. After an overview of the cognitive measures and additional data used is given, the entire set of statistical analyses conducted in each single study is summarized to illustrate the methodological approach underlying the present empirical research.

Recruitment and sample composition

As illustrated in Figure 1, all studies included in the present empirical research are based on the data of two different initial samples: a standardization sample and a clinical sample.

Given that the present doctoral thesis is part of a large-scale project involving the German adaptation of the Wechsler Memory Scale in its fourth edition (WMS-IV; Lepach & Petermann, 2012; Petermann & Lepach, 2012; Wechsler, 2009), a neuropsychological test battery which is later introduced, data of 696 healthy German adults between 16 and 69 years of age without any history of psychiatric illness was derived from the original standardization sample of the WMS-IV (see Petermann & Lepach, 2012, for a detailed description). For the present research studies, the according data was analyzed before undergoing any adjustment and stratification processes involved in the standardization procedure. While the entire dataset of the standardization sample was used for the investigation on general effects of gender and age in Study I, certain subsamples were drawn from this sample and treated as matched control groups for the comparisons between healthy and depressed individuals in Study II, III, and IV. Since the standardization sample provided a sufficiently large data pool, pairwise matching could be performed by hand to ensure sociodemographic comparability and to control for possible confounding influences. This was accomplished by selecting those healthy control cases that were most similar to the corresponding clinical cases, so that almost perfectly matched cases of healthy and clinically depressed individuals could be obtained with a minimum of case-to-case variations.

Prior to the recruitment of depressed individuals for the clinical sample which took place between April 2012 and January 2013, the sample size needed to test the main hypotheses of the present research studies was *a priori* determined using G*Power[5] (Faul, Erdfelder, Lang, & Buchner, 2007). For this calculation, the expected effect of any between-group differences to be found was conservatively set at medium size (see Cohen, 1988, for an overview). At a predetermined significance level of $a = .05$, power analyses finally indicated a minimum sample size of $N = 176$ required to likely detect medium effect sizes of statistical significance when analyzing differences between the mean test performances of a clinical and control sample. Depending on the type of statistical analysis and the corresponding type of effect size, the required minimum sample sizes ranged from $N = 86$ to $N = 210$. Given that at least some patients who initially agreed to participate were considered to possibly withdraw from the examination later on, it was decided to recruit slightly more patients than indicated by the power analysis. Therefore, a total of 215 currently depressed patients within an age range of 16 to 69 years were recruited from three independently operating inpatient centers located in

[5] G*Power is a calculation tool to compute statistical power analyses for numerous different statistical significance tests. In psychological research, this tool is often used to calculate the minimum sample size needed to detect a statistically significant effect of a given size.

northern regions of Germany. The decision to recruit participants from different inpatient sources simultaneously through external executive employees who were not aware of specific research aims was based on the preliminary consideration to successively collect data from a large number of clinically depressed individuals within a reasonable period of time. In addition, the risk of a possible sampling selection bias could also be reduced as the final clinical dataset was unlikely to be confounded by conditions specific to a certain inpatient center.

To avoid excessive data collection and in consideration of the specific aims of the present research, a set of relevant criteria for inclusion and exclusion was initially defined before eligible patients were finally asked by the responsible executive employee of the corresponding inpatient center to participate in the examination. And although a pre-selection was made by the responsible employees according to the predefined inclusion and exclusion criteria, all of them were blind to any specific research aims or possible outcomes. As the first major prerequisite for participation, depressed patients were selected according to the ICD-10 criteria of a unipolar depression. Since screening and diagnosing procedures had already been carried out by licensed psychotherapists of the corresponding impatient centers as part of their therapeutic treatments, this information could already be obtained from clinical reports. Based on the ICD-10 criteria, only patients who were currently diagnosed with a major depressive disorder (MDD) or with a recurrent depression (RD) were invited by the executive employees to take part in the examination. Although multiple diagnoses of secondary mental disorders and comorbidities were for the most part permitted, all depressed patients suffering from sustained cognitive impairments caused by all kinds of diagnosed brain injuries or dementias, mental retardations, all types of schizophrenia, or as a result of bipolar disorders or a recent history of severe drug addiction were not considered in the present examination. If such diagnoses could be excluded in advance, relevant personal factors such as visual impairments and hearing or speech problems were considered as further exclusion criteria. Additionally, factors specific to the date of examination, including physical illness, fatigue, and lack of motivation, were recorded by the respective examiner using a behavioral observation checklist as part of the neuropsychological assessment battery.

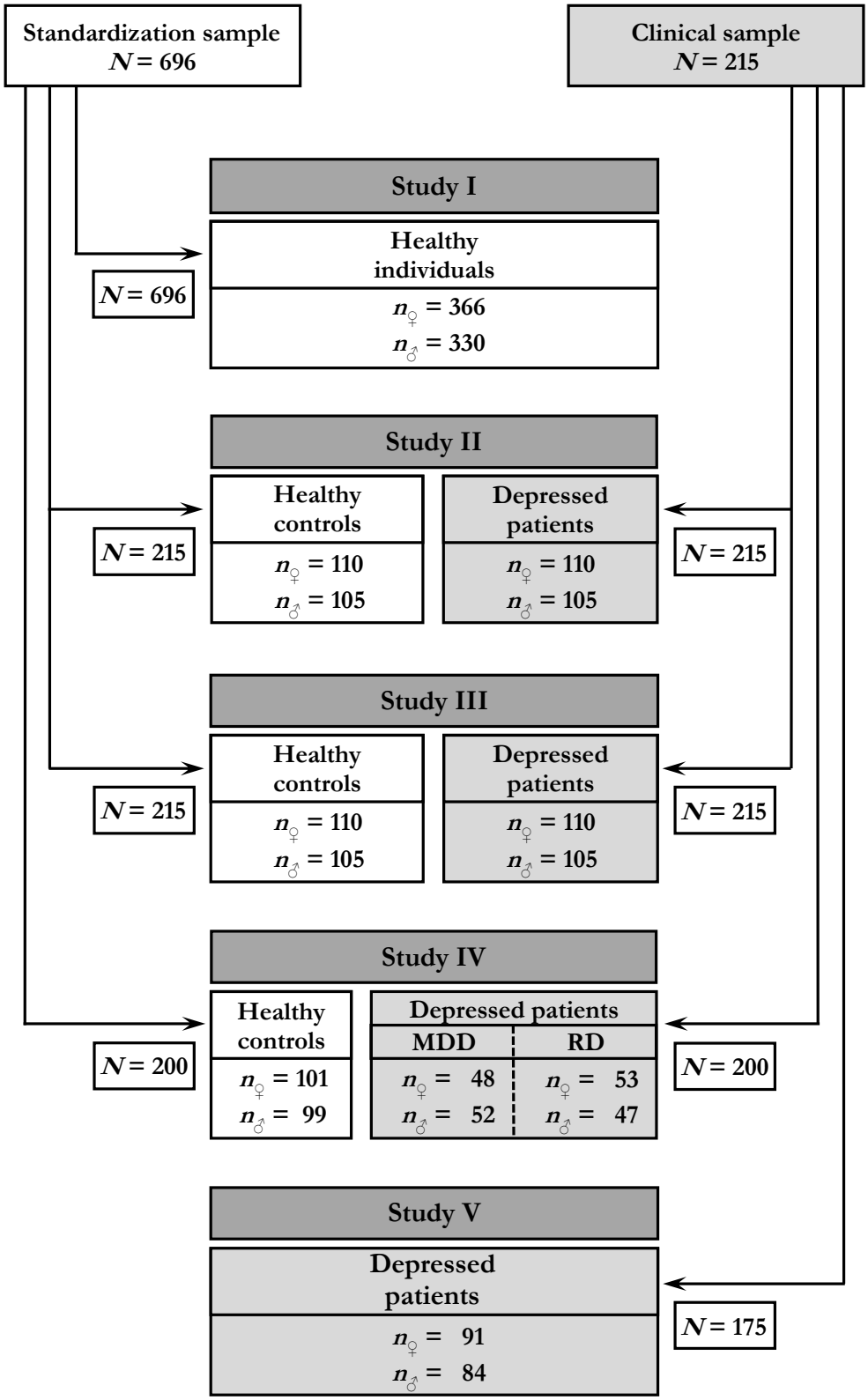

Figure 1.

An overview of the sample compositions and sample sizes in the present research studies.

Note. $n_{♀}$ = Number of female subjects, $n_{♂}$ = Number of male subjects, MDD = Major depressive disorder, RD = Recurrent depression.

Provided that all of the aforementioned criteria were met, eligible patients were finally invited to participate on a voluntary basis. As the focus on demographic sample characteristics varied across the research studies due to study-specific purposes, characteristics of the entire standardization sample (Study I), the matched control sample obtained from the standardizations sample (Study II, Study III, and Study IV), and the clinical sample (Study II, Study III, Study IV, and Study V) are described for each single study of the present research in the according subsections. As illustrated in Figure 1, the sizes of the clinical samples differed slightly across the present research studies because not all additional information relevant for the specific study aims could be obtained from every participating patient.

Neuropsychological examination and additional measures

Procedure

After approval had been obtained from each participating inpatient center, examinations took place in a one-to-one setting on the corresponding inpatient unit. Participants were first welcomed and introduced to one out of three responsible examiners who was either a doctoral candidate or a master student with expertise in the field of neuropsychological diagnostics. After being informed about the general procedure of the testing session, participants were reminded of their right to withdraw from the examination at any time. Additionally, they were advised about the confidentiality of their information and about their data being pseudonymized by using personal numerical codes as the only possibility for identification. Finally, written consent had to be signed and personally dated by each participant before proceeding with the examination. Afterwards, each of the participants was given the opportunity to receive a written report of his or her individual test results on request.

At the beginning of each examination, participants were first administered the Beck's Depression Inventory in its second edition[6] (BDI-II; Beck, Steer, & Brown, 1996) to assess depression severity at baseline. The BDI-II was selected as a suitable screening instrument because it provides a reasonable and time efficient evaluation of depression severity in clinical settings (Siegert, Walkey, & Turner-Stokes, 2009). Following this, relevant demographic information including age at testing date, gender, and duration of education as well as disorder-

[6] Examinees are required to respond to a total of 21 items by selecting one out of a given set of answers that reflects their emotional, vegetative or behavioral symptoms best over the last two weeks. The maximum obtainable score is 63, whereas scores ranging from 0 to 13 points indicate a minimal depression, from 14 to 19 points indicate a mild depression, from 20 to 28 points indicate a moderate depression, and scores within the range of 29 to 63 points indicated a severe depression.

specific information including the number and duration of depressive episodes, medication status, and additional diagnoses of comorbid disorders was collected using a structured interview (Appendix G). Missing information was obtained from clinical reports if permitted. Before memory-related functioning was assessed using the Wechsler Memory Scale in its recent version (WMS-IV; Petermann & Lepach, 2012; Wechsler, 2009), all participants first completed the Brief Cognitive Status Exam (BCSE) as part of the WMS-IV. The BCSE was originally designed to quickly screen for possible cognitive impairments by assessing specific executive functions including mental and inhibitory control as well as further cognitive abilities such as temporal orientation, incidental recall ability, visual perception, and verbal fluency. Those memory-related abilities assessed by the WMS-IV and the BCSE that are of relevance for the present research are briefly described below.

Neuropsychological assessment

Since the aim was to investigate memory-related functioning using internationally accepted, standardized, and validated instruments, the WMS-IV was selected as a comprehensive test battery that provides an individually administered assessment of a broad range of episodic memory and executive functioning measures within the age range of 16 to 69 years. The entire administration time of the WMS-IV and the corresponding BCSE requires approximately 100 minutes on average.

As summarized in Table F1, the WMS-IV includes a total of eight subtests either requiring the immediate or delayed free recall of different auditory and visual components of episodic memory. Auditory memory is assessed by first reading stories in the subtest 'Logical Memory' (LG) or word lists in the subtest 'Verbal Paired Associates' (VPA) to the examinees and by then asking them to recall the earlier-presented information. While performances on those subtests are meant to represent the ability to recall conceptually organized and semantically related information, the WMS-IV subtests for visual memory measure the ability to recall visual details and spatial locations. In particular, visual memory is assessed by first presenting a specific arrangement of abstract designs in the subtest 'Designs' (DE) or geometric figures in the subtest 'Visual Reproduction' (VR) and by then asking the examinees to reproduce them from memory. Additionally, for each of the aforementioned subtests requiring free recall, the WMS-IV also provides the corresponding subtests requiring recognition.

In addition to different episodic memory components, the WMS-IV also offers the opportunity to determine working memory capacity as well as further executive functions

within the associated BCSE (see Table F2). The WMS-IV provides two subtests, 'Spatial Addition' (SA) and 'Symbol Span' (SSP), that measure working memory for visuospatial contents. In addition to the storage of visuospatial contents, SA and SSP also require mental manipulation of spatial information as an essential process of working memory (Gathercole, 2007). After a visual presentation of a specific arrangement of colored dots in SA, examinees are required to recall all colored dots in their correct position while simultaneously adding or subtracting their locations by following a set of certain rules. Mental manipulation is also required in SSP, in which examinees are demanded to recall abstract symbols in the correct order of presentation while simultaneously ignoring distractor symbols. The BCSE tasks of 'Mental Control' (MC) and 'Inhibitory Control' (IC) were selected to assess more specific executive functions and to provide measures of important cognitive processes controlling for limited mental resources (e.g. Mackie, Van Dam, & Fan, 2013).

Data management and statistical analyses

All statistical analyses included in the present research studies were carried out using the statistical software packages IBM SPSS Statistics version 18.0, IBM SPSS Statistics version 20.0, and AMOS version 20.0 (Arbuckle, 2011) for Windows. Before conducting any hypothesis testing analyses, the entire dataset that was obtained from the examination including the assessment of depression severity at baseline (BDI-II), information collected from the structured interview and neuropsychological assessment (WMS-IV and BCSE) was first checked for possible typing errors and missing values. Typing errors were detected by hand and consequently corrected throughout the entire dataset, whereas missing values were detected and replaced by maximum likelihood parameter estimates using the expectation-maximization algorithm (EM algorithm; Dempster, Laird, & Rubin, 1977). Next, total raw scores of auditory memory were computed using the sum of scores achieved on LG I, LG II, VPA I, and VPA II, whereas scores on DE I, DE II, VR I, and VR II were summed to obtain total raw scores of visual memory. Total raw scores on auditory and visual memory requiring recognition were computed using a combination of the equivalent WMS-IV subtests for recognition. Depending on the specific aims of the present research studies, total raw scores for working memory were obtained by combining scores on SA and SSP (Study I) or by using scores on SA as the only indicator (Study III and Study V). All total raw scores obtained this way could later be transformed in the according scaled scores if necessary (Study II). Although the BCSE tasks MC and IC also provide scores of specific executive functions, these were not

considered to be indicative of different levels of executive functioning due to a lack of discriminatory power. Given that each of these BCSE measures only includes one task such as counting backward in MC or naming geometric figures incompatible to those presented in IC, skipped responses and error rates could lead to an unfavorably small variance of raw scores. Therefore, specific executive functions were assessed using processing times in MC and IC, given the fact that using speed components as performance markers is a widely accepted approach (e.g. Jurado & Rosselli, 2007). In addition to episodic memory and executive functioning measures, verbal and visuospatial ability measures had to be selected for the aims of Study I. Thus, performance on the BCSE task 'Verbal Fluency' (VF), which requires the examinee to generate as many color names as possible within a time limit of 30 seconds, was used to operationalize verbal ability. For assessing visuospatial ability, a subscore was isolated from the total raw score of DE and defined as 'Spatial Perception' (SP). As the ability to identify the correct designs in DE was considered to likely be influenced by verbal encoding strategies, only subscores for the identification of correct design locations were used to provide a visuospatial measure being at least largely unaffected by verbal ability.

After computing all relevant raw scores, the suitability of each single statistical analysis used in the present research studies was checked by ensuring that the according requirements and assumptions were met. Whenever main effects were caused by continuous but not normally distributed variables, nonparametric analyses were additionally conducted to double-check the results of parametric analyses in order to verify statistical significance (Study III, Study IV, and Study V). A *p*-value smaller than 0.05 was the definition used to indicate statistically significant results throughout the present research studies. To counteract the problem of increasing type I errors as a result of statistical significance tests being used repeatedly in multiple comparisons, significance levels were adjusted using the Bonferroni-Holm method where necessary (Study III and Study IV). After completing the aforementioned steps required for data management, certain pre-analytical procedures had to be carried out before main analyses specific to each study could be performed.

Pre-analyses in the present research studies

In each of the studies included in the present research, data was first checked for possible between-group differences in crucial demographic variables such as age, gender, and educational background. Pre-analyses included comparisons between gender and age distributions within different age groups (Study I) as well as additional comparisons of educational backgrounds of male and female examinees across the clinical and the control

sample (Study II, Study III, and Study IV). In particular, these analyses comprised Kruskal-Wallis tests for independent samples (Study I, Study II, and Study IV) and additional Mann-Whitney *U* test statistics (Study III) for nonparametric and categorical data. Beside demographic variables, Kruskal-Wallis tests for nonparametric and univariate *F*-tests from a multivariate analysis of variance (MANOVA) for parametric data were performed in order to check for gender differences on certain disorder-related variables (Study V). The latter included illness duration, number of prior depressive episodes, depression severity, medication status, and the number of comorbid disorders or additional diagnoses. In Study III and Study IV, internal consistencies of the WMS-IV and BCSE subtests were additionally checked by computing and evaluating the value of Cronbach's *a*. Table 1 gives an overview of all pre-analyses provided in the present research studies.

Main analyses of the present research studies

Table 2 shows the main analyses included in the present research studies. For the main analyses in Study I, subgroup-specific levels of memory-related functioning were analyzed by comparing neuropsychological test performances of male and female subjects across different age groups using multivariate and univariate MANOVA test statistics. All gender differences included were indicated by standardized values of Cohen's *d* in due consideration of the pooled variances (Hartung, Knapp, & Sinha, 2008). This value of effect size allowed the comparison of gender-related effects on different measures of memory-related functioning within or across the age groups. Single independent-samples *t*-tests with adjusted significance levels according to Bonferroni's and Scheffé's criteria were then used to detect different levels of verbal and visuospatial ability across the age groups. Additionally, *F*-test statistics as part of one-way analyses of variance (ANOVAs) were used to investigate gender differences in memory-related functioning within each age group. Hierarchical regression analyses were finally conducted in Study I to determine whether gender differences in memory-related functioning could be explained by aging effects or gender-specific advantages in verbal and visuospatial ability.

As a major prerequisite for all subsequent between-group comparisons in Study III and Study IV, single confirmatory factor analyses (CFAs) and multigroup confirmatory factor analyses (MGCFAs) were performed in Study II in order to test for measurement invariance of the WMS-IV across the clinical and healthy control samples. Performing CFAs and MGCFAs required the comparison of different model solutions by evaluating a set of different

Table 1.

An overview of the statistical pre-analyses performed in the present research studies

Study	Statistical analysis	Application purpose	Description of use
Study I	• Kruskal-Wallis tests (χ^2 distribution)	Test of distribution homogeneity	To test whether age distributions and educational backgrounds (quantitative and qualitative) of female and male subjects are comparable within each age group
Study II	• Kruskal-Wallis tests (χ^2 distribution)	Tests of distribution homogeneity	To test whether age distributions and education duration are comparable between female subjects of the clinical and control sample, male subjects of the clinical and control sample, or between both samples in total
	• Skewness / kurtosis evaluation	Test of normality	To provide univariate and multivariate normality values for the WMS-IV subtests
Study III	• Kruskal-Wallis tests (χ^2 distribution) • Mann-Whitney *U*	Test of distribution homogeneity	To test whether gender distributions, ages, and education durations are comparable across the clinical and control sample within and between the age groups
	• Internal consistencies (Cronbach's *α*)	Reliability analysis	To provide standardized measures of internal consistency of for the WMS-IV and BCSE subtests assessing episodic memory and executive functioning
Study IV	• Kruskal-Wallis tests (χ^2 distribution)	Test of distribution homogeneity	To test whether distributions of age, gender, and education duration are comparable between the two clinical groups (MDD and RD patients) and the control sample
Study V	• Internal consistencies (Cronbach's *α*)	Reliability analysis	To indicate internal consistencies of the WMS-IV free recall measures and the corresponding recognition measures of auditory and visual episodic memory as well as internal consistencies of the BCSE measures assessing executive functioning
	• Kruskal-Wallis tests (χ^2 distribution) • univariate *F*-tests	Test of distribution / variance homogeneity	To test whether ages, educational backgrounds, illness durations, the numbers of prior depressive episodes, the levels of depression severity, medication statuses, and the number of additional diagnoses are comparable across female and male examinees

Note. WMS-IV = Wechsler Memory Scale – Forth Edition, MDD = major depressive disorder, RD = recurrent depression.

fit indexes and chi-square difference tests. Model comparisons also included the examinations of factor loadings and interfactor correlations.

In Study III, the size of depression-related effects on components of episodic memory and executive functioning were indicated using Cohen's *d* for pooled variances and tested for heterogeneity either across the age groups within single memory-related measures or within single age groups across different memory-related measures. Furthermore, MANOVAs were carried out in order to investigate possible effects of age group and depression on certain components of episodic memory and executive functioning, whereas ANOVAs were used to analyze depression-related effects on those memory-related functioning measures within single age groups. A series of hierarchical regression analyses was also performed to determine whether depression-related effects on different episodic memory components could be the result of executive dysfunctions in depression.

As required for the aims of Study IV, the main analyses included one-way ANOVAs to investigate performances of two clinical subsamples (MDD and RD patients) and a healthy control sample on different episodic memory measures. Performances of these groups were then compared with each other within each single episodic memory measure using independent-samples *t*-tests with adjusted significance levels according to the Bonferroni-Holm method for multiple comparisons. Finally, effect sizes for those comparisons were again computed using Cohen's *d* formula for pooled variances and tested for heterogeneity within and across the episodic memory measures.

In Study V, a correlational analysis was carried out to initially detect significant non-directional associations among certain demographic variables, disorder-related variables, and all memory-related measures included. Based on these empirically-derived correlations, directional associations between exogenous and endogenous variables were specified in advance and a SEM-based path model was then developed to fit the empirical data. This required different steps such as testing correlated variables for multicollinearity using the variance inflation factor (VIF; O'Brien, 2007) and evaluating fit indexes between modified path models. Following this, direct and indirect effects of demographic and disorder-related variables on single components of memory-related functioning could be analyzed on the basis of the final path model.

Table 2.

An overview of the main statistical analyses performed in the present research studies

Study	Statistical analysis	Application purpose	Description of use
Study I	• Effect size calculations (Cohen's *d*)	Standardization of group differences	To provide standardized measures for gender-related effects on auditory and visual memory within each single age group
	• MANOVAs (Wilk's λ, *F*-tests)	Test of main effects and interactions	To test for effects of age group and gender on educational background, cognitive status, verbal fluency, spatial perception, and on auditory and visual memory
	• *t*-tests	Post hoc analyses	To test for differences in verbal fluency and spatial perception between the age groups
	• One-way ANOVAs	Univariate analyses	To test for effects of gender on auditory and visual memory within each age group
	• Cochran's *Q*-tests, I^2- and z-test statistics	Test of effect size heterogeneity	To determine whether the sizes of gender-related effects on auditory and visual memory are different across the age groups
	• Hierarchical regression analyses	Controlling for effects	To determine whether gender- and age-related effects on auditory and visual memory still remain after controlling for effects on verbal fluency or spatial perception
Study II	• Single confirmatory factor analyses (CFAs)	Testing for factor structure	To determine whether the model out of six hypothesized factor models that best fits the empirical data is the same for the clinical and control sample
	• Multigroup CFAs (MGCFA)	Test of measurement invariance	To compare four successively restricted factor models in order to test for full or partial metric, scalar, and residual invariance across the clinical and control sample
	• Analysis of factor loadings	Comparing factor loadings	To determine whether there are differences in the factor loadings on the memory scales across the clinical and control sample
	• Analysis of interfactor correlations	Testing for significant correlations	To examine correlations between the memory scales in the clinical and control sample
Study III	• Effect size calculations (Cohen's *d*)	Standardizing mean raw score differences	To provide standardized measures indicating the size and direction of depression-related effects on auditory and visual memory performances within each single age group

(Table 2 to be continued on the following page)

(Table 2 continued)

Study	Statistical analysis	Application purpose	Description of use
Study III	• Cochran's *Q*-tests, I^2-statistics, z-values	Test of effect size heterogeneity	To determine whether depression-related effects within/across the age groups vary within/across auditory or visual memory measures requiring free recall or recognition, as well as within/across executive functioning measures
	• MANOVAs (Wilk's λ, *F*-tests)	Test of main effects and interactions	To test for effects of age group and depression on auditory/visual memory measures requiring free recall/recognition as well as on executive functioning measures
	• One-way ANOVAs (*F*-tests)	Univariate analyses	To test for depression-related effects on auditory/visual memory requiring free recall/recognition as well as on executive functioning measures within the age groups
	• Hierarchical regression analyses	Controlling for effects	To determine whether depression-related effects on auditory/visual memory measures requiring free recall/recognition remain after controlling for executive functioning
Study IV	• One-way ANOVAs (*F*-tests)	Test of main effects and interactions	To test for differences in free recall and recognition performances on the auditory and visual memory measures across two clinical and one control group
	• *t*-tests	Post hoc analyses	To test for between-group differences in free recall/recognition performances on the auditory/visual memory measures by comparing two clinical and one control group with each other
	• Effect size calculations (Cohen's *d*)	Standardizing mean raw score differences	To provide standardized measures indicating the size and direction of between-group differences in auditory and visual memory measures requiring free recall or recognition
	• Cochran's *Q*-tests, I^2-statistics, z-values	Test of effect size heterogeneity	To determine whether the sizes of between-group differences significantly vary across the free recall and recognition performances within/across the auditory and visual memory measures
Study V	• Correlational analysis	Testing for significant correlations	To indicate significant associations among demographic variables, disorder-related variables and all episodic memory and executive functioning measures included
	• SEM-based path analysis	Test of direct and indirect effects	To develop a path model to demonstrate the associations between demographic and disorder-related variables and their individual effects on episodic memory and executive functioning measures included

Chapter 5

General Effects on Episodic Memory

Before clarifying how episodic memory could be affected by depressive disorders, it was deemed necessary to first gain a deeper inside into those factors that are commonly suggested to be associated with memory in order to take them into account in the following research studies. Among those factors, age and gender have frequently been found to affect episodic memory functioning in previous investigations and were therefore closely addressed in the first study of the present research.

5.1 The role of gender and age for episodic memory (Study I)

As noted earlier, declines in episodic memory performance associated with increasing age are suggested to be either a result of age-related encoding and retrieval difficulties (Glisky et al., 2001; Spaniol et al., 2006), limited processing capacities (Brickman & Stern, 2009) or declines in perceptual-motor abilities with age (Veiel & Storandt, 2003). In addition to age, the impact of gender on a variety of brain functions and processing strategies also seems to be quite ubiquitous. However, the claim that neurobiological gender differences in brain organization and morphology extend to more behavioral manifestations such as episodic memory performance has been typically discussed more controversial (see Andreano & Cahill, 2009, for a review). Previous investigations reporting a general female advantage over men in episodic memory performance (Bloise & Johnson, 2007; Herlitz & Rehnman, 2008; Pohl, Bender, & Lachmann, 2005) are challenged by other studies suggesting gender differences in episodic memory to either rely on verbal processing (Sommer et al., 2004) favoring women over men or visual processing with a slight advantage of men over women (de Frias, Nilsson, & Herlitz, 2006; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005). Furthermore, little effort has been made so far in clarifying whether gender-related effects on episodic memory, if existing, remain stable throughout life or if such effects vary across different stages in life such as adolescence or young and older adulthood. Therefore, the main purpose of Study I was not only to examine possible gender-related effects on auditory and visual components of

episodic memory but also to determine whether such effects can be generalized across three different age groups including adolescents, young adults, and older adults. Another aim was to clarify whether specific advantages in verbal and visuospatial ability could explain possible gender differences in auditory and visual memory due to the congruence of processing modality.

Sample characteristics

Study I was carried out on the basis of the neuropsychological data of 696 healthy individuals that were collected as part of the German standardization project of the WMS-IV. The main demographic characteristics of the study sample including age, gender, and education duration are presented in Table 3.

Table 3.

Demographic characteristics of study participants across the age groups in Study I

			Age (years)			Education (years)		
Age group	**Gender**	***N***	***M***	***SD***	***Min/Max***	***M***	***SD***	***Min/Max***
16-24 years [a]	Female	92	18.83	2.36	16 / 24	10.66	1.65	8 / 16
	Male	87	18.72	2.29	16 / 24	10.84	1.70	8 / 17
	Total	179	18.78	2.32	16 / 24	10.49	1.68	8 / 17
25-44 years [b]	Female	73	34.99	6.32	25 / 44	10.59	2.72	8 / 18
	Male	103	33.48	6.02	25 / 44	11.06	2.55	8 / 18
	Total	176	34.10	6.17	25 / 44	10.86	2.62	8 / 18
45-69 years [c]	Female	201	59.24	7.74	45 / 69	10.37	2.29	8 / 18
	Male	140	58.59	7.66	45 / 69	10.34	2.56	8 / 18
	Total	341	58.98	7.70	45 / 69	10.36	2.40	8 / 18
16-69 years [d]	Female	366	44.25	18.60	16 / 69	10.49	2.24	8 / 18
	Male	330	40.24	17.82	16 / 69	10.56	2.38	8 / 18
	Total	696	42.35	18.33	16 / 69	10.52	2.31	8 / 18

Note. [a] Adolescents, [b] young adults, [c] older adults, [d] total sample with pooled age groups.

Although the standardization project required the implementation of sampling procedures to obtain representative age and gender distributions within a total of nine age subgroups, Kruskal-Wallis test statistics indicated significantly different gender distributions across these original age subgroups. For this reason and in due consideration of the study aims, data from the age subgroups were pooled into three different age groups before undergoing any further analyses. Theses age groups finally comprised 179 adolescents from 16 to 24 years of age, 176 young adults between 25 and 44 years of age, and 341 older adults aged between 45 and 69 years.

Results and discussion

The main purpose of Study I was to clarify the role of gender and age on episodic memory functioning. More specifically, the question was addressed whether a gender difference could be the cause of differences in episodic memory performances due to the processing modality required for either auditory or visual memory tasks and if so, whether such differences remain stable across different age groups. Multivariate statistics of the MANOVA indicated that gender (Wilk's $\lambda = .968$, $F(2, 689) = 11.566$, $p < .001$[7]) and age group (Wilk's $\lambda = .825$, $F(4, 1378) = 34.705$, $p < .001$[7]) both significantly affected auditory and visual memory performances of the study participants. Further analyses of variances and effect sizes confirmed small but for the most part significant gender-related effects on all episodic memory measures whereas the direction of those effects was found to depend on the type of memory measure or the processing modality required.

As illustrated in Figure 2, the findings of Study I indicated that women showed an advantage in the auditory memory performance over men ($F(1, 694) = 5.199$, $p < .05$, $d = 0.17$) whereas men generally outperformed women on visual memory measures ($F(1, 694) = 4.734$, $p < .05$, $d = -0.23$). Although not changing in direction, these advantages appeared to vary in magnitude across the age groups. In contrast to young female adults ($F(1, 174) = 4.626$, $p < .05$, $d = 0.33$) and older female adults ($F(1, 393) = 4.734$, $p < .05$, $d = 0.24$), who both outperformed their male counterparts on auditory memory measures, no significant gender difference was found favoring female adolescents over male adolescents. While male adolescents ($F(1, 177) = 4.453$, $p < .05$, $d = -0.23$) and older male adults ($F(1, 339) = 4.103$, $p < .05$, $d = -0.15$) showed higher performances on visual memory measures compared to

[7] These multivariate statistics slightly deviate from the original statistics reported in Study I because working memory as a third dependent variable was excluded from the MANOVA.

women of the equivalent age group, a similar male advantage could not be confirmed for the young adult age group. Since further analyses failed to find any heterogeneity of gender-related effects in both auditory memory and visual memory across the age groups, such small variations in effect sizes could be interpreted as reflecting differing interests, different levels of semantic knowledge and familiarity with the WMS-IV test materials, and varying hormonal levels (e.g. McEwen, 2002) across females of different ages.

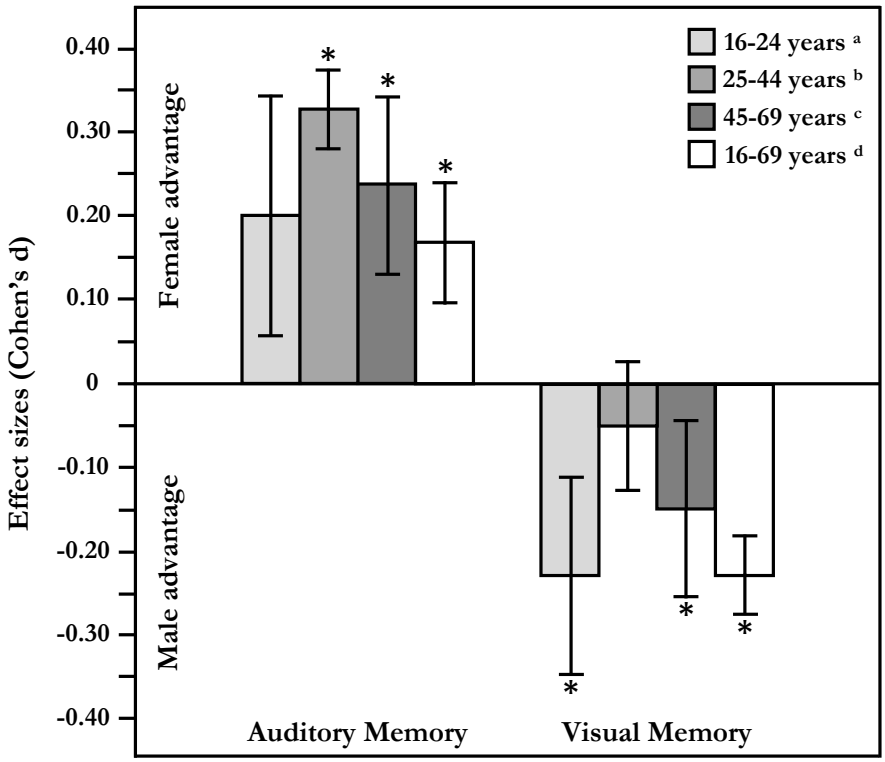

Figure 2.

Effect sizes for gender differences in auditory and visual memory across the age groups in Study I.

Note. [a] Adolescents, [b] young adults, [c] older adults, [d] total sample with pooled age groups. *$p < .05$.

Since further analyses also indicated gender differences in verbal ability favoring female over male examinees ($F(1, 690) = 15.763$, $p < .001$) and in visuospatial ability favoring male over female examinees ($F(1, 690) = 10.611$, $p < .01$), these gender-specific advantages were considered to substantially contribute to those gender-related effects found on auditory and visual memory measures. Although regression analyses revealed that varying levels of verbal ability significantly contributed to the variance found in both the auditory ($\beta = .194$ $p < .001$, $R^2 = .040$) and visual memory measures ($\beta = -.192$ $p < .001$, $R^2 = .030$), statistical control of

verbal ability only eliminated the gender-related effect on auditory memory (β = -.060 p > .05, ΔR^2 = .004). Female advantages in verbal ability could thus be confirmed as the main reason for female advantages in auditory memory due to the verbal processing required. As in the case of verbal ability, additional regression analyses disclosed that visuospatial ability significantly contributed to the variance across the auditory (β = .393 p < .001, R^2 = .135) and visual memory performances (β = .842 p < .001, R^2 = .030). As soon as gender differences in visuospatial ability were controlled, gender-related effects on visual memory disappeared (β = -.028 p > .05, ΔR^2 = .001). Consequently, a male advantage in visual memory could be fully explained by a more pronounced visuospatial processing ability of men compared to women.

5.2 Implications for the present research

In conclusion, the findings of Study I support the idea of a slight but consistent female advantage in auditory memory and a male advantage in visual memory functioning which appear to be quite stable in direction and magnitude across different age groups. Since previous investigations have already suggested certain demographic factors to affect various memory components, the present results emphasize the important role of gender and age on episodic memory functioning. In future studies investigating episodic memory functioning on the basis of neuropsychological examinations, age- and gender-related effects should thus be considered in general and especially when the measures used require different processing modalities. Therefore, this issue has carefully been addressed in all subsequent studies of the present research. In Study II, Study III, and Study IV, the clinical and control samples were first matched by gender and age to avoid possible confounding effects before undergoing any group comparisons. Finally, the effects of gender and age were subjected to the main analyses in Study V rather than being statistically controlled by conducting matching procedures.

Chapter 6

Episodic Memory and Depression

The issue of establishing construct validity is often neglected in neuropsychological research. However, testing for measurement invariance across different groups is a major prerequisite for between-group comparisons to be permissible and meaningful. Before comparing performances of healthy controls and depressed individuals on episodic memory measures, it was deemed indispensable to initially prove that the WMS-IV test battery measures the same memory dimensions across both samples under examination.

6.1 Prerequisites for between-group comparisons (Study II)

Given that the structure of the WMS-IV was originally validated on the basis of the standardization sample, testing for measurement invariance was considered necessary in order to establish sufficient validity evidence and clinical utility of the WMS-IV. In Study II, this technique was thus used to check whether healthy individuals from the standardization sample and depressed patients from the clinical sample ascribe the same meanings to the WMS-IV memory scales and items (see Gouveia, Milfont, da Fonseca, & Coelho, 2009, for another application). Evaluating construct validity of the WMS-IV required different steps to establish measurement invariance across both samples. First, a series of single CFAs was performed to determine which of six theoretical models could best fit the empirical data in the clinical and control samples. Provided that the model with the best fit was proved to be equivalent across the samples (configural invariance[8]), MGCFAs could then be conducted on both samples simultaneously in order to test for different subtypes of measurement invariance. This included successively determining whether examinees of both samples responded to the WMS-IV test items the same way (metric invariance[9]), whether examinees of both samples with the same estimated score on a certain latent memory dimension were given the same score on the

[8] The overall model structure is equally conceptualized by both samples without any constraints.
[9] Factor loadings are constrained to be equal across the samples.

observed memory measure (scalar invariance[10]), and whether measurement errors were invariant across both samples (residual invariance[11]). Each of those types of invariance were tested by comparing an unconstrained baseline model with the corresponding invariance model including certain parameters that were constrained to be equal across the samples depending on which of them were expected to be invariant. Only if successively constraining parameters within the invariance models did not significantly worsen model fit compared to the baseline model, the according subtype of measurement invariance could then be considered to be confirmed.

Sample characteristics

As has already been described earlier, neuropsychological data of a total of 215 clinically depressed patients (51.6% women, 48.4% men) between 16 and 69 years of age were collected for the clinical sample in Study II using the WMS-IV. Apart from those patients who were solely diagnosed with either an MDD or a RD (46.7%), 53.3% of all depressed patients in the clinical sample featured comorbid disorders. The latter comprised additional diagnostic categories such as various types of anxiety disorders (33.6%), substance abuse (5.6%), personality disorders (4.5%), further affective disorders (3.3%), somatoform disorders (2.7%), obsessive-compulsive disorders (1.8%), eating disorders (0.9%), and attention-deficit/hyperactivity disorder (ADHD; 0.9%).

For the control sample, data of 215 healthy examinees (51.6% women, 48.4% men) were collected from the standardization sample of the WMS-IV. In due consideration of previous study findings (Study I), suitable control sample cases were selected by hand using pairwise matching with gender, age, and education duration as matching variables. This was done in order to achieve a better sociodemographic comparability between the clinical and control sample and to control for possible confounding effects arising from unequal distributions of gender, age, and educational background across both samples. Thus, perfect matches between paired cases could be obtained for gender, whereas slight age variations were permitted as long as ranging within the same age group[12] and deviations not exceeding ±1 year

[10] Factor loadings and item intercepts are constrained to be equal across the samples.
[11] Factor loadings, item intercepts, and error variances are constrained to be equal across the samples.
[12] Refers to those three age groups which have already been described for the sample in Study I including adolescents aged between 16 and 24 years, young adults aged between 25 and 44 years, and older adults aged between 45 and 69 years.

were allowed for education durations. Demographic characteristics of the final clinical and matched control sample are shown in Table 4.

Table 4.

Demographic characteristics of the clinical and matched control samples in Study II

			Age (years)			Education duration (years)		
Sample	**Gender**	***N***	***M***	***SD***	***Min/Max***	***M***	***SD***	***Min/Max***
Clinical	Female	110	38.69	16.40	16 / 68	10.17	1.80	8 / 16
	Male	105	37.64	15.75	16 / 69	10.52	1.78	8 / 17
	Total	215	38.19	16.06	16 / 69	10.34	1.80	8 / 17
Control	Female	110	38.45	16.14	16 / 68	10.37	1.81	8 / 18
	Male	105	37.94	15.96	16 / 69	10.69	2.19	8 / 17
	Total	215	38.20	16.02	16 / 69	10.53	2.00	8 / 18

Finally, Kruskal-Wallis test statistics confirmed the accuracy of the matching procedure by indicating that neither ages differed between the clinical and control samples ($\chi^2(1, N = 430) = 0.001, p > .05$), nor did education duration differ between these samples ($\chi^2(1, N = 430) = 0.064, p > .05$). Neither ages ($\chi^2(1, N = 210) = 0.013, p > .05$) differed between male examinees of both samples nor did education durations ($\chi^2(1, N = 210) = 0.043, p > .05$). Comparable ages ($\chi^2(1, N = 220) = 0.011, p > .05$) and education durations ($\chi^2(1, N = 220) = 0.038, p > .05$) were also found for female examinees across the clinical and control sample.

Results and discussion

Addressing a major prerequisite for subsequent between-group comparisons in the present research, Study II aimed to confirm construct validity and clinical utility of the WMS-IV by establishing measurement invariance across a clinical sample including depressed patients and a matched sample including healthy individuals. When comparing competitive model solutions with each other, chi-square difference tests and additional indexes of model fit indicated that a three-factor oblique model could best explain performances on the WMS-IV measures

observed in the clinical sample ($\chi^2(28, N = 215)$[13] = 34.337, $p > .05$; lowest SRMR[13] = .039; lowest RMSEA[13] = .041; highest NNFI[14] = .990; highest CFI[15] = 994) and the matched control sample ($\chi^2(28, N = 215)$[13] = 38.243, $p > .05$; lowest SRMR[13] = .037; lowest RMSEA[13] = .039; highest NNFI[14] = .990; highest CFI[15] = 994). For both samples, the three-factor oblique model was found to support two interdependent episodic memory dimensions and one working memory dimension (see Figure 3). Consistent with previous research on the structure of the WMS-IV (e.g. Holdnack, Zhou, Larrabee, Millis, & Salthouse, 2011), the episodic memory dimensions found in Study II included auditory memory as measured by the WMS-IV subtests LG I, LG II, VPA I, and VPA II, and visual memory underlying the performances on DE I, DE II, VR I, and VR II. The working memory dimension comprised the subtests SA and SSP which both require visual processing.

Although the abovementioned findings indicated that the WMS-IV most likely assess similar memory dimension across the clinical and control sample, chi-square difference tests revealed that constraining all factor loadings to be equal across the samples significantly worsened model fit when compared with the baseline model ($\Delta\chi^2(10) = 23.622$, $p < .01$). Therefore, full metric invariance could not be confirmed. Factor loadings of the episodic memory measures appeared to be of comparable sizes in the clinical and control sample, while, by contrast, factor loadings of the WMS-IV subtest SSP measuring working memory were found to be significantly different across both samples ($z = -3.74$, $p < .05$). Given that the factor loading of SSP turned out to be the smallest and the only one being not significant among all other factor loadings in the clinical sample ($\lambda = .22$, $p > .05$) but not in the control sample ($\lambda = .61$, $p < .001$), SSP was considered to not adequately measure working memory capacity in depressed patients. Once factor loadings of SSP were allowed to vary across both samples, partial metric invariance ($\Delta\chi^2(8) = 7.902$, $p > .05$), as well as full scalar invariance ($\Delta\chi^2(18) = 28.023$, $p < .05$) and full residual invariance ($\Delta\chi^2(32) = 45.667$, $p < .05$) could be established.

In summary, the analyses in Study II provided the same compelling support for the suitability of a three-factor model solution for depressed patients in the clinical sample as that established for healthy individuals in the matched control sample. Analyses of factor loadings additionally supported two episodic memory dimensions, respectively auditory and visual memory, to be similarly assessed by the WMS-IV across both samples. It can therefore be concluded that the WMS-IV is a useful instrument for assessing episodic memory performance

[13] The likelihood ration chi-square statistic (χ^2), the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA) are absolute fit indexes.
[14] The nonnormed fit index (NNFI) is an incremental fit index.
[15] The comparative fit index (CFI) is a parsimonious fit index.

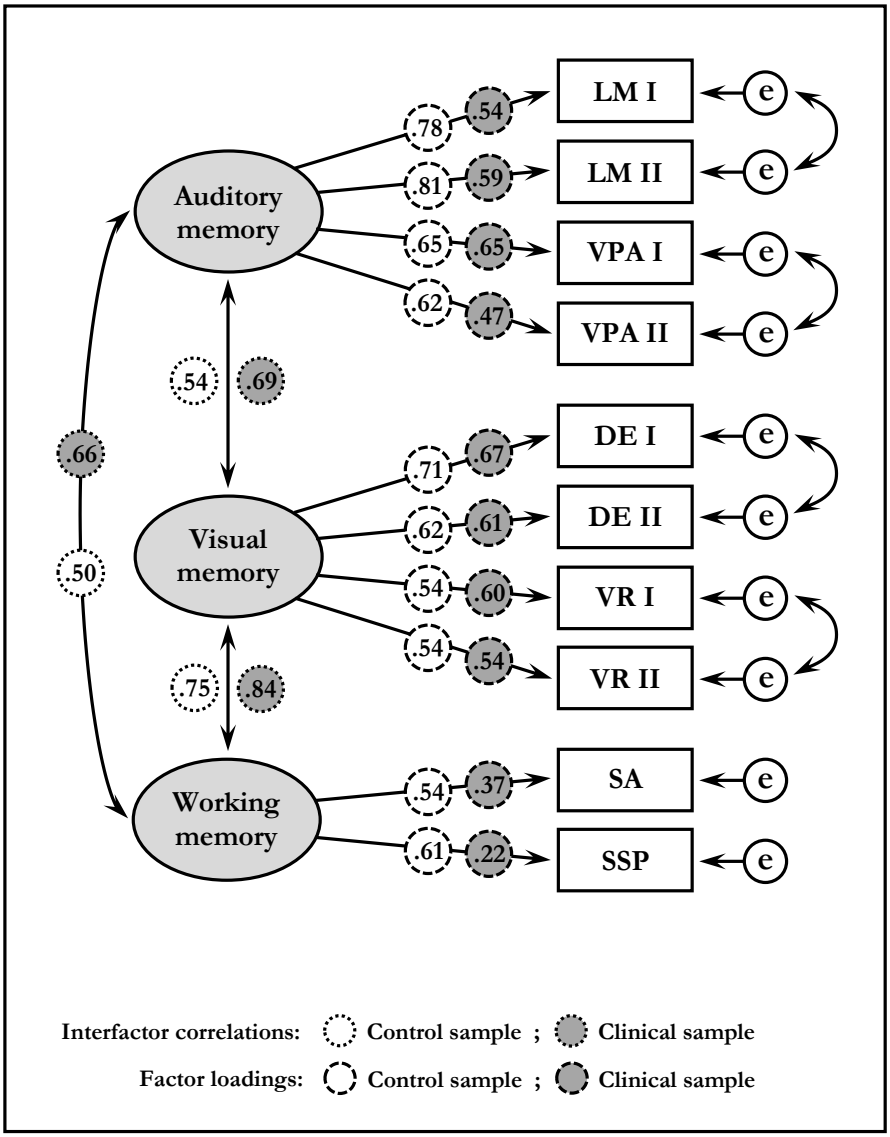

Figure 3.

The three-factor oblique model of the WMS-IV including parameter estimates for the clinical and control samples in Study II.

Note. LG = 'Logical Memory'; VPA = 'Verbal Paired Associates', DE = 'Designs', VR = 'Visual Reproduction', SA = 'Spatial Addition', SSP = 'Symbol Span', I = Immediate recall, II = Delayed recall.

of depressed patients in order to compare them with those of healthy individuals. However, clinical utility could not be confirmed for one measure of working memory. Regardless of whether this partial non-invariance of the working memory measures might reflect effects of considerable variations in cognitive functioning or differing disorder-related characteristics

among depressed patients in the clinical sample, SSP was found to not assess the same memory dimension across the clinical and control samples. As a consequence of the findings in Study II, all WMS-IV measures of episodic memory were utilized for between-group comparisons in Study III and Study IV, as well as for pure clinical examinations in Study V. In Study III and Study V, however, only performances on the WMS-IV measure SA were used to adequately assess working memory capacity without compromising validity.

6.2 The link between depression and episodic memory (Study III)

Although previous investigations could demonstrate that depressive disorders are likely accompanied by several cognitive deficits, empirical findings on this topic appear to be marked by large discrepancies so far. Since some studies have reported considerable episodic memory impairments in depression (e.g. Airaksinen et al., 2004; Williams et al., 2007) while others could not find any of those effects on memory-related functioning at all (e.g. Fossati et al., 2004; Grant et al., 2001), it is not yet fully understood, why some but not all depressed individuals are affected by such cognitive deficits (McCall & Dunn, 2003). In this context, varying characteristics of the individuals examined, including wide age ranges, as well as differing episodic memory measures used in neuropsychological examinations, have been suggested to be one explanation for such inconsistent results across the studies. In due consideration of these patient and task characteristics, the first major aim of Study III was therefore to analyze episodic memory performances of depressed patients in comparison to healthy individuals in order to check for possible depression-related effects. Moreover, comparing episodic memory performances across different age groups and different memory measures additionally allowed to determine whether certain depression-related memory impairments, if existing, might be increasing with age and whether such impairments are specific to certain episodic memory components rather than being general in nature. In particular, it was aimed to clarify whether lower performances on the WMS-IV episodic memory measures could be regarded as an effect of depression, and if so, whether depression-related effects are generalizable across different age groups, auditory and visual memory, and across free recall and recognition performances.

Provided that possible effects of depression on different components of episodic memory could be observed, the second major aim of Study III was to further investigate the contribution of executive dysfunctioning to episodic memory impairments in depression. For this purpose, the question was addressed whether any deficits in certain executive functions

could also be expected to be prominent in depressed patients. Given the strong association between executive functioning (EF) and declarative memory components, executive dysfunctions were, at least to some extent, suggested to explain depression-related effects on episodic memory performances. It has to be noted that the extent to which executive processes contribute to episodic memory performances might vary depending on the specific executive function examined. Therefore, multiple measures, including mental control (MC), inhibitory control (IC), and a broader measure of working memory (WM), were used in Study III in order to obtain a more differentiated picture of the role of executive dysfunctioning for the link between episodic memory and depression.

Sample characteristics

The same neuropsychological datasets of 215 clinically depressed patients for the clinical sample and the corresponding data of healthy individuals for the matched control sample that had already been used in Study II were also subjected to the analyses in Study III. This way, the comparability of both samples could be ensured without the need to conduct any additional matching procedures or pre-analyses to check for possible sociodemographic differences across the samples. Table 5 summarizes the demographic characteristics of the samples examined in Study III.

Results and discussion

Regarding the first aim of Study III, multivariate results of the MANOVAs indicated that healthy individuals in the control sample generally outperformed depressed patients in the clinical sample on all WMS-IV measures of episodic memory (Wilk's $\lambda = .796$, $F(4, 421) = 27.032$, $p < .001$). Episodic memory performances also appeared to be significantly different across the age groups in both samples (Wilk's $\lambda = .700$, $F(8, 842) = 20.592$, $p < .001$). As illustrated in Figure 4, considerable depression-related effects were found on both the auditory memory measures either requiring free recall ($F(1, 428) = 77.312$, $p < .0001$, $d = 1.01$) or recognition ($F(1, 428) = 30.577$, $p < .0001$, $d = 0.53$), and the visual memory measures either requiring free recall ($F(1, 428) = 38.324$, $p < .0001$, $d = 0.92$) or recognition ($F(1, 428) = 47.231$, $p < .0001$, $d = 0.66$). While depression-related effects found on free recall measures are consistent with the general consensus in previous literature (e.g. Jermann et al., 2005) that depressed individuals are most likely affected by memory-related impairments due to a lack of

cognitive effort (e.g. Hammar & Årdal, 2012), the present results unexpectedly revealed lower recognition performances in depressed patients as well.

Table 5.

Demographic characteristics of the clinical and matched control samples in Study III

				Age (years)			Education (years)		
Age group	**Sample**	**Gender**	***N***	***M***	***SD***	***Min/Max***	***M***	***SD***	***Min/Max***
16-24 years [a]	**Clinical**	Female	33	19.18	2.37	16 / 24	10.12	1.32	9 / 13
		Male	31	19.52	2.67	16 / 24	10.61	1.61	9 / 13
		Total	64	19.34	2.50	16 / 24	10.36	1.47	9 / 13
	Control	Female	33	19.24	2.42	16 / 24	10.15	1.44	9 / 13
		Male	31	19.45	2.67	16 / 24	10.84	1.85	9 / 15
		Total	64	19.34	2.53	16 / 24	10.48	1.67	9 / 15
25-44 years [b]	**Clinical**	Female	31	34.19	6.10	25 / 44	10.71	1.77	9 / 16
		Male	33	33.76	6.79	26 / 44	10.64	1.82	8 / 13
		Total	64	33.97	5.90	25 / 44	10.67	1.78	8 / 16
	Control	Female	32	34.87	6.29	25 / 44	10.94	2.34	9 / 18
		Male	33	33.82	5.63	26 / 44	10.85	2.32	8 / 16
		Total	65	34.29	5.93	25 / 44	10.89	2.31	8 / 18
45-69 years [c]	**Clinical**	Female	47	55.36	6.67	45 / 68	9.85	2.05	8 / 14
		Male	40	54.90	6.52	46 / 69	10.35	1.90	8 / 17
		Total	87	55.15	6.57	45 / 69	10.08	1.99	8 / 17
	Control	Female	45	55.16	6.40	45 / 68	10.13	1.55	8 / 16
		Male	41	55.24	6.77	46 / 69	10.44	2.34	8 / 17
		Total	86	55.20	6.54	45 / 69	10.28	1.96	8 / 17
16-69 years [d]	**Clinical**	Female	110	38.69	16.40	16 / 68	10.17	1.80	8 / 16
		Male	105	37.64	15.75	16 / 69	10.52	1.79	8 / 17
		Total	215	38.19	16.06	16 / 69	10.34	1.80	8 / 17
	Control	Female	110	38.45	16.14	16 / 68	10.37	1.81	8 / 18
		Male	105	37.94	15.96	16 / 69	10.69	2.19	8 / 17
		Total	215	38.20	16.02	16 / 69	10.53	2.00	8 / 18

Note. [a] Adolescents, [b] young adults, [c] older adults, [d] total sample with pooled age groups.

Thus, it is conceivable that, in addition to automatic processes, certain effortful processes might also be involved in performing on recognition measures of the WMS-IV. Anyhow, effect sizes appeared to vary across both types of measures, indicating larger depression-related effects on free recall measures of auditory memory ($\tilde{z}$ = 3.181, p < .001, α_{adjust} = .0025) compared to the corresponding recognition measures. Concerning visual memory, depression-related effects on free recall measures turned out to be significantly larger than those on recognition measures in the older adult age group ($\tilde{z}$ = 2.291, p = .011, α_{adjust} = .0125).

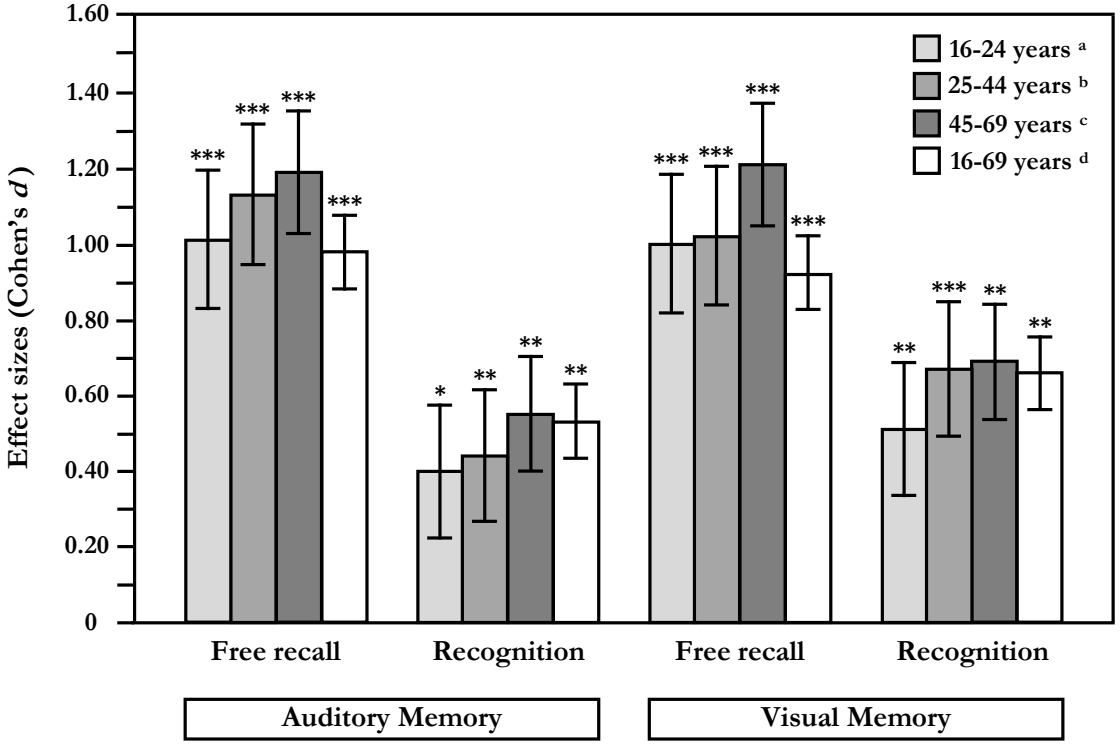

Figure 4.

Depression-related effects on auditory and visual memory measures requiring free recall and recognition across the age groups in Study III.

Note. [a] Adolescents, [b] young adults, [c] older adults, [d] total sample with pooled age groups. Positive values of *d* indicate higher performances of healthy controls compared to depressed patients of the clinical sample. *p < .05/.025/.0167/.0125, **p < .01/.005/.0033/.0025, ***p < .001/.0005/.00033/.00025 (according to Bonferroni-Holm adjusted significance levels).

In conclusion, depression-related effects on episodic memory performance seem to partly depend on the extent to which effortful processing is required. Further on, depression-related effects found on free recall ($Q(2)$ = .524, p > .05; I^2 = 0%) and recognition measures ($Q(2)$ = .441, p > .05; I^2 = 0%) of auditory memory, as well as on free recall ($Q(2)$ = .911, p > .05; I^2

= 0%) and recognition measures ($Q(2) = .627$, $p > .05$; $I^2 = 0\%$) of visual memory were found to be of quite homogenous size across the age groups. Following these findings, episodic memory impairments in depression can thus be suggested to remain stable across different stages in life.

In addition to lower episodic memory performances of depressed patients compared to healthy individuals, the results of Study III also demonstrated depression-related effects on all measures of EF (Wilk's $\lambda = .760$, $F(3, 422) = 44.344$, $p < .001$). This included longer processing times of depressed patients on MC ($F(1, 428) = 37.087$, $p < .0001$, $a_{adjust} = .00025$) and IC ($F(1, 428) = 35.154$, $p < .0001$, $a_{adjust} = .00025$) as well as lower performances of depressed patients on WM ($F(1, 428) = 86.247$, $p < .0001$, $a_{adjust} = .00025$) when compared to healthy controls. These findings support the idea that, because attentional resources in depression are typically used for the retention of disorder-driven cognitions, the amount of those cognitive resources left to be allocated to EF performances is reduced. When comparing depression-related effects across the EF measures, WM turned out to be the most affected by depression ($d = 1.15$), followed by IC ($d = 0.75$), and MC ($d = 0.55$) being the least affected by depression. On the basis of these findings, the question of whether executive dysfunctions may explain episodic memory impairments in depressed individuals could be addressed by statistically controlling for effects of either single or multiple executive functions. Accordingly, results from the regression analyses indicated that executive dysfunctions significantly contributed to both the auditory and visual memory performances either requiring free recall or recognition. In particular, varying processing times on MC significantly contributed to the variations in auditory memory performances requiring free recall ($\beta = -.190$ $p < .001$, $R^2 = .081$) and recognition ($\beta = -.082$ $p < .01$, $R^2 = .022$), as well as to the variations in visual memory performances requiring free recall ($\beta = -.266$ $p < .001$, $R^2 = .204$) and recognition ($\beta = -.137$ $p < .001$, $R^2 = .046$). Concerning IC, varying processing times also significantly contributed to variations in auditory memory performances either requiring free recall ($\beta = -.283$ $p < .001$, $R^2 = .137$) or recognition ($\beta = -.166$ $p < .001$, $R^2 = .051$) and to variations in visual memory performances either requiring free recall ($\beta = -.239$ $p < .001$, $R^2 = .221$) or recognition ($\beta = -.215$ $p < .001$, $R^2 = .082$). Compared to both specific executive functions, varying levels of WM performances provided the largest contribution to variations in auditory memory performances requiring free recall ($\beta = .410$ $p < .001$, $R^2 = .251$) and recognition ($\beta = .252$ $p < .001$, $R^2 = .100$), as well as to variations in visual memory performances requiring free recall ($\beta = .582$ $p < .001$, $R^2 = .363$) and recognition ($\beta = .476$ $p < .001$, $R^2 = .276$).

Despite the aforementioned findings, depression-related effects on certain executive functions could only be confirmed to fully explain depression-related effects on visual memory performances requiring free recall. This means that effects on the latter were found to disappear as soon as single depression-related effects on working memory performances (β = -.068 p > .05, ΔR^2 = .001) and cumulated effects on mental and inhibitory control (β = -.059 p > .05, ΔR^2 = .006) were first taken into account. In consequence, cumulated effects on all three measures of EF also eliminated the variance accounted for by depression in visual memory performances requiring free recall (β = -.044 p > .05, ΔR^2 = .001). This is in line with the assumption that the extent to which executive dysfunctions may explain episodic memory impairments in depression might vary depending on whether specific or more global executive functions are examined. However, it should be noted that the analyses in Study III failed to find any depression-related effects on auditory memory being fully attributable to executive dysfunctioning. Given that the EF measures used in the present research studies are suggested to require visual encoding for the most part, the role of executive dysfunctioning for explaining auditory memory impairments in depression might thus have been slightly underestimated due to unequal task modalities across both measures.

6.3 Effects of recurrent depression on episodic memory (Study IV)

Since previous investigations reported various cognitive deficits in patients with a history of multiple depressive episodes (Lampe et al., 2003), it has been suggested that episodic-memory impairments in depression may vary depending on the number of prior depressive episodes. In their study, Smith, Muir, and Blackwood (2006), for example, found even greater memory-related impairments in patients suffering from recurrent depressive episodes (RD) than in patients experiencing their first depressive episode (MDD). In contrast, other studies could not find any additional effects accounted for by RD (e.g. Lampe et al., 2004). Given that previous studies have already underlined that quite distinct cognitive processes might be affected by MDD and by RD, information-processing has been suggested to be more impaired in patients who have already experienced more than one depressive episode (Lewinsohn, Allen, Seeley, & Gotlib, 1999). Despite the controversial findings on the specific role of RD for memory-related functioning, it is possible that multiple depressive episodes in the past might at least contribute to the development of episodic-memory impairments or even reinforce already existing deficits.

Based on these considerations, the question was raised in Study IV whether changes in episodic memory functioning might also depend on the subtype of depressive disorder. This is due to the fact that although Study III could already demonstrate considerable impairments of depressed patients in different episodic memory components, however, specific patterns of those impairments have not been differentiated between patients with MDD and patients with RD. In contrast to the investigations on a mixed clinical sample in Study III including patients with both subtypes of depressive disorder, the clinical sample in Study IV was first subdivided into two clinical subsamples either comprising MDD or RD patients before being compared with a healthy control sample. In this way, Study IV aimed to clarify whether depression-related effects on auditory and visual memory performances requiring free recall and recognition vary across MDD and RD patients when compared to healthy individuals, or if such effects can be suggested to be generalizable across both subtypes of depressive disorder.

Sample characteristics

For the purposes of Study IV, the neuropsychological data of 215 depressed patients that had already been subjected to the analyses in Study II and Study III was first subdivided into two clinical subsamples, each either including data of MDD patients only or data of RD patients only. To obtain clinical subsamples of equal sizes, data of 15 MDD patients in total were randomly excluded so that each, the MDD subsample (48% women, 52% men) and the RD subsample (53% women, 47% men), finally consisted of 100 depressed patients in total. Among the MDD patients aged between 16 and 69 years, 54% featured additional diagnoses including anxiety disorders (35.5%), substance abuse (4.6%), personality disorders (4.2%), somatoform disorders (3.0%), attention-deficit/hyperactivity disorder (ADHD; 2.4%), obsessive-compulsive disorders (2.2%), and eating disorders (2.1%). At the time of the present investigation, ages of the RD patients ranged between 16 and 68 years and those patients were on average affected by their fourth depressive episode. A total of 48% of them featured additional diagnoses including anxiety disorders (33.7%), substance abuse (8.2%), personality disorders (2.9%), somatoform disorders (1.9%), further affective disorders (1.9%), and obsessive-compulsive disorders (1.0%).

For each of the 15 MDD cases that had initially been excluded from the original clinical sample, the corresponding paired case was additionally excluded from the matched control sample used in Study II and Study III. Accordingly, the final control sample in Study IV consisted of 200 healthy individuals (50.5% women, 49.5% men) aged between 16 and 69

years. In this way, it was ensured that all samples included still featured comparable distributions of gender, age, and education durations even after conducting the aforementioned sample modifications. This was additionally confirmed by Kruskal-Wallis test statistics. Table 6 shows the demographic characteristics of each sample included in Study IV.

Table 6.

Demographic characteristics of the clinical subsamples and the control sample in Study IV

			Age (years)			Education duration (years)		
Sample	**Gender**	***N***	***M***	***SD***	***Min/Max***	***M***	***SD***	***Min/Max***
MDD [a]	Female	48	35.48	15.96	16 / 65	10.17	2.11	7 / 14
	Male	52	33.12	15.66	16 / 69	10.33	1.59	8 / 13
	Total	100	34.25	15.77	16 / 69	10.25	1.85	7 / 14
RD [b]	Female	53	34.17	14.70	16 / 65	10.28	1.57	7 / 16
	Male	47	35.09	14.96	17 / 68	10.62	1.75	8 / 13
	Total	100	34.63	14.88	16 / 68	10.44	1.67	7 / 16
Control [c]	Female	101	35.46	15.23	16 / 65	10.45	1.83	8 / 18
	Male	99	35.92	15.79	16 / 69	10.63	2.06	8 / 17
	Total	200	35.69	15.47	16 / 69	10.54	1.94	8 / 18

Note. [a] Clinical subsample including patients with a major depressive disorder, [b] clinical subsample including patients with a recurrent depression, [c] matched control sample.

Results and discussion

When first analyzing the overall variations across episodic memory performances of the clinical subsamples and the control sample, results of the ANOVAs indicated significant differences between the performances on auditory memory measures requiring free recall ($F(2, 397) = 39.630$, $p < .0001$) and recognition ($F(2, 397) = 17.028$, $p < .0001$), as well as on visual memory measures requiring free recall ($F(2, 397) = 22.986$, $p < .0001$) and recognition ($F(2, 397) = 19.420$, $p < .0001$). Healthy individuals from the control sample were found to show the highest levels of performances on all episodic memory measures, whereas RD patients showed the lowest. Effect sizes for the between-group comparisons across all episodic memory measures are illustrated in Figure 5.

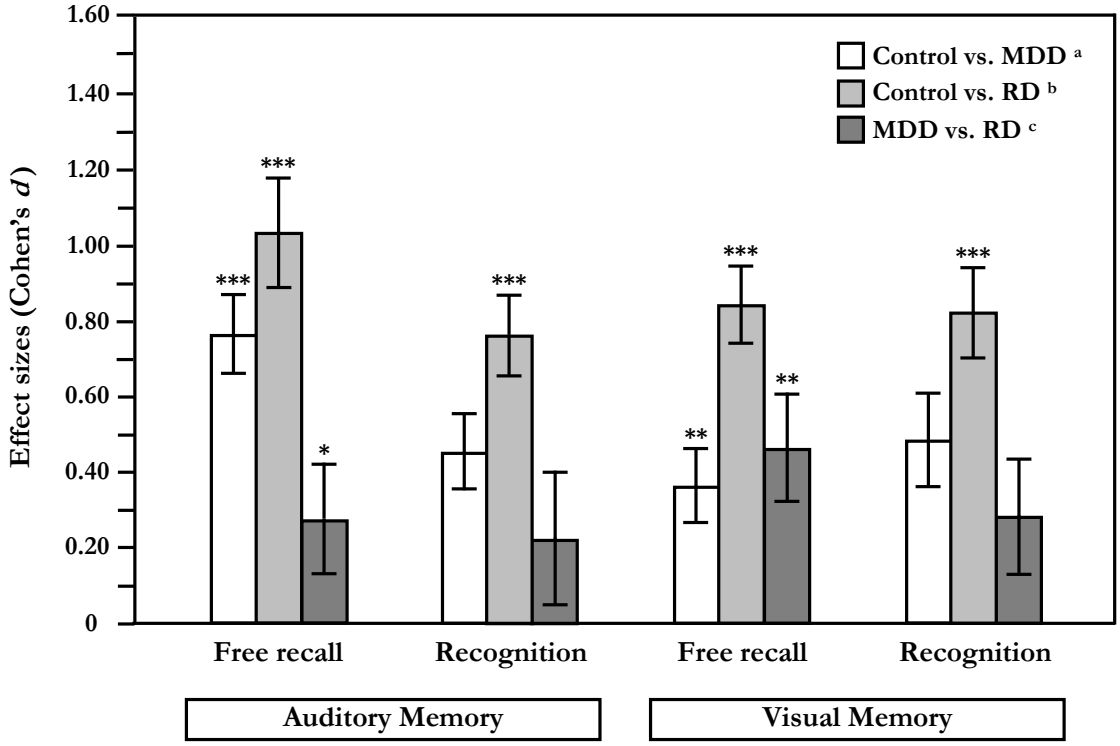

Figure 5.

Depression-related effects on auditory and visual memory measures requiring free recall and recognition across the clinical subsamples and the control sample in Study IV.

Note. [a] Effect for the comparison between healthy controls (Control) and patients with a major depressive disorder (MDD), [b] effect for the comparison between healthy controls (Control) and patients with a recurrent depression (RD), [c] effect for the comparison between patients with a major depressive disorder (MDD) and patients with a recurrent depression (RD). *p < .05/.025 /.0167/ .0125, **p < .01/.005/.0033/.0025, ***p < .001/.0005/.00033/.00025 (according to Bonferroni-Holm adjusted significance levels).

When comparing episodic memory performances across the samples, the largest effect sizes were found for the comparison between performances of RD patients and healthy controls on auditory memory measures requiring free recall (t = 8.447, p < .0003, a_{adjust} = .0003, d = 1.03) and recognition (t = 6.192, p < .0003, a_{adjust} = .0003, d = 1.03), as well as on visual memory measures requiring free recall (t = 6.843, p < .0003, a_{adjust} = .0003, d = 0.84) and recognition (t = 6.659, p < .0003, a_{adjust} = .0003, d = 0.82). For the comparison between healthy controls and MDD patients, significant depression-related effects were also found on the auditory (t = 6.191, p < .0005, a_{adjust} = .0005, d = 0.76) and visual memory performances (t = 2.901, p < .010, a_{adjust} = .010, d = 0.36) requiring free recall. In contrast, performances of healthy controls and

MDD patients turned out to be not significantly different on the recognition measures of auditory (t = 2.003, p > .025, a_{adjust} = .025, d = 0.45) and visual memory (t = 2.013, p > .025, a_{adjust} = .025, d = 0.48). A similar pattern of finding was also found when both clinical subsamples were compared with each other. While RD patients were outperformed by MDD patients on free recall measures of auditory (t = 1.977, p < .05, a_{adjust} = .05, d = 0.27) and visual memory (t = 3.323, p < .005, a_{adjust} = .005, d = 0.46), performances of both clinical subsamples did not significantly differ on recognition measures of auditory (t = 1.859, p > .05, a_{adjust} = .05, d = 0.22) and visual memory (t = 1.873, p > .05, a_{adjust} = .05, d = 0.28).

Moreover, tests of heterogeneity contrasting depression-related effects between both clinical subsamples disclosed that episodic memory impairments tended to be even more pronounced in RD patients than in MDD patients. Although not significant, slightly larger effects were found for the comparison between RD patients and healthy controls on auditory memory measures requiring free recall than for the comparison between MDD patients and healthy controls on the same measures (χ = 1.492, p > .05). However, depression-related effects turned out to be significantly larger for the comparison between RD patients and healthy controls on free recall measures of visual memory (χ = 2.710, p < .01), as well as on recognition measures of auditory (χ = 1.752, p < .05) and visual memory (χ = 1.916, p < .05), than for the comparison between MDD patients and healthy controls on the corresponding measures. In light of these results, it can be concluded that the severity of episodic memory impairments in depression seems to depend on the subtype of depression with RD patients being affected the most. For patients with a history of multiple depressive episodes, such impairments seem to be generalizable across all types of memory measures, whereas episodic memory impairments in MDD patients might be most apparent in the free recall of auditory and visual memory contents.

6.4 Implications for the present research

For comparisons between episodic memory performances of healthy and depressed individuals to be valid, meaningful, and interpretable, clinical utility of the WMS-IV could be confirmed in Study II by establishing sufficient measurement invariance across the clinical and healthy control samples under examination. With the exception of the working memory measure SSP that appeared to be not invariant across both samples, the WMS-IV measures

were finally proved to provide neuropsychological data that means the same for both healthy and depressed individuals.

Under the assumption of construct validity, Study III could then demonstrate that although depressed patients of each age group showed considerable impairments in all components of episodic memory functioning, the ability to recall either auditory or visual memory contents turned out to be more affected by depression than the ability to recognize the same memory contents. The observed moderate to large depression-related effects can thus be suggested to be mostly independent of task modality and to remain stable in size across adolescents, young adults, and older adults. In addition to episodic memory functioning, depression was further shown to negatively influence different executive functions, with working memory being the most affected, followed by inhibitory control and mental control being less affected due to the extent to which cognitive resources were involved. Since these executive functions are generally suggested to require visual rather than verbal processing, depression-related effects on the free recall of visual memory contents were finally found to be caused by deficits in inhibitory control and working memory.

Given that the findings of Study III were based on a mixed clinical sample, the latter was divided into two subsamples in Study IV to contrast the observed effects of depression on episodic memory functioning between MDD and RD patients. Since Study IV disclosed more severe episodic memory impairments in RD patients compared to MDD patients, episodic memory functioning can be at least assumed to deteriorate with an increasing number of experienced depressive episodes. Depression-related effects observed for RD patients were found to be quite similar across auditory and visual memory and, unlike with MDD patients, across free recall and recognition measures as well. While depression was demonstrated to negatively affect performances on all recognition measures in Study III, such depression-related effects turned out to be not significant in size as soon as only the MDD patients were considered in Study IV. This leads to the assumption that, in addition to the number of prior depressive episodes, variations between MDD and RD patients in certain disorder-related characteristics might also contribute to the severity of episodic memory impairments in depression. Based on these considerations, Study V finally aimed to examine the role of different demographic and disorder-related characteristics for episodic memory functioning in depression. The main aspects of this investigation is addressed in the following chapter focusing on the examination of possible risk factors for the development of memory-related impairments in depression.

Chapter 7

Predicting Memory Functioning in Depression

Since Study IV could demonstrate that depression-related effects on episodic memory functioning can even vary in size depending on which type of depressive disorder is examined, it can be assumed that there are further patient characteristics influencing episodic memory performances in depression. On the one hand, taking certain demographic and disorder-related variables into account when examining memory-related impairments in depressed patients could explain why previous investigations have yet failed to provide consistent findings on this topic. On the other hand, examining the effects of those variables on memory-related functioning could also enhance the overall knowledge about possible risk factors for cognitive decline in the course of depressive disorders.

7.1 The role of patient characteristics for episodic memory (Study V)

While possible effects of demographic variables such as age, gender, and education on episodic memory functioning have already been suggested by previous studies, the role of disorder-related variables is less understood. This is due to the fact that although illness duration (Elderkin-Thompson et al., 2011), the number of prior depressive episodes (MacQueen et al., 2002), depression severity (McDermott & Ebmeier, 2009), and medication (Gualtieri et al., 2006) have been considered as potential risk factors for cognitive declines in depression, no serious attempts have so far been made to examine these variables at the same time. However, simultaneously investigating an array of crucial demographic and disorder-related variables in a comprehensive manner is considered indispensable to clearly depict the complex interactions between those variables as well as their adjusted effects on memory-related functioning. Proceeding from these considerations, Study V therefore aimed to simultaneously examine the role of patient characteristics for episodic memory functioning in depression. Given that depression-related effects on certain episodic memory components might vary in size depending on the type of measure used (Study III and Study IV), possible effects of demographic and disorder-related variables were separately examined on measures

either assessing free recall or recognition of auditory or visual memory contents. Moreover, patient characteristics were for the most part not only expected to contribute to varying performances of depressed individuals on episodic memory measures but also on executive functioning measures. Due to the fact that Study III already indicated that impairments in certain episodic memory components are likely to be a result of executive dysfunctioning, it was further aimed to clarify whether patient characteristics also affect executive functioning and whether possible effects of patient characteristics on episodic memory are indirectly caused by such effects on certain executive functions. Among those executive functions that have been examined in Study III, mental control turned out to not sufficiently explain episodic memory impairments in depression, so that only measures of inhibitory control and working memory were subjected to the analyses in Study V.

Sample characteristics

For the clinical sample in Study V, data of 30 depressed patients who had initially denied to provide any personal information during the structured interview (Appendix G) were excluded from the original clinical sample used in Study II and Study III. Additionally, data of the corresponding 30 matched control cases were also excluded from the control sample so that analyses in Study V were finally based on the data of 175 MDD (48%) and RD patients (52%) in the clinical sample and 175 healthy individuals in the matched control sample. A total of 54% of the depressed patients in the clinical sample featured additional diagnoses including anxiety disorders (38%), personality disorders (4%), other affective disorders (4%), somatoform disorders (3%), substance abuse (2%), obsessive-compulsive disorders (2%), and eating disorders (1%). Table 7 shows further patient characteristics including those demographic and disorder-related variables which were relevant for the purposes of the subsequent analyses. When checking for possible gender differences in demographic characteristics, ages ($\chi^2(1, N = 175) = 0.200, p > .05$) and education durations ($\chi^2(1, N = 175) = 1.068, p > .05$) did not differ across female and male patients in the clinical sample. Concerning disorder-related characteristics, gender differences were neither found in illness durations ($\chi^2(1, N = 175) = 0.175, p > .05$), the numbers of prior episodes ($\chi^2(1, N = 175) = 0.783, p > .05$), the levels of depression severity ($\chi^2(1, N = 175) = 2.907, p > .05$), and in the numbers of patients medicated with antidepressants ($\chi^2(1, N = 175) = 1.387, p > .05$), nor in the numbers of patients featuring comorbid disorders ($\chi^2(1, N = 175) = 2.139, p > .05$).

Table 7.

Demographic and disorder-related characteristics of the clinical sample in Study V

	Females (n = 91)		Males (n = 84)		Total (N = 175)	
Patient characteristics	***M (SD)***	***Min/Max***	***M (SD)***	***Min/Max***	***M (SD)***	***Min/Max***
Age (years) [a]	36.30 (16.10)	16 / 68	34.90 (15.24)	16 / 69	35.63 (15.67)	16 / 69
Education duration [b]	10.18 (1.82)	8 / 16	10.67 (1.77)	8 / 17	10.41 (1.82)	8 / 17
Duration of MDD [c]	7.38 (7.93)	1 / 23	7.70 (9.57)	1 / 26	7.54 (8.73)	1 / 26
Number of MDDs [d]	2.89 (2.53)	1 / 10	2.48 (1.97)	1 / 12	2.69 (2.28)	1 / 12
Depression severity [e]	28.38 (9.99)	10 / 43	26.19 (7.78)	5 / 53	26.85 (9.12)	5 / 53
Medication status [f]	79.1		71.4		75.4	
Comorbidity status [g]	49.9		58.3		54.2	

Note. [a] Age at date of examination (in years), [b] number of education years, [c] duration of the current depressive episode (in months), [d] number of prior depressive episodes including the current one, [e] severity of the current depressive episode (BDI-II total score), [f] percentage of patients currently medicated with antidepressants, [g] percentage of patients currently diagnosed with one or more additional diagnoses.

Results and discussion

As has already been suggested by previous investigations, correlational analyses in Study V revealed that most of the patient characteristics including demographic and disorder-related variables were significantly associated with episodic memory and executive functioning in depression. Regarding those demographic variables examined, higher ages and shorter education durations of depressed patients were found to be associated with lower performances on auditory memory measures requiring free recall (r = -.49, p < .01, for age; r = .34; p < .01, for education duration) and recognition (r = -.32, p < .01, for age; r = .21; p < .01, for education duration), visual memory requiring free recall (r = -.55, p < .01, for age; r =

.24; $p < .01$, for education duration) and recognition ($r = -.35$, $p < .01$, for age; $r = .27$; $p < .01$, for education duration), and on the working memory measure ($r = -.48$, $p < .01$, for age; $r = .26$; $p < .01$, for education duration). However, a diminution in inhibitory control only appeared to be significantly associated with shorter education durations ($r = -.31$, $p < .01$). Male gender turned out to be significantly associated with lower performances on auditory memory measures requiring free recall ($r = -.20$, $p < .01$), whereas female gender was found to be associated with lower performances on measures requiring free recall ($r = .21$, $p < .01$) and recognition ($r = .15$, $p < .05$) of visual memory contents as well as on the working memory measure ($r = .30$, $p < .01$). This gender specificity in episodic memory and working memory performances due to females' advantages in verbal ability and males' advantages in visuospatial ability has already been supported by the findings of Study I and is consistent with previous research as well (Sommer et al., 2004).

Furthermore, analyses indicated that most of the disorder-related variables examined were also significantly correlated with performances of depressed patients on episodic memory measures. Thus, longer illness durations, higher numbers of prior depressive episodes, and higher levels of depression severity were found to be associated with lower performances on auditory memory measures requiring free recall (lowest $r = -.17$, $p < .05$, for number of prior depressive episodes; highest $r = -.34$; $p < .01$, for illness duration) and recognition (lowest $r = -.21$, $p < .01$, for depression severity; highest $r = -.25$; $p < .01$, for illness duration and number of prior depressive episodes). In a similar way, disorder-related variables were also associated with performances on visual memory measures requiring free recall (lowest $r = -.23$, $p < .01$, for depression severity; highest $r = -.34$; $p < .01$, for number of prior depressive episodes) and recognition (lowest $r = -.16$, $p < .05$, for number of prior depressive episodes; highest $r = -.20$; $p < .01$, for illness duration). Interestingly, neither medication nor comorbidity appeared to be significantly correlated with any measure of memory-related functioning. While the role of comorbidity for cognitive deficits in depression has not yet been fully understood, the present findings for medication are for the most part in agreement with previous investigations reporting less to no specific effects of antidepressant treatments on cognitive functioning in depressed patients (Borkowska et al., 2007; Kalb et al., 2006). All patient characteristics featuring significant associations with measures of memory-related functioning were finally subjected to a path analysis in order to extend the present correlational findings and to detect potential risk factors for the development of episodic memory impairments in depression.

As illustrated in Figure 6, all path analytical results were summarized within the final SEM-based path model which provided a good fit with the empirical data ($\chi^2(44, N = 175) =$

50.077, $p > .05$; lowest SRMR = .073; lowest RMSEA = .045; highest NNFI = .962; highest CFI = 979). First, these results indicated that, although significant correlations were previously found between demographic variables and all episodic memory measures, age, gender, and education duration directly affected performances on free recall (lowest $\beta = -0.29$, $p < .001$, for gender; highest $\beta = -0.46$, $p < .001$, for age) and recognition measures (lowest $\beta = 0.18$, $p < .05$, for education duration; highest $\beta = -0.25$, $p < .01$, for age) of auditory memory only. In contrast, effects of age and gender on visual memory performances requiring free recall (lowest $\beta_{ind} = 0.17$, $p < .05$, for gender; highest $\beta_{ind} = -0.39$, $p < .001$, for age) and recognition (lowest $\beta_{ind} = 0.12$, $p < .05$, for gender; highest $\beta_{ind} = -0.28$, $p < .001$, for age) were found to be fully mediated by their effects on working memory. As has already been discussed in Study III, this is in line with the assumption that the WMS-IV working memory measure mainly assesses visual processing and is therefore closely connected to measures of visual rather than auditory memory.

When examining the role of disorder-related variables for explaining memory-related functioning in depression, the final path model disclosed that longer illness durations ($\beta = -0.21$, $p < .01$) and higher levels of depression severity ($\beta = -0.27$, $p < .001$) negatively affected performances on the auditory memory measures requiring free recall. However, performances on auditory memory measures requiring recognition were only found to be negatively affected by depression severity ($\beta = -0.19$, $p < .01$). Performances on visual memory measures requiring free recall were negatively affected by higher numbers of prior depressive episodes ($\beta = -0.18$, $p < .05$), while performances on visual memory requiring recognition were neither directly nor indirectly affected by any disorder-related variable. Given that the effects of depression severity on working memory performances turned out to be fully mediated by such effects on inhibitory control ($\beta_{ind} = -0.12$, $p < .05$), it can be concluded that depression-related impairments in working memory functioning might be growing as a result of growing deficits in inhibitory control with increasing levels of depression severity.

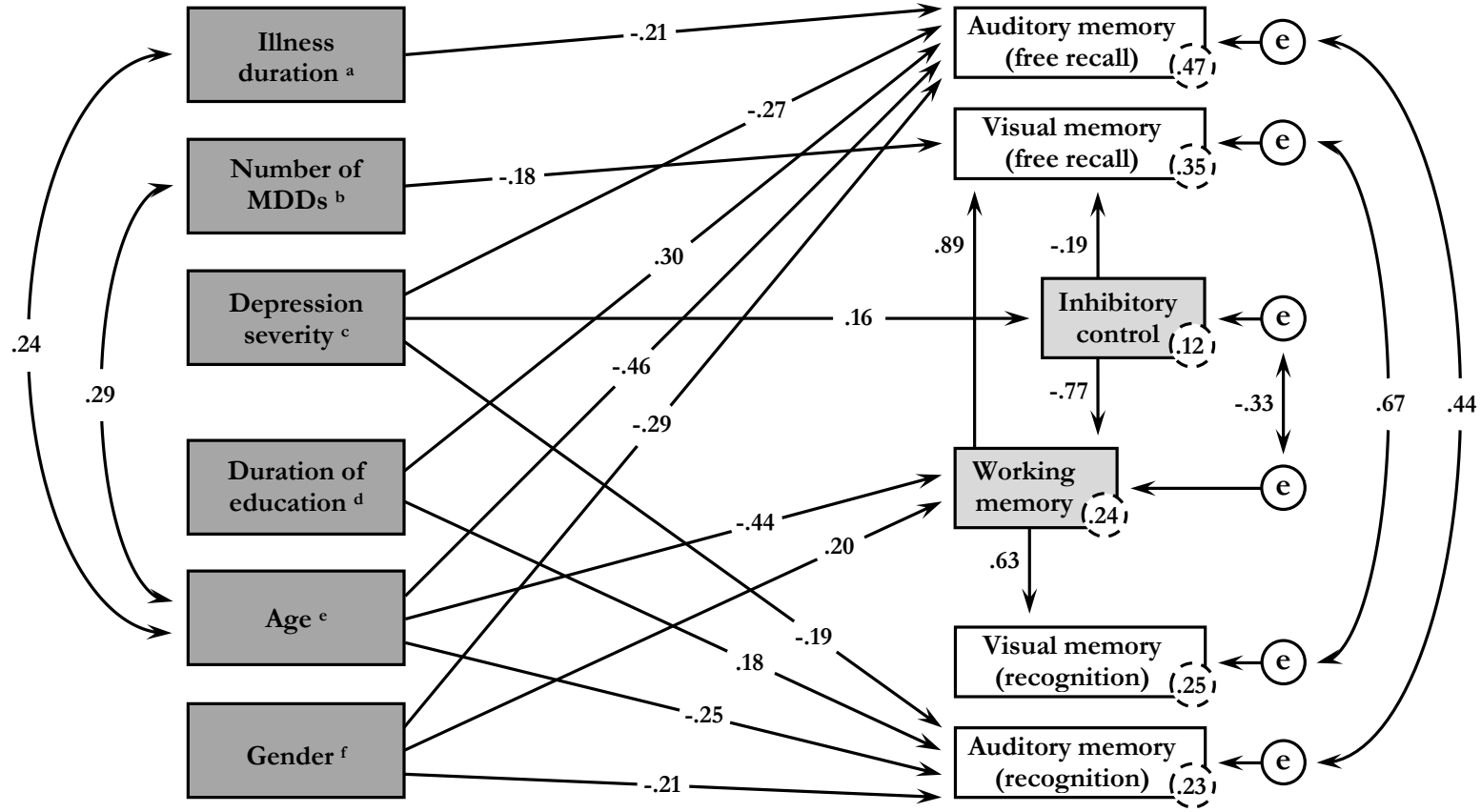

Figure 6.

The final path model including all significant associations among patient characteristics and memory-related functioning measures.

Note. [a] Duration of the current depressive episode (in months), [b] number of prior depressive episodes, [c] depression severity at baseline (BDI-II score), [d] years of education, [e] age at examination date, [f] gender is defined as female = 0 and male = 1. Proportions of explained variances (R^2) are marked by dashed circles. Non-significant paths ($p > .05$) are excluded.

7.2 Implications for the present research

In accordance with the initial expectations, the findings of Study V suggest certain patient characteristics to be, for the most part, strongly associated with several components of memory-related functioning in depression. Moreover, the effects of demographic and disorder-related variables on measures of episodic memory and executive functioning were found to vary in size and direction depending on which types of variables and measures were analyzed. While performances on auditory memory measures appeared to be directly and negatively affected by certain patient characteristics, performances on visual memory measures turned out to be indirectly and negatively affected through the mediation of executive functioning due to similar modalities across both constructs.

It should be noted that the findings of Study IV are slightly challenged by the fact that only higher numbers of prior depressive episodes had a direct and negative effect on performances of visual memory requiring free recall in Study V. As has already been suggested in Study IV, the results of Study V support the idea that episodic memory and executive functioning in depression are likely to be affected by an array of different patient characteristics rather than just by the subtype of depression.

In conclusion, Study V highlights the crucial role of patient characteristics for explaining memory-related functioning in depressed individuals. Given that certain demographic and disorder-related variables were found to sufficiently predict variations in episodic memory and executive functioning, some of those variables could be regarded as possible risk factors for the development and maintenance of cognitive deficits in depression.

Chapter 8

General Discussion

Given that a comprehensive review of the current literature has not yet satisfactorily brought to light whether depressive disorders are really accompanied by specific cognitive deficits, little is still known especially about the link between memory-related functioning and depression. Since cognitive deficits related to depressive disorders may result in severe and long-lasting psychosocial difficulties, it is thus of high relevance to detect those memory-related impairments which may contribute to the development and maintenance of depression. Based on these considerations, the present doctoral thesis goes some way towards enhancing already existing knowledge about the link between episodic memory and depression. Accordingly, the present research studies addressed the questions whether one could suggest depression-specific patterns of episodic memory impairments and whether such impairments are predictable by certain factors related to executive dysfunctions and patient characteristics. Taking due account of the strengths and limitations of each study included, the newly acquired knowledge is finally discussed regarding its implications for future research and clinical practice.

8.1 The present research and newly acquired knowledge

While numerous attempts have been made in the past to demonstrate that depressive symptoms may indeed cause specific cognitive deficits in those individuals affected, not all of the investigations undertaken could confirm this assumption. Consequently, the major aim of the present research was to address the problem of inconsistent empirical findings on this topic by giving special consideration to further relevant but previously less-studied demographic and clinical factors. Clarifying the role of such factors for memory-related impairments in depression could not only explain why previous research has so far provided quite divergent views on this matter but may also give some idea of how depressive symptoms might change cognition in general.

Summary of the present research findings

As summarized in Table 8, the present research included a total of five empirical studies among which the first two were conducted in order to lay the foundations for all subsequent analyses. When examining how certain demographic variables might affect memory-related functioning in healthy individuals, the findings of Study I supported that gender-related effects on different components of episodic memory are a result of gender-specific advantages in verbal and visuospatial ability. These effects were also found to be for the most part homogenous across different age groups. The phenomenon of gender specificity in episodic memory has already been reported by previous research studies proposing environmental factors as possible explanations (Bloise & Johnson, 2007; Herlitz & Lovén, 2009; Herlitz & Rehnman, 2008). Since Study I additionally indicated that gender specificity in episodic memory is even observable among younger age groups, biological differences in brain organization and morphology should also be taken into account when explaining gender-related effects on memory (see Andreano & Cahill, 2009, for an overview). Taking these findings together, Study I finally confirmed that gender and age are indeed crucial factors for episodic memory functioning. Both should thus be closely considered whenever neuropsychological data is collected for research or clinical purposes.

One major aim of the present research was to initially clarify whether depression is really accompanied by severe memory-related impairments. First and foremost, this required the selection and application of a suitable instrument that enables the detection of such cognitive deficits in depressed individuals on the basis of behavioral data. Only if such an instrument could be shown to meet the psychometric criterion of construct validity, group comparisons then allowed to determine whether performances on measures of memory-related functioning significantly differ across a healthy and a clinical group. Addressing this issue, Study II provided evidence that the WMS-IV most likely assesses the same episodic memory components across both groups. The WMS-IV could thus be proved to be a suitable instrument allowing for episodic memory performances to be compared between healthy and depressed individuals. Concerning executive functioning, however, only one out of two WMS-IV working memory measures was found to meet the requirement of measurement invariance so that only performances on this measure were used for group comparisons in all subsequent analyses.

Table 8.

An overview of the major aims, general findings, and specific findings of the present research studies

Study	Major study aims	General study findings	Specific study findings
Study I	• Clarifying the role of age and gender for episodic memory in healthy individuals	• There is a female advantage in auditory and a male advantage in visual memory • Gender specificity in episodic memory is mostly stable across the age groups	• A female advantage in auditory memory is a result of women's higher verbal ability and a male advantage in visual memory is fully explainable by men's higher visuospatial ability
Study II	• Testing for measurement invariance of the WMS-IV as a prerequisite for later group comparisons	• Episodic memory measures provide clinical utility • Working memory measures are only interpretable under reserve	• Episodic memory performances can be compared between healthy and depressed individuals • Only working memory performances on SA can be compared between healthy and depressed individuals
Study III	• Identifying depression-related effects on episodic memory • Clarifying the role of executive dysfunctions for episodic memory impairments in depression	• Depression negatively affects episodic memory and executive functioning • Episodic memory impairments are partly caused by executive dysfunctions	• Depression-related effects on episodic memory are independent of task modality, larger for free recall than for recognition, and stable across the age groups • Deficits in working memory and inhibitory control can explain impairments in visual memory requiring free recall
Study IV	• Checking for depression-related effects on episodic memory in due consideration of the type of depression	• Episodic memory impairments differ across MDD and RD patients • Episodic memory functioning is likely to deteriorate with an increasing number of prior depressive episodes	• RD patients feature more severe episodic memory impairments than MDD patients • Depression-related effects on episodic memory are independent of task modality and deficits in free recall and recognition are only of similar size in RD patients
Study V	• Identifying possible risk factors for the development of memory-related impairments in depression	• Patient characteristics affect memory-related functioning in dependence on which types of variables are examined	• Auditory memory is directly affected by certain patient characteristics and effects on visual memory are mediated by certain executive functions

Note. WMS-IV = Wechsler Memory Scale – Forth Edition, MDD = major depressive disorder, RD = recurrent depression.

The findings of Study III indicated that depression can be suggested to negatively affect episodic memory functioning, whereas, compared to recognition, the resulting deficits were found to be most pronounced in the ability to recall memory contents. According to the cognitive effort hypothesis, this outcome is not surprising given that depressive symptoms have already been shown to diminish especially those memory performances that require effortful processing (e.g. Jermann et al., 2005). Since depression also turned out to negatively affect recognition performances in Study III, it is conceivable that not only automatic but also effortful processes play a role in recognition performances as assessed by the WMS-IV. Even though these findings are in line with the previous literature suggesting that depression-related impairments in episodic memory functioning may already emerge at young ages (e.g. Smith et al., 2006), severity levels of such deficits were currently found to remain stable across different stages in life rather than to increase with age. That is, the effects of cognitive aging on episodic memory turned out to be not different in size between healthy and depressed individuals. In addition to episodic memory impairments, considerable deficits in broad and specific components of executive functioning could also be confirmed to be present in depressed patients. This is compatible with the idea that depressive symptoms may cause structural and functional changes in those prefrontal brain regions that are strongly associated with executive functioning (Alvarez & Emory, 2006). As would be expected from the close connection between both cognitive constructs (e.g. Busch et al., 2005), Study III further revealed that certain executive dysfunctions may likely explain depression-related impairments in episodic memory components of similar modality. Given that several executive processes such as the inhibition of irrelevant information contribute to the encoding and retrieving of episodic memories, executive dysfunctions could even be suggested to be the main cause of memory-related impairments.

Challenging previous studies that reported quite similar levels of memory-related impairments across different subtypes of depression (Lampe et al., 2004), Study IV clearly demonstrated that patients with a history of recurrent depressive episodes are more likely to develop greater impairments than depressed patients suffering from the first episode. On the one hand, depression-related effects on free recall measures of episodic memory were found to be the largest in size for RD patients. On the other hand, recognition ability turned out to be considerably impaired in RD patients, whereas performances of MDD patients on the according measures did not significantly differ from those of healthy individuals. From a biological perspective, varying effects of the neuroendocrine system on memory-related brain regions could at least partially explain why the severity of memory-related impairments likely

depends on the specific subtype of depression. An increasing number of depressive episodes might lead to a more frequent exposure to abnormally high cortisol levels, thus causing greater cognitive deficits due to hippocampal atrophy (e.g. Thomas et al., 2007).

It should be noted that the number of prior depressive episodes is only one among several crucial variables being suggested to negatively impact cognitive abilities in depression. Thus, the final research study was conducted in order to determine the role of further demographic and disorder-related variables for memory-related functioning in depression. With reference to the findings of Study III and Study IV which suggested memory-related impairments to likely represent attendant symptoms in depressed patients, Study V aimed to additionally identify those characteristics in depressed patients which could be regarded as possible risk factors for the development of episodic memory impairments. Among those factors, demographic characteristics such as higher ages, shorter durations of education, and male gender turned out to predict lower levels of auditory memory either requiring free recall or recognition. This could already be expected by the findings of Study I on healthy individuals. Against the background that depression-related impairments in episodic memory appear to remain quite stable across different age groups (Study III), age-related effects in Study V should be interpreted with caution. That is, age seems to be strongly related to cognitive functioning in general and regardless of whether individuals are depressed or not. Unlike with auditory memory, the effects of age and gender on visual memory performances were found to be fully mediated by their effects on working memory, thus emphasizing the role of task modality. The executive functioning measures used in the present research, at least for the most part, rely on visual rather than auditory processes. Keeping this in mind, it is conceivable that the effects of age and gender on auditory memory might also be fully mediated by executive functioning performances requiring auditory processing. Provided that task modality is controlled, this would further support the idea that executive dysfunctions are the main cause for episodic memory impairments in depression (Joormann, 2005). The results of Study V further indicated that higher levels of depression severity likely predict lower performances on auditory memory requiring either free recall or recognition as well as longer processing times in inhibitory control. By contrast, longer illness durations were only found to be associated with lower auditory memory performances requiring free recall. According to the cognitive effort hypothesis, one explanation could be that illness duration most likely affects those episodic memory performances that require effortful processing, whereas depression severity exerts a general effect on episodic memory functioning regardless of whether effortful or automatic processing is demanded. Moreover, the results of Study IV should be put into perspective due

to the fact that in Study V the number of prior depressive episodes turned out to only affect performances on visual memory measures requiring free recall. Nevertheless, the findings of both studies are not necessarily considered to be contradictory, given that the path-analytical approach in Study V serves as a kind of extension of Study IV. Hence, it can be concluded that, compared to MDD patients, severe episodic memory impairments in RD patients are not only caused by the mere number of recurrent depressive episodes. Instead, it is more likely that there were more differences between the MDD and RD patients examined than just in the number of prior depressive episodes experienced.

Although episodic memory impairments are said to arise from many pathological conditions that affect different brain regions rather than being exclusive to depression (see Hodges, Erzinclioglu, & Patterson, 2006, for a review), the present research could nevertheless highlight the link between depression and memory-related functioning. Above and beyond this, the present research claims that depression-related effects on episodic memory functioning should always be predicted or interpreted in the context of further contributing conditions. Only if certain associations between demographic backgrounds, disorder-related characteristics, and relevant memory-related components are taken into consideration, questions regarding the development and maintenance of episodic memory impairments in depression can be clarified without ambiguity.

Strengths and limitations of the present research studies

Even though the first major literature reviews have already suggested a considerable impact of depression on cognitive, perceptual, and motor functioning a long time ago (see W. R. Miller, 1975, for an overview), investigations have just recently begun to focus on the complex nature of cognitive dysfunctions in depression (e.g. Braw et al., 2011; Gohier et al., 2009; Matthews et al., 2008). Given that investigations on this topic for the most part appear to be quite fragmentary and inconsistent, the main purpose of the present doctoral thesis was to enhance knowledge about cognitive functioning in depression on an empirical basis. Compared to previous investigations, the present research studies thus aimed to provide a comprehensive and more differentiated view on which specific memory-related impairments are likely associated with depression. This mainly required several methodological improvements on previous studies in order to clarify unresolved issues from the past. Among those improvements, the use of a widely accepted neuropsychological assessment instrument is worth mentioning. When examining the role of age, gender, and depression on memory-

related functioning, for example, previous research mostly focused on single cognitive components and isolated the processes involved using a large variety of different assessment tools rather than applying an entire test battery that would offer the examination of multiple memory-related functions at the same time. In contrast, the present research studies could demonstrate that the WMS-IV provides multiple episodic memory measures that allow for comparisons between auditory and visual memory and between free recall and recognition performances. Using the WMS-IV as a multifaceted instrument additionally provides the opportunity to draw conclusions from the performances on more narrow executive functioning measures such as inhibitory control. Not only that the general use of neuropsychological test batteries may generate a coherent picture of the current levels of cognitive functioning, it also allows to obtain a holistic and therefore more realistic representation of the examinees' current cognitive statuses.

Apart from the application of advanced statistical methods, another strength of the present research, although exclusively relying on cross-sectional data, is to be seen in its cumulative structure comprising empirical studies which are successively built upon each other. The decision to follow a hierarchical step-by-step approach as illustrated in Figure 7 enabled the thorough exploration of relevant sample characteristics, particularly age and gender, which were suggested to exert an effect on memory-related functioning (Study I). These variables, once identified, could then be considered in subsequent studies by either statistically controlling for or by including them in later analyses. Since testing for construct validity of the neuropsychological instrument used has been widely disregarded in previous investigations, establishing measurement invariance of the WMS-IV was considered necessary before proceeding with any between-group comparisons (Study II). While episodic memory impairments could then be detected by comparing the performances of depressed patients with those of healthy individuals on the according memory measures in Study III, Study IV additionally provided a more differentiated view by taking the subtype of depression into account. In Study V, these findings were finally extended by conducting a comprehensive path analysis in order to clarify the role of demographic and disorder-related variables for memory-related impairments in depression.

Despite the aforementioned strengths of the present research studies, there are certain methodological issues that also need to be considered when interpreting the study findings. Therefore, general limitations are first addressed before specific shortcomings of the present research studies are discussed in the following.

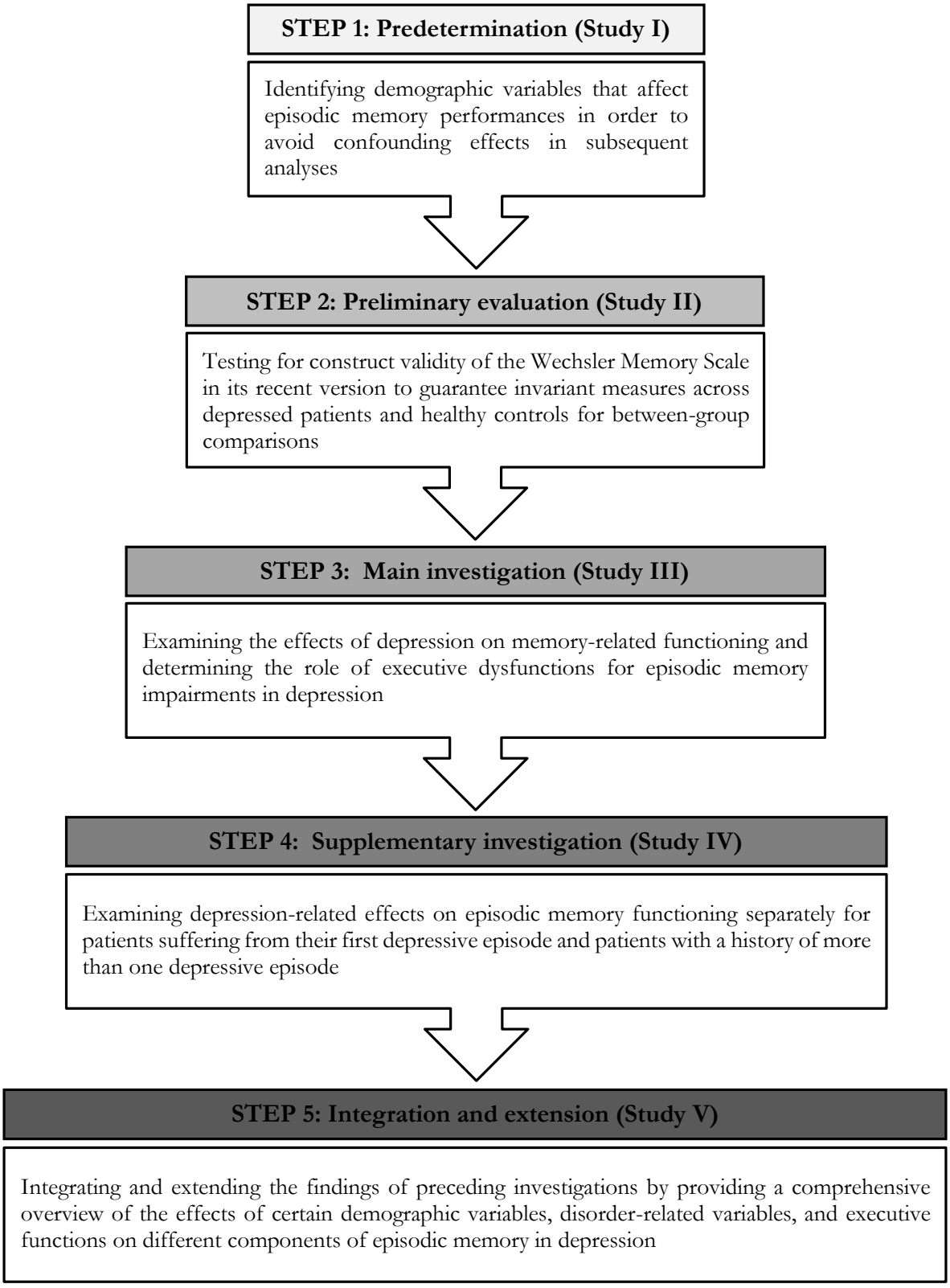

Figure 7.

The hierarchical step-by-step approach indicating the cumulative structure of the present research.

General limitations

While the healthy control sample was derived from the large and representative standardization sample of the WMS-IV, the first limitation rather pertains to the recruitment procedure required for composing the clinical sample. According to predefined inclusion and exclusion criteria, depressed patients aged between 16 and 69 years had been recruited by previously selected inpatient and outpatient centers. In this way only those depressed patients had finally been invited to take part in the research project who were intrinsically motivated to do so on a voluntary basis and were, in a certain sense, not randomly assigned to the clinical sample. Conversely, it is conceivable that depressed patients suffering from more or less severe cognitive impairments had not been included in the present research from the outset due to a lack of willingness and compliance. Even though later dropouts could be avoided this way, a recruitment procedure like this might nevertheless have led to a biased and not representative composition of the clinical sample.

Another issue that should also be discussed in this context directly refers to the varying sample sizes across the present research studies. Although the original clinical sample was slightly over-sampled according to power analysis to capture as many suitable depressed patients as possible, certain study samples still appeared to be small in size. In Study II and Study V, for example, the validity of crucial factor-analytical and path-analytical outcomes could thus have been increased by using neuropsychological data of a larger sample size. Although being still in an acceptable range, only small sample sizes could further be obtained especially when both the clinical and healthy control samples were subdivided into different age groups (Study III), thus compromising the generalizability of the study results. Nevertheless, recent research focusing on sample size requirements for structural equation models claim that, with respect to the number of parameter estimates in a given model, detecting moderately high effect sizes might even require smaller sample sizes than would be expected by commonly known rules of thumb (Wolf, Harrington, Clark, & Miller, 2013). In addition to those limitations which might have resulted from a less favorable recruitment procedure and sample composition, another shortcoming of the present research refers to more general characteristics of the chosen research design. Given that the present research findings are totally based on cross-sectional data, thus not implying causality, it is impossible to definitely clarify whether memory-related impairments could be suggested as premorbid markers of depression or whether depressive symptoms are preceding such cognitive deficits.

Despite the fact that all statistical analyses included in the present research were based on neuropsychological data that was obtained from a comprehensive test battery, the use of WMS-IV measures does not only provide advantages but should also be critically scrutinized. First, it has to be mentioned that the use of a single neuropsychological test battery restricts quantitative data by those subtests included, thus bearing the risk of limiting the generalizability of findings. Since the results of the present research strictly depend on the selection of the memory tasks used, it somehow appears to be difficult to compare them to the findings of previous investigations. Second, and perhaps even more important, the WMS-IV does not allow for direct comparisons between the memory scales included since auditory and visual memory tasks are not only different in their modality but also in their contents. Therefore, it is quite difficult to determine whether those age-, gender-, and depression-related effects that were found to vary in size or direction across the auditory and visual memory performances were exclusively caused by the respective modalities. In this context, crucial limitations of those WMS-IV and BCSE tasks which were used to assess executive functioning should also be as critically regarded as in the case of episodic memory. Since there is still no consensus in literature of how to define and grasp the concept of executive functioning (Morton, Ezekiel, & Wilk, 2010), it remains questionable if those specific and broad executive functions used in the present research are conceptually distinguishable rather than just representing two sides of the same coin (Mostofsky & Simmonds, 2008). And even if they represent different concepts, interpretations on the basis of executive functioning measures included in the WMS-IV and BCSE are likely to be restricted by the task-specific processes required. Thus, the effects of executive functions on certain episodic memory components could also be biased by the mere fact that the measures for working memory, mental control, and inhibitory control for the most part require visual processing and the WMS-IV does in turn not provide any equivalent measures demanding auditory processing to the same extent. This leads to the conclusion that it was impossible to examine depression-related effects on auditory components of executive functioning as well as to determine the role of such executive functions for episodic memory impairments in depression within the scope of the present research.

Specific limitations of the present research studies

Beside the more or less general limitations outlined above, there are further methodological shortcomings specific to each single research study that need to be mentioned as well. Regarding subgroup comparisons, one issue in Study I is that the rationale for binning healthy individuals into three different age groups could be called into question. For

methodological reasons, the original nine age subgroups of the standardization sample were pooled to obtain three broader age groups in order to avoid insufficiently small sample sizes and significantly different age distributions across female and male examinees within each single age group. However, it could be argued that the age ranges for adolescents (16 to 25 years), young adults (25 to 44 years), and older adults (45 to 69 years) are too wide to draw meaningful conclusions about the effects of age or the stability of gender-related effects on episodic memory functioning over time.

Another issue that arises refers to the overall clinical utility of the WMS-IV which has been partially supported by the findings of Study II. Although measurement invariance of this test battery could be established on the basis of factor-analytical procedures, thus allowing for later comparisons between clinically depressed and healthy individuals, however, such results are likely restricted to the characteristics of those samples being analyzed. With special regard to sampling error, this means that the fit of the empirically derived data to a given theoretical model might easily change when conducting a simulation study. Furthermore, it has to be considered that, although both samples were matched by relevant demographic variables, further characteristics related to depression were left uncontrolled in the clinical sample. Accordingly, it is conceivable that the effects of different subtypes of depression, illness duration, depression severity, and comorbidity could have confounded performances especially on the WMS-IV working memory measures. Therefore, it remains to be clarified whether the nonequivalence found for the subtest SSP is a result of conceptual differences in working memory functioning between depressed patients and healthy individuals or if it simply reflects nothing but a sample selection bias.

Furthermore, those depression-related effects that were found on different components of memory-related functioning in Study III should also be interpreted with caution. First, the findings implicate that depression tends to negatively affect episodic memory functioning independent of task modality and relatively stable across different age groups. And although depression-related effects were found to be the largest in size for free recall, thus being consistent with the cognitive effort hypothesis, recognition performances also appeared to be considerably low for depressed patients. As has been discussed earlier, a possible explanation might be that recognition as measured by the WMS-IV also requires effortful processing. In contrast, this may also be due to the fact that the WMS-IV measures requiring free recall and recognition are highly interdependent. Since episodic memory subtests are administered in the same order according to the predetermined sequence of the WMS-IV, each free recall task was always followed by the corresponding recognition task including the same

content. With due respect to possible task order effects, it should be taken into account that the first presentation of the contents to be recalled might have facilitated the recognition of the same contents for depressed patients later on.

While it may be concluded from the findings of Study IV that RD patients are most likely to develop more severe episodic memory impairments than patients diagnosed with an MDD, however, the results do not allow to make general statements about the true cause of this phenomenon. From a methodological perspective, the lack of clarity can be attributed to the fact that, although the clinical and control samples were initially matched for age, gender, and education duration, the clinical groups of MDD or RD patients were not sufficiently checked for any differences in their disorder-specific characteristics. That is, beside the number of prior depressive episodes, further differences between both groups of patients, such as in illness duration, depression severity, medication, and comorbidity, could be suggested to additionally contribute to varying levels of episodic memory impairments across the MDD and RD patients.

Finally, Study V aimed to extend the findings of Study III and Study IV by comprehensively examining possible risk factors for the development of episodic memory impairments in depression. When interpreting the effects of certain demographic and disorder-related variables within a complex path model, however, one should bear in mind that the results in Study V greatly depend on those variables included in the model. This means that, albeit aiming to imply causality, the final path model just portrays a simplified picture of which constellation of patient characteristics is likely to increase the risk for depressed individuals to develop certain episodic memory impairments over the course of the disease. Against this background, it is indispensable to examine the role of further proximal and distal determinants, such as those being associated with medical or psychotherapeutic treatments for example (Culang et al., 2009; Naismith, Redoblado-Hodge, Lewis, Scott, & Hickie, 2010), in order to obtain a more complete picture of the link between depression and memory-related functioning.

8.2 Main conclusion and future directions

In general, the present doctoral thesis provides an array of empirical findings that extend the existing knowledge on the complex nature of cognitive functioning in depression. Even though difficulties in several memory-related functions are often reliably observed with

the onset and progression of depressive episodes (Matthews et al., 2008), little has so far been done to come to an agreement on a characteristic cognitive profile in depression. In this regard, this thesis goes some way towards providing an initial understanding of the link between memory-related functioning and depression. Among those memory-related functions, episodic memory has been suggested to be affected the most by depressive symptomatology (Ahdidan et al., 2011; Cheng et al., 2010; Pu et al., 2011; Tae et al., 2011). Since the empirical findings on this topic still appear to be quite inconsistent, the present research studies aimed to gradually indicate the extent to which depression might be accompanied by deficits in episodic memory. On the basis of certain cognitive and neuropsychological explanations discussed earlier, the present research also provides possible approaches that help clarify why some depressed individuals are affected by such impairments while others are not.

Concluding from the empirical findings of the present thesis, there are now reasonable indications for depressive symptomatology to represent a condition that negatively affects cognitive ability in general and episodic memory functioning in particular. Accordingly, it could be demonstrated that even depressed patients who have already gained access to healthcare services may develop such episodic memory impairments in the course of the disorder. Moreover, certain executive dysfunctions could be identified to explain declines especially in those episodic memory components that mostly require effortful processing. Given that depressed individuals may, but do not necessarily have to develop cognitive deficits, the risk for the development and maintenance of episodic memory impairments in depression was shown to strongly depend on further conditions associated with demographic and disorder-related characteristics. For each individual patient, considering the constellation of those characteristics might then help predict whether certain cognitive deficits are likely to occur over the course of a depressive disorder.

The present doctoral thesis at least reinforces the need of taking memory-related impairments into consideration when developing individualized therapeutic treatment plans to improve social and cognitive functioning in depressed patients. Indeed, memory-related impairments may have a large impact, not only for the working and social lives of the affected individuals, but also for society as a whole. This very fact stresses the need for conducting further research and the importance of improving neuropsychological instruments for early detection and adequate treatment of cognitive dysfunctioning in depression. Concerning the latter, the WMS-IV could finally be shown to provide clinically useful measures that are at least sensitive enough to detect certain memory-related impairments in depressed patients.

Implications for future research

In light of the limitations that have been discussed earlier, there are still some remaining issues where clarifications could be given to by future research. Concerning recruitment procedure and sample composition, it is recommended for future studies to collect neuropsychological data from carefully selected depressed patients within a large-scale project in order to minimize sampling and measurement errors. The examination of population-based samples in addition to those exclusively drawn from a clinical population should further enable to obtain a randomized and thus more representative sample framework. Given that it is extremely difficult to draw causal inferences from cross-sectional data, longitudinal studies might thus help determine whether those memory-related impairments currently found should be regarded either as a result or a cause of depression. By systematically monitoring one group of depressed patients, clinical follow-up studies would also provide the opportunity to closely examine how certain episodic memory impairments that are detected at baseline progress and what influences its prognosis. In particular, this could then help determine to what extent episodic memory impairments develop subsequent to disorder onset, whether such deficits are the result of progressive effects over the course of illness, and to what extent they might precede the onset of depressive episodes. An approach like this would finally give a deeper insight into the mechanisms that underlie cognitive aging in depression.

As far as possible and reasonable, it is further recommended for future studies to initially consider all relevant factors that might affect the specific topic under investigation. In addition to the selection of appropriate assessment tools, this especially requires a precise definition of those demographic and disorder-related variables that are associated with cognitive dysfunctioning in depression. Following this, demographic characteristics such as age, gender, and education, as well as disorder-related characteristics describing illness duration, depression severity, medication, and comorbidity, should then be either controlled for or subjected to more extensive investigations.

Depending on the specific topic under investigation, it is further important to initially decide how to assess cognitive functioning in depressed individuals so that outcomes are meaningfully interpretable afterwards. Although some researchers often chose to apply an array of single subtests selected from different neuropsychological test batteries in order to obtain as many differential information as possible, in most cases, however, this strategy is hardly conducive to achieve the intended objectives. Given that findings from the

corresponding measurement data might likely be flawed by psychometric inadequacies of the subtests used and therefore inconclusive at all (Goldstein & McNeil, 2004), neuropsychological examinations in clinical settings would thus lead to unnecessary effort with negligible benefit for those involved. In contrast, fully applying neuropsychological test batteries, if possible, has the advantage to create a more reliable and holistic picture of the cognitive functions under examination. Despite all advantages, even those test batteries should be selected and applied with the utmost caution. For instance, it has to be noted that the proven WMS-IV used in the present research does not assess any executive functions requiring auditory processing. Therefore, it is advisable for all subsequent investigations to additionally provide the according data in order to fully determine the role of executive functioning for episodic memory impairments in depression. In order to solve further issues related to the WMS-IV assessment procedure, future studies using comparable test batteries should first check whether performances on measures requiring free recall and recognition can be suggested to be, at least for the most part, independent of each other. Finally, it is recommended for future research to control for possible order effects on episodic memory functioning by manipulating the sequence of presentation or by using independent measures of free recall and recognition.

Implications for the clinical practice

As described in the introduction section of the present doctoral thesis, enduring cognitive dysfunctions such as severe memory-related impairments can have far-reaching implications for individuals suffering from depressive disorders. Currently, such cognitive declines are even suggested to play an important role in functional recovery for those affected (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Fortunately, a growing body of research has already demonstrated that relevant cognitive functions related to attentional processes and memory could at least be trained in healthy individuals of different ages (E. A. Holmes, Lang, & Shah, 2009; Tran, Hertel, & Joormann, 2009; Wadlinger & Isaacowitz, 2008). Regarding memory-related impairments in depression, promising new studies found that cognitive training was strongly associated with changes in memory-related functioning that were later accompanied by a significant reduction in depressive symptoms (Raes, Williams, & Hermans, 2009; Watkins, Baeyens, & Read, 2009). In line with the findings of the present research on the role of executive functioning for depression, some investigations also emphasized that brief interventions targeted at increasing inhibitory control may be an effective treatment in depression (Joormann, Hertel, LeMoult, & Gotlib, 2009; Siegle, Ghinassi, & Thase, 2007).

Accordingly, a comprehensive examination of memory-related dysfunctions and an early detection of those variables that affect memory in depressed individuals is of significant clinical value. In clinical settings, for instance, cognitive and behavioral strategies that were trained as part of therapeutic treatments might not be appropriately learned by depressed patients due to deficits in keeping contents with temporal-spatial contexts in mind. Besides this, the identification of certain patterns of episodic memory impairments in particular may further extend the knowledge about depression-specific cognitive profiles. This knowledge would allow for preliminary assumptions about the development of certain cognitive deficits over the course of the disorder which could then be used to adjust individual intervention strategies in order to ensure treatment efficacy.

However, it sometimes might be quite a hard challenge for clinicians to distinguish between memory-related impairments as a concomitant effect of cognitive aging and impairments as a possible result of depression. As the findings of the present research indicated, an array of different demographic and disorder-related variables should always be considered for each individual case when aiming to determine whether cognitive deficits are of clinical significance. For this purpose, neuropsychological assessments may provide an objective pre-treatment identification of depression-related deficits in cognitive functioning and further influencing factors. Supplementary to other diagnostic tools including self-reports and behavioral observations, such assessments could therefore be considered as part of routine patient evaluation in psychiatric context. Bearing in mind that such cognitive dysfunctions might significantly reduce the overall adaptive functioning, treatment compliance, response to treatments, and rehabilitation (Greer et al., 2010), the role of fully standardized assessment tools becomes increasingly more important to improve clinical decision making. Therefore it is advisable for comprehensive neuropsychological examinations in clinical settings to include an administration of intrinsically performance-based neuropsychological tests (see P. D. Harvey et al., 2007; Lezak, Howieson, & Loring, 2004, for overviews). Although additional self-reports and behavioral observations may indeed provide critically important information, these are often affected and confounded by the presence of neuropsychiatric conditions, thus having less value than standardized psychometric tests (Bowie et al., 2007). The latter aim to objectively assess individual strengths and, even more importantly, enable possible deficits to be detected in different cognitive domains. Thoroughly using standardized assessment tools could thus contribute to the quality of therapeutic programs by enabling more target-oriented and efficient treatments that are adaptable to the patients' needs.

In this context, it could be argued that neuropsychological assessment is time-consuming and requires the patients examined to remain sufficiently concentrated and persevering throughout the entire testing session. In the present doctoral thesis, however, clinical utility could be confirmed for the WMS-IV which is only one among numerous standardized assessment instruments available. The WMS-IV offers two different test versions, the WMS-IV Adult battery for the examination of young adults aged between 16 and 69 years and the slightly modified and shortened WMS Older Adult test battery for the examination of elder adults in the age range of 65 to 90 years. As both test versions overlap for the age range of 65 to 69 years, the WMS-IV allows examiners to individually select the most appropriate version for patients at these ages. Having the opportunity to choose a shorter test version may improve the usability of the WMS-IV by reducing possible interferences such as fatigue and loss of motivation, thus ensuring psychometric functioning of the WMS-IV. An interesting approach to facilitate the practice of neuropsychological assessment in psychiatric contexts has also been presented by Iverson, Brooks, and Young (2009) who proposed to use computerized test batteries in adjunct to traditional methods to make assessments more feasible in clinical practice.

Given that the general benefits of neuropsychological assessment strategies have not yet been fully recognized in clinical practice, the present doctoral thesis at least aims to raise awareness for the diagnostic value of detecting memory-related dysfunctions in depressed individuals as early as possible. Therefore, the quintessence is that possible effects of episodic memory impairments on the everyday lives of depressed individuals should by all means be a focus of evaluation and ongoing treatment. It is very likely that especially those intervention programs and rehabilitative treatments that enhance cognitive functioning in addition to relieving depressive symptoms may finally lead to the best functional outcomes.

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Appendices

Appendix A

Study I

Pauls, F., Petermann, F., & Lepach, A. C. (2013). Gender differences in episodic memory and visual working memory including the effects of age. *Memory, 21*, 857-874.

Appendix B

Study II

Pauls, F., Petermann, F., & Lepach, A. C. (2013). Memory assessment and depression: Testing for factor structure and measurement invariance of the Wechsler Memory Scale – Fourth Edition across a clinical and matched control sample. *Journal of Clinical and Experimental Neuropsychology, 35*, 702-717.

Appendix C

Study III

Pauls, F., Petermann, F., & Lepach, A. C. (2014). Episodic memory and executive functioning in currently depressed patients compared to healthy controls. *Cognition and Emotion*. Advance online publication. doi: 10.1080/02699931.2014.915208

Appendix D

Study IV

Pauls, F., Lepach, A. C., & Petermann, F. (2013). Depression und Gedächtnis: Gedächtnisleistungen im Vergleich zwischen Depressiven und Gesunden. [Depression and memory: Comparison of memory performances in depressive and healthy adults]. *Gesundheitswesen, 75*, 754-760.

Appendix E

Study V

Pauls, F., Lepach, A. C., & Petermann, F. (2014). *The role of patient characteristics for explaining episodic memory and executive functioning in depression: A path-analytical approach*. Manuscript submitted for publication.

Appendix F

Description of the WMS-IV

Table F1.

Description of the episodic memory measures included in the Wechsler Memory Scale – Fourth Edition

Table F2.

Description of the executive functioning measures included in the Wechsler Memory Scale – Fourth Edition

Table F1.

Description of the episodic memory measures included in the Wechsler Memory Scale – Fourth Edition

Scale	Subtest	Condition	Subtest description	Scoring procedure	Raw scores
Auditory memory	**Logical Memory (LM)**	free recall	LM measures memory for narrative stories. For each of two different stories, the examinee has to retell the plot immediately (LM I) or after a 20- to 30-minute delay (LM II) using as many details as possible.	One score point is awarded for each correctly recalled detail.	LM I = 50 LM II = 50
		recognition	By responding to 15 yes-or-no questions about each of the LM stories, the examinee has to judge whether certain contents are true or false.	One score point is awarded for each correct answer.	LM = 30
	Verbal Paired Associates (VPA)	free recall	VPA measures memory for word pairs. After a verbal presentation of 14 word pairs in each out of four trials, the examinee is cued with the first word of each pair and has to respond with the associated second word immediately (VPA I) or after a 20- to 30-minute delay (VPA II).	One score point is awarded for each correctly recalled second word.	VPA I = 56 VPA II = 14
		recognition	The examinee is read a list of 40 word pairs and asked to identify each as either one of the previously presented VPA word pairs, responding with 'yes', or as a new word pair, responding with 'no'.	One score point is awarded for each identification.	VPA = 40
Visual memory	**Designs (DE)**	free recall	DE measures spatial memory for visual images. After a presentation of grids with abstract designs, each grid is removed and the examinee has to reproduce the display immediately (DE I) or after 20- to 30-minute delay (DE II) by selecting the correct designs from a set of cards and placing them in a blank puzzle grid in their correct location.	One score point is awarded for each correct design and each correct location. Two bonus points are given if both criteria are met.	DE I = 120 DE II = 120
		recognition	For each 4 x 4 grids including target and distractor designs, the examinee has to identify those two designs which had been presented in DE I.	One score point is awarded for each identified design.	DE = 24
	Visual Reproduction (VR)	free recall	VR measures visual memory for geometric designs. After one out of five figures is presented and removed, the examinee has to draw it from memory immediately (VR I) or after a 20- to 30-minute delay (VR II).	Scoring procedure is based on standardized criteria for presence and accuracy.	VR I = 43 VR II = 43
		recognition	Each of a total of seven identification tasks require the examinee to select one out of six figures which was already presented in VR I.	One score point is awarded for each identified figure.	VR = 7

Table F2.

Description of the executive functioning measures included in the Wechsler Memory Scale – Fourth Edition

Scale	Subtest	Subtest description	Scoring procedure	Raw scores
Executive functions (broad)	**Spatial Addition (SA)**	SA measures working memory and requires storage and manipulation of visuospatial information. After two grids featuring different patterns of red and blue dots are presented one after the other in each of a maximum of 24 items, the examinee is then asked to create a pattern by placing red, blue, or white dots in a blank grid following a series of certain rules.	One score point is given for each correctly solved item and only if all correct dots are placed in the correct location according to the predefined rules.	SA = 24
	Symbol Span (SSP)	SSP measures working memory for a visual sequence of abstract symbols. First, an array of different symbols is presented to the examinee in each of a maximum of 26 items. After the array is removed, the examinee is shown a set of target and distractor symbols and asked to identify those previously shown in the correct order.	Two score points are given for each correctly solved item and only if all correct symbols are identified in the correct order. One score point is given for the correct symbols in the incorrect order.	SSP = 26
Executive functions (specific)	**Mental Control (MC)**	MC measures the ability of retrieving and mentally manipulating already existing knowledge. After being asked to count backwards from 20 to 1 as fast as possible, the examinee is then asked to name the months of the year in reverse order.	Up to four score points are awarded depending on the processing time needed and up to eight score points are awarded depending on the error rate.	MC_{time} = 4 MC_{error} = 8
	Inhibitory Control (IC)	IN measures the ability to inhibit irrelevant behaviors in favor of goal-oriented actions. In the first trial including compatible stimulus-response-mappings with a total of 24 symbols (rectangles or triangles), the examinee has to name the correct symbols in the sequence in which they appear. In the second trial the examinee has to say 'triangle' whenever a rectangle appears and vice versa.	Up to four score points are given depending on the processing time needed, up to four points are given depending on the number of missing responses, and up to eight points are given depending on the error rate.	IC_{time} = 4 IC_{miss} = 4 IC_{error} = 8

Note. MC_{time} = Obtainable raw score on MC for the processing time needed, MC_{error} = Obtainable raw score on MC for the error rate, IC_{time} = Obtainable raw score on IC for the processing time needed, IC_{miss} = Obtainable raw score on IC for the number of missing responses, IC_{error} = Obtainable raw score on IC for the error rate.

Appendix G

Structured Interview

Anamnese

-Ein strukturiertes Interview-

1. Allgemeine Angaben über den Patienten

Testleiter (ID):	Datum:
Einrichtung:	Patient (ID):
Hauptdiagnose:	ICD-10 Kodierung:

2. Beschreibung des Störungsverlaufs

Wie lange dauert die aktuelle depressive Episode bereits an?	Dauer (Monaten):
Wie häufig traten depressive Episoden, einschließlich der aktuellen, in der Vergangenheit auf?	Anzahl:
In welchem Lebensalter trat eine depressive Episode das erste Mal auf?	Alter (Jahre):
Falls andere psychische Störungen/Diagnosen außer einer affektiven Störung vorliegen, welche sind das?	Störungen nach ICD-10:

3. Beschreibung der Interventionsbedingungen

Wie lange dauert der aktuelle Aufenthalt in der Klinik aufgrund der depressiven Episode bereits an?	Dauer (Wochen):
Wie häufig kam es insgesamt bisher zu Klinikaufenthalten aufgrund depressiver Episoden?	Anzahl:
Falls Medikamente aufgrund der depressiven Episode aktuell eingenommen werden, welche sind das?	Medikationsart:
Wie lange wurden Medikamente aufgrund depressiver Episoden insgesamt seit Beginn der ersten Episode eingenommen? (bei Unterbrechungen Dauern addieren)	Dauer (Monate):

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Appendix H

Statement of the Candidate's Contribution to each Publication

The present doctoral thesis was conducted by the candidate Franz Pauls according to § 6 subparagraph 5 of the formal requirements for doctoral candidates at the University of Bremen. The thesis comprises a total of five empirical research studies which were either published in or accepted for publication by internationally renowned and peer-reviewed journals.

The first steps needed to accomplish the present empirical research project required the conceptualization of each study included (conceptual framework), and the review of previous literature on the according subject (literature research). Further working steps included the recruitment of suitable participants and conducting neuropsychological examinations (data collection), the manipulation of the observed data into a form suitable for further analyses (data preparation), and carrying out statistical analyses in order to address the main research aims (data analyses). Additionally, the results had to be correctly interpreted (data evaluation) and put into the proper context (classification of findings). Finally, manuscripts had to be prepared, submitted, and revised for publication in order to make scientific knowledge accessible to the interested public (manuscript preparation and revision). Addressing the aforementioned working steps, Table H1 displays the candidate's individual contribution to each publication.

The extent of this contribution is evaluated using three different categories denoting whether the candidate solely contributed to a specific working step (fully), whether he made the most important contribution to a specific working step (mostly), or whether the candidate and at least one further contributor shared the same amount of contribution (partly). Apart from this, all contributors were kept informed on the progress of the present research.

Table H1.

The candidate's contribution to each published research study

	Present research studies				
Working steps	**Study I**	**Study II**	**Study III**	**Study IV**	**Study V**
Conceptual framework	Fully	Fully	Fully	Fully	Fully
Literature research	Fully	Fully	Fully	Fully	Fully
Data collection	Partly	Partly	Partly	Partly	Mostly
Data preparation	Partly	Fully	Fully	Fully	Fully
Data analyses	Fully	Fully	Fully	Fully	Fully
Data evaluation	Fully	Fully	Fully	Fully	Fully
Classification of findings	Mostly	Fully	Fully	Mostly	Fully
Manuscript preparation	Mostly	Fully	Mostly	Partly	Fully
Manuscript revision	Mostly	Mostly	Mostly	Partly	Mostly

Accordingly, Dipl.-Psych. Franz Pauls and the other contributors, Prof. Dr. Franz Petermann and Dr. Anja Christina Lepach, herewith certify that the statement made by the candidate on his own contribution to each publication is accurate and that permission is granted for these publications to be included in the candidate's doctoral thesis.

Bremen, November 2014

(Prof. Dr. Franz Petermann)

(Dr. Anja Christina Lepach)

(Dipl.-Psych. Franz Pauls)

Appendix I

Declaration of Originality

In accordance with § 6 subparagraph 5 of the formal requirements for doctoral candidates at the University of Bremen, the candidate Dipl.-Psych. Franz Pauls hereby declares that the present doctoral thesis represents his own original work except where specifically acknowledged. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature. Franz Pauls further declares that his doctoral thesis does not contain any material which has previously been accepted and is not currently considered for the award of any other university degree in his name. In addition, Franz Pauls certifies that no part of this work will, in the future, be used in a submission in his name, for any other degree in any university without the prior approval of the University of Bremen.

Bremen, November 2014

(Dipl.-Psych. Franz Pauls)