Aging and Functional Reorganization of Striatum- and Medial-Temporal Lobe-Dependent Memory Systems

D i s s e r t a t i o n
zur Erlangung des akademischen Grades

Doctor rerum naturalium (Dr. rer. nat.)

im Fach Psychologie

eingereicht an der

Mathematisch-Naturwissenschaftlichen Fakultät II

Humboldt-Universität zu Berlin

von Dipl.-Psych. Nicolas Wolfgang Schuck

Präsident der Humboldt-Universität zu Berlin:
Prof. Dr. Jan-Hendrik Olbertz
Dekan der Mathematisch-Naturwissenschaftlichen Fakultät II:
Prof. Dr. Elmar Kulke

Gutachter:
Prof. Shu-Chen Li, PhD, Technische Universität Dresden
Prof. Dr. Torsten Schubert, Humboldt-Universität zu Berlin
Prof. Dr. Lars Bäckman, Karolinska Institutet, Stockholm, Schweden

Eingereicht am: 8. Mai. 2013

Datum der Verteidigung: 28. Juni 2013

Erklärung

Hiermit erkläre ich,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,

- dass ich die Dissertation an keiner anderen Universität eingereicht habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze und

- dass mir die Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät II vom 17.01.2005, zuletzt geändert am 13.02.2006, veröffentlicht im Amtlichen Mitteilungsblatt Nr. 34/2006 bekannt ist.

Berlin, den 8. Mai 2013

Nicolas Schuck

Unterschrift_____

Datum_____

ACKNOWLEDGMENTS

This dissertation was conducted within the research project "Neuromodulation of Lifespan Cognition" at the Center for Lifespan Psychology of the Max Planck Institute for Human Development in Berlin. I was also a member of the General Psychology research group at Humboldt-Universität zu Berlin and a fellow of the International Max Planck Research School "The Life Course: Evolutionary and Ontogenetic Dynamics (LIFE)". All research was funded by the Max Planck Society, except the experiments reported in *Paper II*, which were funded by the Princeton Center for Health and Well-being. I am obliged to all these sources of funding who made this dissertation possible.

I am most grateful to my supervisor Shu-Chen Li. Shu-Chen, your innumerable efforts, your continued guidance, your enthusiasm and supervision were the foundation of my dissertation. I am deeply grateful for all the time you invested in this research and your excellent support in all intellectual and everyday matters. I am also thankful to my supervisor Peter Frensch, who has always been an inspiration and who has provided me with many opportunities already very early in my academic career. These opportunities ignited my passion for the science of the mind. Furthermore, I want to express my gratitude to Ulman Lindenberger for providing me with an outstanding and unique research environment at the Max Planck Institute and for inspiring and challenging discussions. I am very obliged to Torsten Schubert for giving me the opportunity to continue to be a member of the General Psychology research group and for investing the time and effort to evaluate this thesis. I also would like to thank Lars Bäckman, whose work has inspired many aspects of this dissertation. It is a great honor that you are a member of my dissertation committee.

I am very thankful for the support from all members of the Neuromodulation project. Thank you Ben for all the inspiring and challenging discussions we had. It was great working with you and I hope we will continue to collaborate. Goran, thanks for listening and advising. Dorothea, thanks you for letting me help working on your dataset. I am also indebted to all other members of the Neuromodulation group who helped with data acquisition.

Among the many important intellectual influences, I would like to highlight Christian Doeller and Robert Gaschler. Christian, I admire your work and I enjoyed visiting you. I hope we will continue to collaborate for many years to come. Robert, you have been a truly inspiring supervisor, colleague and friend in the past eight years. My thanks go also to Thad Polk for arranging the visit at his lab and assisting me with the initial steps of the data analysis. Additionally, I am very grateful that I could collaborate with Lars Bertram, Julia Schröder and Brit-Maren Schjeide from the Max Planck Institute for Molecular Genetics.

Thank you Garvin for being a great office mate. Thank you Elisabeth for being always so helpful and high-spirited. Thank you all members of LIFE and the Lifespan Psychology department that I had the pleasure to work with.

I would also like to express my gratitude to my family, for their support and understanding.

Finally, I would like to express my most sincere gratitude to Anne for being such a wonderful, lovingly and passionate partner. I cannot imagine being without you.

TABLE OF CONTENTS

Summary

Previous research has indicated the existence of two cognitively and neurally separable memory systems in young adults. Specifically, it has been distinguished between a declarative memory system that stores flexible representations and is subserved predominantly by the medial-temporal lobe (MTL) and a procedural memory system that expresses past experiences through improved actions and is based mainly on the striatum. Few investigations have begun to address the question of age-related changes in the functioning and interaction of these memory systems. These studies indicated that aging is accompanied by a complex pattern of neural degradation in both systems, elevated MTL activity as well as partially spared procedural memory functions. In addition, a literature review suggests that overactivity within the MTL can be caused by multiple factors which are either beneficial or detrimental for memory. The present dissertation is based on four papers and investigated the effects of human aging on the relations of brain networks and genetic factors to declarative and procedural memory functions. In *Paper I*, age differences in a procedural memory task gradually emerged over the course of extended training and were linked to negative effects of aging on the transition from procedural to declarative memory. In addition, this study showed that genetic factors related to striatal dopaminergic functioning (*DARPP-32*, rs907094 and *DAT*, VNTR) affected declarative knowledge in older but not younger adults. The results from *Paper II* indicated that the computation of prediction error signals in the human brain, a key neural computation associated with striatal learning functions, was partially impaired in older adults. *Paper III* demonstrated that the phenomenon of partially intact procedural memory functions in older adults could also be found in a spatial memory task and was modulated by a genetic factor that influences hippocampal long-term potentiation (rs17070145 in *KIBRA/WWC1*). Finally, the study reported in *Paper IV* investigated representations and computations related to striatum- and MTL-dependent spatial navigation on the levels of behavior and neural activity. In this study, it was shown that representations subserving spatial memory qualitatively differed between younger and older adults. The performance and neural activation of younger adults showed unique properties of MTL-dependent declarative memory. Older adults, in contrast, showed behavioral and neural indications of procedural memory but the localization of the neural signatures did include both the striatum and the MTL.

In summary, these results confirm partially spared procedural memory abilities in older adults. While *Paper II* suggested that memory-related neural computations in the striatum are impaired, *Paper IV* showed that the localization of memory-related brain functions might also be changed by aging. Neurogenetic investigations in *Papers I* and *III* further supported a changed brain-cognition relation in older adults. Moreover, in line with the resource modulation hypothesis, it was found that genetic factors played an increasingly large role for these memory functions in senescence. These results show that the definition of memory systems based on younger adults does not capture the behavior-to-brain relations in older adults and highlight the need to study the interactions of declarative and procedural memory at the behavioral and neural level. The present dissertation provides a starting point for this endeavor.

Zusammenfassung

Bisherige Forschungsergebnisse legen eine Unterscheidung zwischen zwei Gedächtnissystemen nahe. Auf der einen Seite wurde das sog. deklarative Gedächtnis (DG) identifiziert, das sich durch die Fähigkeit vergangene Lebensereignisse bewusst zu erinnern auszeichnet und mit dem lobus temporalis medialis (MTL) in Verbindung steht. Das prozedurale Gedächtnis (PG), auf der anderen Seite, beinhaltet erlernte Fertigkeiten und scheint vom Corpus striatum abhängig zu sein. Über der Einfluss von Alterungsprozessen auf Gedächtnissysteme ist bislang wenig bekannt. Insgesamt hat diese Forschung ergeben, dass Alterung von neurologischen Schäden in beiden Systemen, teilw. erhöhter Aktivität im MTL und einer relativ geringeren Beeinträchtigung des PG begleitet ist. Hyperaktivität im MTL wurde dabei sowohl mit verbesserten, als auch verschlechterten Gedächtnisleistungen in Verbindung gebracht. Die hier vorgelegte Dissertation befasst sich mit dem Einfluss von Alterung auf die Beziehungen zwischen o.g. Hirnnetzwerken und genetischen Faktoren zu prozeduralen und deklarativen Gedächtnisfähigkeiten. *Studie I* zeigte, dass Altersunterschiede in einer prozeduralen Gedächtnisaufgabe graduell im Verlaufe des Trainings entstehen und vmtl. mit negativen Einflüssen von Alterung auf den Übergang von PG zu DG in Zusammenhang stehen. Desweiteren konnte gezeigt werden, dass genetische Faktoren, die das striatale Dopaminesystem beeinflussen (*DARPP-32*, rs907094 und *DAT*, VNTR), sich auf das DG älterer aber nicht jüngerer Erwachsener auswirkten. Die Ergebnisse aus *Studie II* indizierten, dass die Berechnung von Vorhersagefehlern, die ein zentrales neuronales Lernsignal im Striatum darstellen, in älteren Probanden teilweise beeinträchtig war. *Studie III* konnte demonstrieren, dass teilweise intaktes PG sich auch für räumliches Gedächtnis nachweisen lässt und durch einen genetischen Faktor, der sich auf hippocampale Lanzeitpotenzierung auswirkt (rs17070145 in *KIBRA/WWC1*), moduliert wird. In *Studie IV* wurden Repräsentationen während einer räumlichen Gedächtnisaufgabe auf neuronaler und Verhaltensebene untersucht. Während jüngere Probanden in dieser Studie neuronale und kognitive Anzeichen von MTL-basiertem DG zeigten, wiesen ältere Teilnehmer Anzeichen von PG auf. Die neuronalen Signaturen älterer Erwachsener waren jedoch nicht auf das Striatum beschränkt, sondern konnten auch im MTL nachgewiesen werden.

Zusammenfassend bestätigen die berichteten Ergebnisse, dass PG bei älteren Menschen teilweise intakt ist. Während *Studie II* zeigte, dass kognitive Einbußen mit entsprechenden Einbußen in der Funktionsweise des Striatums in Zusammenhang standen, zeigte *Studie IV*, dass Alterungsprozesse auch die Beziehungen zwischen Hirnprozessen und Gedächtnisfunktionen veränderten. Diese Schlussfolgerung wurde ebenfalls von den genetischen Untersuchungen in *Studien II* und *IV* unterstützt. Zusätzlich haben diese Studien ergeben, dass genetische Einflussfaktoren eine größere Rolle für kognitive Fähigkeiten im Alter spielen und daher kongruent mit den Vorhersagen der 'resource modulation' Hypothese sind. Die vorgelegten Ergebnisse legen nahe, dass Alterung deklarative und prozedurale Gedächtnissysteme selektiv beeinträchtig sowie die Beziehungen zwischen PG, DG und neuronalen Funktionen verändert.

List of Papers

This doctoral dissertation is based on the following original papers:

Paper I

Schuck, N.W., Frensch, P.A., Schjeide, B.M., Schröder, J., Bertram, L. & Li, S.-C. (under revision). Effects of aging and dopamine genotypes on the emergence of explicit memory during incidental sequence learning. Revision invited by *Neuropsychologia* on April 25, 2013, resubmitted June 25, 2013.

Paper II

Eppinger, B., **Schuck, N.W.**, Nystrom, L.E., & Cohen, J.D. (2013) Reduced striatal responses to reward prediction errors in older compared to younger adults. *Journal of Neuroscience*, *33*, 9905–9912. doi:10.1523/JNEUROSCI.2942-12.2013

Paper III

Schuck, N.W., Doeller, C.F., Bisenack, J., Schjeide, B.M., Frensch, P.A., Bertram, L. & Li, S.C. (2013). Aging and KIBRA/WWC1 genotype affect spatial memory processes in a virtual navigation task. *Hippocampus*. Advance online publication. doi:10.1002/hipo.22148.

Paper IV

Schuck, N.W., Doeller, C.F., Polk, T.A., Lindenberger, U. & Li, S.-C. (in preparation). Human aging alters neural computations and representations during spatial navigation.

List of Abbreviations and Glossary

ALLOCENTRIC: Linked to an external spatial reference frame independent of one's own position.

BOLD: Blood oxygenation level dependent.

BOUNDARY-BASED LEARNING/BOUNDARY DISTANCE: Euclidean distance of current position $\mathbf{p} = (x, y)$ to the nearest boundary in direction θ. In a circular environment with radius r, as in *Studies III* and *IV*, the boundary distance was calculated as

$$\begin{aligned}\Delta_B(r, \mathbf{p}, \theta)^2 =& r^2 + d_{\mathbf{p}}^2 \\ & -2rd_{\mathbf{p}} \cos\left(\arctan 2(y, x) - \theta + \arcsin\left(\frac{d_{\mathbf{p}} \sin\left(\pi - \arctan 2(y, x) + \theta\right)}{r}\right)\right)\end{aligned}$$

whereby $d_{\mathbf{p}} = \sqrt{(x - x_0)^2 + (y - y_0)^2}$ is the euclidean distance of point $\mathbf{p}$ to the center of the environment. This compuation is central to place cell models as in (O'Keefe & Burgess, 1996), meaning that in boundary-based learning the boundary distance is keep roughly constant if the environment changes.

D1/D2: D_1-like and D_2-like receptors, respectively. D_1-like receptors include D_1 and D_5 dopamine receptors, D_2-like the D_2, D_3 and D_4 receptors.

DA: Dopamine.

DARPP-32/PPP1R1B: Dopamine- and cAMP-regulated neuronal phosphoprotein gene/Protein phosphatase 1 regulatory subunit 1B gene.

DAT: Dopamine transporter gene.

DECLARATIVE MEMORY: Ability to consciously recall facts or events. Usually further subdivided into episodic and semantic memory. Here it will be used to refer to memory that is primarily MTL-dependent, such as explicit, episodic and spatial memory.

EGOCENTRIC: Relative to one's own position, i.e. distance and orientation relative to the own current position.

(F)MRI: (Functional) magnetic resonance imaging.

HD: Huntington's Disease.

KIBRA/WWC1: Kidney and brain expressed protein gene/WW and C2 domain containing 1 gene

LANDMARK-BASED LEARNING/LANDMARK DISTANCE: Distance of $\mathbf{p}$ to the landmark/visual cue as described by the translation vector $v = \mathbf{p}_{LM} - \mathbf{p}$, such that the distance and direction are given by $\Delta_{LM} = |v|$ and $\theta_{LM} = \tan^{-1}(y_v/x_v)$. Landmark-based learning means that this distance keeps constant even when the position of the landmark $\mathbf{p}_{LM}$ is translated (shifted) by an arbitrary translation v, such that $\hat{\mathbf{p}}_{LM} = \mathbf{p}_{LM} + v$ implies $\hat{\mathbf{p}} = \mathbf{p} + v$.

LTD/LTP: Long-term depression/Long-term potentiation.

LTM: Long-term memory.

MEMORY SYSTEM: A system of interconnected neural structures that can be regarded as the biological implementation of a specific memory function.

(A)MCI: (Amnestic) Mild cognitive impairment.

MTL: Medial-temporal lobe. Here MTL refers to the hippocampus proper, subiculum, the parahippocampal and rhinal cortices.

PD: Parkinson's disease.

PKMζ: Protein kinase Mζ.

PREDICTION ERROR: The difference between the predicted and the obtained reward, in its simplest form calculated as $\delta = r_t - V_t$, whereby r_t notates the obtained reward and V_t the expected reward at time t.

PROCEDURAL MEMORY: Memory that is characterized by gradual acquisition of stimulus-based behaviors, mostly expressed through performance and not accessible by conscious recall.

SNP: Single nucleotide polymorphism.

SRTT: Serial reaction time task.

VNTR: Variable number tandem repeat.

Chapter 1

INTRODUCTION

Human aging is accompanied by profound changes in the brain. This involves impairment on structural (e.g., reduced myelination/white matter loss), neurochemical (e.g., reduced acetylcholine production) and biophysical (e.g., impaired long-term potentiation, LTP) levels (Hof & Mobbs, 2009; Yeoman, Scutt, & Faragher, 2012). Likewise, a plethora of studies have demonstrated changes in many cognitive functions (e.g., Lindenberger, Smith, Mayer, & Baltes, 2010; Schaie, 1996), such as working memory or executive functions. While age-associated changes in brain and cognition are widespread, progressive loss of memory functions is among the most pronounced (Li et al., 2004), and memory relevant brain structures are very vulnerable to age-related losses (Raz & Rodrigue, 2006). Accordingly, describing and understanding the relation of physiological decline and memory functioning is an important step for promoting successful aging. With the present dissertation, I attempted to contribute to a better understanding of the changes in memory functions that accompany healthy aging. In doing so, I studied this phenomenon from two perspectives: First, I studied the effects of age on different memory functions assumed to be rooted in different brain systems (i.e., memory systems, see below). Second, I scrutinized the relations between these memory functions and different brain processes.

While memory is a complex, multi-faceted phenomenon, the present dissertation focused on two specific types of long-term memory (LTM). In particular, I studied the effects of aging on two memory systems, one that has been related to the medial-temporal lobe (MTL) and another that has been related to the striatum (Eichenbaum & Cohen, 2001; White, 2007). In essence, the MTL system has been linked to declarative memory, i.e., the ability to recall past events and facts in a flexible manner. The most common phenomena arising from this memory system are episodic memory, which is the ability to consciously recall previous events (Tulving, 1983, 2002) and spatial memory that relies on a flexible representation of the spatial environment, hence termed

a 'cognitive map' (Burgess, Maguire, & O'Keefe, 2002). Semantic memory, which is also subsumed under the term declarative memory, will not be considered here. Throughout the thesis, the term declarative memory is used to refer to episodic and cognitive map-like spatial memory. The striatal system, in contrast, is related to procedural memory, i.e. the ability to acquire skilled behavior. Procedural memory is typically characterized by the gradual acquisition of constant relations between stimuli and responses, such that responses lead to the most successful outcome (Squire, 2004). The striatal system has also been linked to processing information about expected reward during reinforcement learning (Dayan & Niv, 2008). A more detailed description of these memory systems is given below.

Although at its core the term memory refers to the storage of specific content, these memory systems are not considered 'information warehouses'. Rather, current knowledge of the neurobiology of memory suggests that memory systems can be seen as information processing systems in which memory arises as a consequence of plasticity (Eichenbaum & Cohen, 2001). This notion is reflected in *Papers III* and *IV*, where different information processes (computations related to boundary distance and prediction errors, respectively) will be explicitly defined and studied on the level of brain activity.

Equally manifold as the entity memory itself are the changes that occur parallel to its aging (for reviews, see Hoyer & Verhaeghen, 2006; Salthouse, 2003; Verhaeghen, Marcoen, & Goossens, 1993). Of particular relevance, previous work indicated an asymmetry between the cognitive and neural decline of procedural and declarative memory (e.g., Dennis & Cabeza, 2011; Rieckmann, Fischer, & Bäckman, 2010, for a review, see Rieckmann & Bäckman, 2009). Importantly, this work gives rise to the notion that physiological decline in brain structures might not only lead to decline in associated functions, but potentially also to changes in the relations between brain and cognitive variables.

Before the empirical work that was conducted within the scope of this thesis (see Chapter 4 and Appendices C-F), will be described, the relevant empirical and theoretical background is provided in Chapter 2. A major goal of this background information shall be to give foundation to some central premises of my empirical work. As I outlined above, a first central premise was that memory functions are not monolithic and

different sub-components can be divided into (more or less independent) memory systems. Hence, evidence will be presented that supports the notion of an MTL-based and a striatum-based memory system and their differential aging (sections 2.1 and 2.2.1). The idea of differentiable memory systems also gives rise to the logical possibility that the deterioration of memory does not necessarily have to be unitary (Schacter, 2009). A second premise of this thesis was that physiological decline in the MTL and the striatum not only leads to impairment of the associated memory functions, but might also lead to changes in the functions that are associated with the hippocampus and the striatum. I will therefore review literature relevant to this idea. Finally, the results of the empirical work, its limitations and implications for future research will be discussed in Chapter 5.

Chapter 2

THEORETICAL BACKGROUND

2.1 Distinguishable Systems of Long-Term Memory

A key mechanism of information storage in the brain is to change synaptic strengths between neurons dependent on their activity (i.e., *activity-dependent synaptic plasticity*). The major biochemical basis of such activity-dependent plasticity is LTP, which induces a long lasting change in the synaptic connectivity between two neurons following prolonged concurrent activation (Bliss & Lomø, 1973; Cooke & Bliss, 2006). LTP has been found in many brain areas related to memory, including the hippocampus, the amygdala and the striatum (Lynch, 2004). On a broader level of neural networks and cognitive functions, it has been proposed that memory functions can be dissociated with respect to the kinds of information that are stored and the brain networks which are involved (henceforth *memory systems*; for reviews, see Squire, 2004; Rolls, 2000). Research has provided an entire taxonomy of distinguishable memory systems, but one of the most basic distinctions has been made between memory of *Knowing How* and memory of *Knowing That* (Cohen & Squire, 1980). Within my dissertation, I focused on these two types of memory, henceforth termed procedural and declarative memory. As I will show below, from a biological perspective, declarative memory could be described as a primarily MTL-dependent memory system, whereas procedural memory is considered primarily striatum-dependent.

A classic example from the animal literature that supports such a distinction between different memory systems is provided by Packard, Hirsh and White (1989; for similar studies, see Packard & McGaugh, 1992; McDonald & White, 1994; a review can be found in White, 2007). In this study, rats with either dorsal striatum or fornix lesions (the latter results in a disconnection of the hippocampus from the rest of the brain) were subjected to different conditions of a memory task. Packard *et al.* tested those rats in a radial eight-arm maze where the animal had to find food under two conditions: in the Win-Shift condition, locations of food pellets were defined in a

spatial manner. One food pellet was placed in each of the eight arms and the animal had to remember *where* it had already been in order to find more food. In the Win-Stay condition the food pellets were always placed in a lit arm but there was no spatial relation between the locations of the food in successive trials. Hence, in order to find food effectively in this condition, the animals had to learn an association between a stimulus (the light) and a specific behavior (walking towards the light) rather than allocentric spatial memory. Strikingly, Packard and colleagues found that fornix lesioned animals were impaired in the Win-Shift but not the Win-Stay conditions[1], whereas striatum lesioned animals showed the reverse pattern. Hence, damage of the hippocampus seemed to induce memory deficits only if the memory was based on allocentric spatial knowledge, whereas damage to the striatum led to impairment of memory involving stimulus-response learning. Studies with human patients also showed a double dissociation between the disease that affected either the hippocampus (amnesia) or the striatum (Parkinson's disease, PD, which involves a severe damage in the DA system) and performance in declarative vs. procedural memory tasks (Knowlton, Mangels, & Squire, 1996, see also Shohamy et al., 2004). Further evidence comes also from neuroimaging with healthy humans (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999), where it was shown that probabilistic classification learning is related to striatal activation and hippocampus deactivation. Together, these findings can be interpreted as pointing to independent memory systems in the hippocampus and the dorsal striatum. Furthermore, many observations implicated that not the hippocampus alone, but rather a system of tightly interconnected areas in the vicinity of the hippocampus are linked to memory functions. Accordingly it has been often assumed that a broader network referred to as MTL (here: hippocampus proper, subiculum, the parahippocampal and rhinal cortices) is linked to this form of memory (Squire & Zola-Morgan, 1991). Below I describe this MTL-dependent memory in more detail.

2.1.1 MTL-dependent memory

Several prominent hypotheses about the nature of the MTL-based memory system posit that the MTL is linked to declarative memory (Tulving & Markowitsch, 1998;

[1]Indeed, fornix lesioned animals were slightly better than control animals in this condition. See Chapter 3, for a discussion of this effect.

Squire & Zola-Morgan, 1991; Eichenbaum & Cohen, 2001). Declarative memory is thereby an umbrella term that subsumes different forms of memory for facts or events that can be consciously recalled. Moreover, it can be further distinguished between episodic memory, the capacity to recall or re-experience past events (Tulving, 1983, 2002), and semantic memory, our knowledge for general facts which are independent of time. I will not consider semantic memory within this dissertation.

The foundations for the idea that the MTL is linked to declarative memory come from groundbreaking observations made on patient H. M. (Scoville & Milner, 1957; for a review, see Tulving, 2002). In their 1957 paper, Scoville and Milner described the effects of a surgical removal of H.M.'s hippocampi[2] (as an attempt to cure epilepsy). Their main observation was that following the surgery H.M. had a servere anterograde and a temporally graded retrograde amnesia (see also Milner, Corkin, & Teuber, 1968). Most notably, however, his memory impairment was confined to episodic (and semantic) memory, but he showed (partially) intact skill learning (Corkin, 1968) and working memory abilities (Milner et al., 1968; see also Baddeley & Warrington, 1970 for different patients and Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995 for comparisons of H.M. with another patient with a different lesion). Following these initial discoveries, numerous studies in healthy humans have confirmed the importance of the MTL for declarative memory (Eichenbaum, 2000; Eichenbaum & Cohen, 2001; Eichenbaum, 2004).

The hippocampus as a cognitive map

Additional insights in the memory functions of the MTL came from neurophysiological studies of spatial navigation in animals. In particular, various cell types specialized in spatial information processing have been found in the rat hippocampus, subiculum and entorhinal cortex. Most prominently, O'Keefe and Dostrovsky reported cells that signal that an animal is in a specific location within the environment and termed them place cells (O'Keefe & Dostrovsky, 1971; for evidence for place cells in humans, see Ekstrom, Kahana, & Caplan, 2003). The function of these striking representational properties of place cells has been studied extensively and it has been proposed that they indeed constitute a 'cognitive map' (O'Keefe & Nadel, 1978) as proposed by Tolman

[2]His parahippocampal gyri and amygdalae were also affected.

(1948). Three decades later, Hafting *et al.* identified cells in the entorhinal cortex which seem to signal locations on the edges of a hexagonal grid, which were therefore termed grid cells (Hafting, Fyhn, Molden, Moser, & Moser, 2005; for evidence in humans, see Doeller, Barry, & Burgess, 2010). The functional relevance of the MTL for spatial navigation has been shown in animals (Morris, Garrud, Rawlins, & O'Keefe, 1982; Redish & Touretzky, 1998), and in humans (for a review, see Burgess, 2008). Although some authors have proposed frameworks to incorporate the declarative memory theory and the cognitive map theory of the hippocampus (Burgess et al., 2002; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999), the precise relation between the different lines of evidence remains contested (Kumaran & Maguire, 2005).

2.1.2 Striatum-dependent memory

In addition to the above-cited evidence for an MTL-based memory system, other aspects of memory have also been identified. To yet again refer to patient H.M., it has been shown that this patient could successfully learn bimanual tracking or rotary pursuit tasks over multiple sessions, even though he could not remember even having taken part in previous sessions (Milner, 1966; Corkin, 1965, 1968). Following the initial proposal that a memory system distinct from the hippocampus might be concerned with *Knowing How* (Cohen & Squire, 1980), this memory has been linked to the acquisition of skills and habits and has been termed procedural or habit memory (Cohen & Eichenbaum, 1993; Mishkin, Malamut, & Bachevalier, 1984; Knowlton et al., 1996). Despite some disagreement (Willingham, 1998), procedural memory has been proposed to be characterized by the gradual acquisition of stimulus specific associations that are mostly inaccessible by conscious recollection (Cohen, Poldrack, & Eichenbaum, 1997; Gupta & Cohen, 2002; Knowlton & Moody, 2008). Moreover, procedural memory is typically tested with indirect rather than direct memory tests (it can be inferred from enhanced (motor) performance/skills, rather than from verbalized knowledge). On the neurological level, the striatum (mostly: caudate nucleus, nucleus accumbens and putamen) has been proposed to play a crucial role in procedural memory (Mishkin et al., 1984). Specifically, research has shown that the gradual acquisition of many cognitive skills is related to a cortico-striatal circuit (e.g., Doyon et al., 1997; Poldrack & Gabrieli, 2001; Poldrack et al., 1999, for a review, see Doyon & Benali, 2005) and a cortico-cerebellar

circuit has been proposed to perform similar, yet differentiable functions (Doyon & Benali, 2005). In line with these findings, other studies have also shown striatum activity during implicit motor sequence learning tasks (e.g., Destrebecqz et al., 2005; Rauch et al., 1997; Seidler et al., 2005; Peigneux et al., 2000) and an impairment of PD patients in these tasks (Ferraro, Balota, & Connor, 1993). In addition, the animal studies which are cited above (Packard et al., 1989) indicated that the role of the striatum for learning and memory might not be confined to pure motor tasks (see also Eichenbaum & Cohen, 2001). Rather, these findings also showed that the caudate nucleus seems to be associated to a more general mechanism of stimulus response associations, that for example is capable of learning locations relative to discriminative visual cues (see also, McDonald & White, 1994; Packard et al., 1989; Packard & McGaugh, 1992). A number of other animal studies have indicated further roles of the striatum in spatial navigation related to learning fixed responses (Tolman, Ritchie, & Kalish, 1946), and have shown that such response learning is dissociable from hippocampus-dependent place learning (Packard & McGaugh, 1992). Consistent with these results, recent investigations have demonstrated striatal brain activity during spatial learning based on single visual cues in humans (Doeller, King, & Burgess, 2008). Hence, while many different tasks and approaches have been taken, procedural learning is consistently characterized by the gradual acquisition of mostly inflexible (e.g., stimulus-response-based) knowledge with limited accessibility by consciousness. Although procedural memory involves a broad network involving the basal ganglia, cortical areas and the cerebellum, the role of the striatum is well established and I will focus on this role henceforth.

The role of the striatum and dopamine in processing reward signals

On a neurochemical level, research has suggested that the striatum plays an important role in representing reward prediction errors (Schultz, 2002). Based on theoretical considerations, these reward prediction errors have been proposed as the central learning signal in reinforcement learning models (Rescorla & Wagner, 1972; Sutton & Barto, 1998). Later, they have first been identified in dopaminergic (DA) neurons in the ventral tegmental area (Schultz, Dayan, & Montague, 1997; Schultz, 1998). Further observations indicated a role of the striatum in classical conditioning (Graybiel & Kimura, 1995; Aosaki, Kimura, & Graybiel, 1995) and it has been shown that the activity of

these striatal cells changes as a function of learning (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999). Consistent with the initial findings by Schultz *et al.* (1997), the striatum is heavily innervated by dopaminergic neurons in the ventral tegmental area, probably causing the related cell behavior. Studies with humans have subsequently also found evidence of prediction error signals in the ventral striatum (e.g., O'Doherty et al., 2003). Additional evidence comes from studies with PD patients, who also exhibit reduced reinforcement learning capabilities (Frank, Seeberger, & O'Reilly, 2004). Hence, supplementing the above given characterization of procedural memory, encoding of the prediction errors can be considered as a key mechanism underlying striatal memory functions. These prediction error-related processes, in turn, imply a prominent role of DA for procedural memory. Using a SRTT, Karabanov *et al.* (2010), for example, showed that D2 binding potential in the ventral striatum correlated with implicit, but not explicit learning.

2.1.3 Relation between memory systems

The above-summarized research has indicated two different forms of memory which are subserved by different neural networks. It is likely, however, that most memory tasks, especially those occurring in everyday life, are multi-determined with respect to the involvement of the two memory systems (Tulving, 2002). Hence, an important aspect in many memory tasks might not only be how well these memory systems work independently, but how well they interact. Past research on the interaction of the MTL- and striatum-centered memory systems has indeed indicated multiple forms of interaction, i.e. cooperation as well as competition (Poldrack & Packard, 2003). Specifically, first indications of an interaction of memory systems came from studies showing beneficial effects resulting from lesions to one of the systems. Mitchell and Hall (1988), for example, showed that lesions to the caudate/putamen can lead to superior performance in a spatial memory task when it involves (allocentric) spatial memory. Similarly, Packard, Hirsch and White (1989) showed that lesions to the fornix can result in superior memory performance when it was based on learning stimulus response associations. Generally, these studies have been taken to support the notion that procedural and declarative memory compete over determining behavior to some extent. Hence the removal of one system can lead to less competition and improved

performance (if the task at hand can be solved using only the remaining system).

From a different point of view, the memory systems might not compete, but rather cooperate, because even mutual inhibition can be a means to coordinate the influence of the two memory systems. Indeed, some research has indicated that the relative influence of procedural and declarative memory varies over time and depends on certain conditions. Packard and McGaugh (1996) showed that spatial learning is initially subserved by the hippocampus but becomes increasingly caudate-dependent with training (see also Packard, 1999; Schroeder, Wingard, & Packard, 2002). Neuroimaging research with humans has also shown that during feedback-driven learning the striatum and hippocampus exhibit a similar dynamic of increasing striatum activation and hippocampus deactivation (Poldrack et al., 2001). Additionally, some evidence has shown the reverse pattern, i.e., increases in medial temporal lobe activation with practice (Poldrack et al., 1999). Foerde and colleagues showed that the presence of a secondary task can induce a shift from MTL-dependent declarative to striatum-dependent procedural learning (Foerde, Knowlton, & Poldrack, 2006). Most evidence of such processes is limited to the probabilistic classification task used by Poldrack and colleagues, but the phenomenon itself might be found in different tasks (see also Degonda et al., 2005, for evidence from a different paradigm). For example, behavioral data suggests that memory system shifts are likely to occur during incidental learning, because the initially implicit process might become explicit with practice (Haider & Frensch, 2005; Rünger & Frensch, 2008). Hence, in line with evidence cited above, the increasing (or transient) explicitness of the task could likely be reflected in increased (or transient) hippocampus activation and decreasing striatum activation. All these results confirm a mutual inhibition of memory systems. However, instead of competition leading to a dominance of one system, these results can also be interpreted as an indication of coordination that leads to varying degrees of involvement.

2.2 Aging of Memory Systems

Age-related changes in the brain have been observed on many levels. Volume shrinkage can be found in most areas of the brain and a loss of about 7.5% of the cerebral weight between 26 and 80 years has been reported (Rushton & Ankney, 2009). More fine-grained results indicate pronounced impairment in dendritic arborization, myelination

or acetylcholin- and catecholinergic neurotransmission, for instance (Hof & Mobbs, 2009). Shrinkage of the entorhinal cortex (Raz & Rodrigue, 2006) or neuronal cell loss (West, Coleman, Flood, & Troncoso, 1994), however, are examples of aspects of brain integrity that do not show such marked decline in healthy older adults (much in contrast to cases of pathological aging, such as Alzheimer's disease). In addition, the aging brain is characterized by sustained plasticity (Mora, Segovia, & Arco, 2007) and can even show continued neurogenesis (Kempermann, Gast, & Gage, 2002). Thus, while age-related neurological changes are widespread, they do not occur uniformly on all levels and in all brain areas.

A similar conclusion can be drawn about cognitive aging. Changes on the cognitive level are manifold, but they are not unitary (Li et al., 2004). Senescence does have drastic effects on memory functions, but it does not affect all memory forms to the same extent (e.g., Bäckman, Small, & Wahlin, 2001).

2.2.1 Aging of the MTL and the striatum

On a gross anatomical level, several studies have found volumetric decline of the striatum as well as of the hippocampus (Raz et al., 2005; Walhovd et al., 2011; Shing et al., 2011). For example, Raz, Lindenberger and colleagues (Raz et al., 2005) used a 5-year longitudinal design and reported annual percent changes of 0.75% and 0.79% for the caudate nucleus and the hippocampus, respectively. A meta-analysis of cross-sectional data by Walhovd *et al.* (2011), reported annual percent changes between 0.35% and 0.17% for the caudate and between 0.4% and 0.04% for the hippocampus. In another study (Raz et al., 2003), annual change rates of 0.83% in the caudate, 0.73% in the putamen and 0.51% in the globus pallidus were reported[3]. In addition, it has been shown that the decline of the striatum is characterized by an early onset and linear progression, whereas decline of the hippocampus has a later onset and an accelerated rate (Raz & Rodrigue, 2006). Changes in the synaptic density have been reported in the hippocampus as well as in the striatum (Saito et al., 1994). Furthermore, LTP in the hippocampus as well as LTD in the the nucleus accumbens have been shown to be

[3]All of these numbers, however, have to be taken with a grain of salt as they reflect estimations of linear change, which might not be the case (see Raz et al., 2005; Walhovd et al., 2011) and as they do not take into account important modifying variables, such as hypertension (Raz et al., 2005).

implicated by age (Bach et al., 1999; Wang, 2008). Many of these pathological changes have been linked to performance impairment. Head and Isom (2010), for example showed that hippocampal grey matter volume in older adults correlated with performance in a spatial navigation task and numerous studies have found similar relations for other memory tasks (Van Petten, 2004). In addition, neurophysiological studies in animals have shown age-related changes in cell activity that co-occur with memory impairment (e. g., Wilson, Ikonen, Gallagher, Eichenbaum, & Tanila, 2005; Barnes, Suster, Shen, & McNaughton, 1997; Shen, Barnes, McNaughton, Skaggs, & Weaver, 1997).

2.2.2 The role of dopamine in cognitive aging

Additional to the changes detailed above, both the hippocampus as well as the striatum are heavily affected by changes in the dopamine system (Bäckman & Farde, 2001, see Li, Lindenberger, & Sikström, 2001, for a theoretical account and Bäckman, Lindenberger, Li, & Nyberg, 2010; Li, Lindenberger, & Bäckman, 2010, for recent reviews). Specifically, studies have observed age-related reduction in postsynaptic markers of striatal D2 (Rinne et al., 1993) and D1 (Wang et al., 1998) receptors, in the D1/D2 ratio (Seeman et al., 1987) and in striatal presynaptic makers (Dopamine transporter [DAT] protein availability) (van Dyck et al., 2002; Erixon-Lindroth et al., 2005) as well as decline of dopamine receptors in the medial-temporal cortex (Kaasinen et al., 2000; Rieckmann et al., 2011). Interestingly, it is also known that dopamine affects several aspects of the striatal procedural memory system, such as sequence learning (Shohamy, Myers, Grossman, Sage, & Gluck, 2005; Karabanov et al., 2010; Simon et al., 2011), skill learning (Molina-Luna et al., 2009), reward processing (Flagel et al., 2011; Schultz, 2002) and multi cue category learning (Moustafa & Gluck, 2011; Shohamy, Myers, Kalanithi, & Gluck, 2008). At the same time, dopamine has also been implicated in hippocampal LTP (Frey, Schroeder, & Matthies, 1990) and MTL-based episodic memory (Takahashi et al., 2007; Papenberg et al., 2013; Wittmann et al., 2005, for a theoretical account, see Lisman & Grace, 2005; Lisman, Grace, & Duzel, 2011). On a general level, such and other links between dopamine, cognition and aging have led to the proposal that these three variables form a 'correlative triad' and that dopamine decline has a crucial role for the effects of aging on cognition (Bäckman &

Farde, 2005; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006).

2.2.3 Resource modulation: Magnified genetic effects in older adults

In addition to these resource reductions caused by aging, a non-linear relation between brain resources and cognitive performance has often been observed, as for example the inverted-U function for the case of dopamine (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Lindenberger *et al.* (2008) proposed that this combination might result in magnified effects of genetic factors that influence brain resources. This prediction has been confirmed in a number of studies investigating effects of neurogenetic factors on cognition (Hämmerer et al., 2013; Li, Chicherio, et al., 2010; Li et al., 2013; Nagel et al., 2008; Papenberg et al., 2013, see also Störmer, Passow, Biesenack, & Li, 2012).

2.2.4 Aging of episodic, spatial and procedural memory functions

In longitudinal studies, episodic memory begins to decline in the 60s years of age (Hedden & Gabrieli, 2004; Schaie, 1996)[4]. Moreover, a pattern of decline has also been found in other cognitive modalities, including verbal recall, visuo-spatial memory (D. C. Park et al., 2002), source memory and prospective memory (Bäckman et al., 2001). Similarly, grave impairment of spatial memory during navigation has been shown to occur with advancing age in humans (Moffat, 2009).

Unlike episodic and spatial memory, which are associated with the MTL memory system in younger adults, incidental sequence learning does not show such strong signs of decline. A number of examples come from the serial reaction time task (SRTT; Nissen & Bullemer, 1987), which is an indirect memory test characterized by gradual acquisition of associations. Performance in the SRTT has been shown to be not or only mildly affected by age (e.g., D. Howard & Howard, 1989, for a review, see Rieckmann & Bäckman, 2009) whereby the degree of impairment seems to be influenced by the complexity of the material (D. Howard et al., 2004; Bennett, Howard, & Howard, 2007). In addition, similar patterns have been found for information integration learning (Price, 2005) and artificial grammar learning (D. V. Howard, Howard, Dennis, LaVine, &

[4]Note that cross-sectional studies indicate a much earlier onset of decline (in the 20s), see Nilsson et al., 1997; Salthouse, 1998; Li et al., 2004.

Valentino, 2008, see also Smith, Siegert, McDowall, & Abernethy, 2001), which can also be considered as measures of procedural memory and have been linked to the striatum (Poldrack et al., 1999; Lieberman, Chang, Chiao, Bookheimer, & Knowlton, 2004; Peigneux et al., 2000). Hence, in comparison to episodic memory, procedural memory tasks are not as strongly impaired, even though striatum-dependent memory is not the only form of memory which seems to be relatively spared[5].

2.2.5 Aging and interaction of memory systems

Finally, the question remains how the aging process affects the balance of the striatum- and MTL-based memory systems. In section 2.1.3, it was shown that the interaction between the MTL-based and the striatum-based memory systems is characterized by mutual inhibition and might produce a coordinated time-course of involvement of them. The topic of how aging or diseases that affect relevant brain structures changes this interaction of memory systems, has not been addressed extensively yet.

Indications of a deficiency in the interaction come from a study with animals. Dagnas and colleagues showed that aging impairs the ability to switch between MTL-based and striatum-based memory upon pharmacological intervention (Dagnas, Guillou, Prévôt, & Mons, 2013), and corroborating findings on the behavioral level were made in humans (Harris, Wiener, & Wolbers, 2012). Furthermore, Boyd and Winstein (2004) trained patients suffering from a stroke in the putamen and healthy controls in an implicit motor learning task either with or without additional explicit information. Their results showed that stroke patients where disrupted by additional explicit information, whereas healthy controls benefited from it. Hence, some studies indicated that aging or disease might impact the ability to switch between memory systems or to integrate information from multiple memory systems. From a broader perspective, these findings are also in line with research on age-effect on dual task performance that suggests greater interference in older adults (Hein & Schubert, 2004), although this effect can be partially elevated by practice (Strobach, Frensch, Müller, & Schubert, 2012).

[5]Light and Singh observed already in 1987 that priming is also not impaired in older adults (Light & Singh, 1987, see Rieckmann & Bäckman, 2009 for a review, but see also Fleischman & Gabrieli, 1998, for methodological concerns and data that show at least mild impairment in older adults).

In addition to these studies, an ongoing debate concerns the role of activation in the MTL for memory in older adults. One particularly interesting study comes from Rieckmann and colleagues (Rieckmann et al., 2010). In this study, brain activity of younger and older adults was measured while they were performing the SRTT. In accordance with previous reports (e.g., Seidler, 2006), implicit motor learning did not differ between age groups, and younger adults showed increasing striatum and decreasing MTL activation (Albouy et al., 2008). Moreover, in younger adults, sequence learning was positively related to activation increases in the striatum but to activation decreases in the MTL. Older adults also showed activation increases in the striatum and a correlation thereof with sequence learning. Additionally, however, they also showed activation increases in the MTL, which also correlated with sequence learning. Since sequence memory was largely implicit in both age groups, the additional MTL activation could not be attributed to more explicit knowledge in older adults. Consequently, Rieckmann *et al.* interpreted the MTL activation and its correlation with implicit learning as signs of a compensatory mechanism that is crucial for the preservation of implicit sequence learning capabilities in older adults. Similarly, Dennis and Cabeza (2011) reported also less differentiated MTL and striatum activation of older adults during implicit and explicit memory tasks. Another study (Moody, Bookheimer, Vanek, & Knowlton, 2004) showed MTL activation of PD patients in a probabilistic classification task that contrasted with striatum activation in a control group[6]. Similarly, Voermans and colleagues (Voermans et al., 2004) reported that a route recognition task activated the MTL activity in Huntington's Disease (HD) patients but the striatum in younger adults. In summary, a number of studies indicated a link between aging and diseases affecting the striatum and increased MTL activation during procedural memory tasks. This changed activation pattern co-occurred with relatively spared procedural memory abilities and consequently some authors argued that the elevated MTL activity might compensate for age-related losses in the neural networks subserving procedural memory.

A number of other studies, however, reported diverging results. Increased MTL activation is considered an early marker of AD and is associated with Mild Cognitive

[6]Note that the control group had a mean age of 59.6 years and hence would can be considered a groups of healthy older adults

Impairment (MCI) (Ewers, Sperling, Klunk, Weiner, & Hampel, 2011)[7]. Putcha *et al.* (2011), for instance, showed that hyperactivity within the MTL is associated with cortical thinning and Bakker and colleagues (2012) showed that suppressing this hyperactivity leads to increases in performance of an episodic memory task. Yet other research suggested that aging (Moffat, Elkins, & Resnick, 2006) and non-beneficial genotypes (Banner, Bhat, Etchamendy, Joober, & Bohbot, 2011) are associated with decreased hippocampal activity and memory impairment during a spatial navigation task (see also Grady et al., 1995, for an example using another task), or that aging does not result in changes in hippocampal activity (Schacter, Savage, Alpert, Rauch, & Albert, 1996). To synopsize, few available studies have indicated that aging and disease impair the coordination of the MTL- and the striatum-based memory systems. Moreover, some studies have addressed the consequences of aging and brain pathologies on activity of the hippocampus, but have not converged onto a unitary picture yet. Elevated activity in the hippocampus has been shown in aged rodents (Wilson et al., 2005), MCI patients (Bakker et al., 2012) and older adults (Dennis & Cabeza, 2011). On the one hand, the patient work that focused on episodic memory showed negative effects of this additional MTL activation. The aging work, on the other hand, focused on procedural memory and suggested positive effects. Given these differences in the tested memory function and the studied population groups, it might be that elevated MTL activity affects procedural memory positively but declarative memory negatively. Alternatively, it might be that different mechanisms underlie MTL hyperactivity observed in patient and aging studies.

2.2.6 Theoretical integration: Dedifferentiation, maintenance, and compensation

The above-mentioned patterns of over- and underactivation speak to different theoretical accounts on the relation between cognitive aging and changes in brain activity patterns. In one prominent account, it has been proposed that age-related decline in dopamine function essentially leads to lower neuronal gain and hence noisier information processing (Li, Lindenberger, & Frensch, 2000; Li et al., 2001; Li & Sikström, 2002; Li et al., 2004; Li, Naveh-Benjamin, & Lindenberger, 2005; Li, von Oertzen, & Lindenberger, 2006). This account predicts higher behavioral variability, less distinctive

[7]Note that after the onset of Alzheimer's Disease, most studies observe hippocampal *hypo*activation.

neural representations and higher correlations between tasks in older as compared to younger adults. These predictions are supported by data on behavioral variability (e.g. MacDonald, Li, & Bäckman, 2009), correlations between cognitive capabilities (e.g. Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Li et al., 2004) and neural *dedifferentiation* in humans (D. C. Park et al., 2004; J. Park, Carp, Hebrank, Park, & Polk, 2010; J. Park et al., 2012; Carp, Park, Hebrank, Park, & Polk, 2011; Carp, Park, Polk, & Park, 2011). According to this idea, additional neural activation observed in older adults reflects neural *dedifferentiation*, and hence is a side effect of age-related decline in dopamine functioning. Further studies with aged animals (Schmolesky, Wang, Pu, & Leventhal, 2000; Leventhal, Wang, Pu, Zhou, & Ma, 2003) also showed dedifferentiated representations in visual cortex, which were linked to impairment of γ-Aminobutyric acid (GABA)-ergic inhibitory signals (Lee et al., 2012).

Complimentary to this concept, is has been stressed that less decline on the neural level, and hence more 'youth-like' brain activation, is associated with less cognitive decline (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). In line with this proposal, Düzel and colleagues showed that older adults had greater brain and cognitive healthiness when their brain activity patterns were more similar to the patterns of younger adults (Düzel, Schütze, Yonelinas, & Heinze, 2011). Moreover, Persson *et al.* (Persson et al., 2012) showed that longitudinal decline in hippocampal activity and volume was associated with decline in episodic memory (see also Persson et al., 2006). This idea of *maintenance* would also emphasize that hippocampal overactivation (or underactivation) is a sign of the adverse effects of aging on brain functioning. Finally, a third theoretical approach has been offered that proposes that different brain activation patterns in older adults might be related to compensatory mechanisms, without which more cognitive decline would result (Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Cappell, 2008; D. C. Park & Reuter-Lorenz, 2009). This account is supported by a large number of studies showing overactivation in older adults, many of which also show positive correlations between performance and overactivation (for a review, see Eyler, Sherzai, Kaup, & Jeste, 2011). However, most of the studies and theories have concentrated on decreased laterality (Cabeza, Anderson, Locantore, & McIntosh, 2002) and overactivation in the prefrontal cortex (D. C. Park & Reuter-Lorenz, 2009), rather than hippocampal hyperactivation.

In summary, the varying findings about the role of hippocampal and striatal activity for episodic and procedural memory in older adults might reflect multiple phenomena. According to the dedifferentiation and maintenance accounts, hippocampal overactivity might reflect signaling deficiencies and should be related to worse performance. A compensation account, in contrast, predicts that this activity is an adaption to the challenges caused by declining neural resources. While each of the above named three hypotheses is supported by some empirical evidence, to date no account can explain the diversity of findings.

In the face of this picture, one important step might be to investigate the properties of the neural activation in the hippocampus in more detail. Specifically, making precise predictions about the time course of activity based on computational models could can be used to differentiate between activity that reflects meaningful computational processes and activity related to signaling deficiencies.

Table 1 summarizes a selection of relevant studies discussed in the Introduction. The table illustrates the effect of brain damage, aging and hippocampal hyper-/hypoactivity on declarative and procedural memory. Each row represents one study/condition that examined the effect of brain damage on memory performance. As can be seen, many studies showed that lesion- or disease-induced damage to one system leads to impairment of its proposed function. Interestingly, some studies showed that impairing MTL functioning led to an increase in procedural memory functions (Packard et al., 1989; McDonald & White, 1993; Schroeder et al., 2002), and that impairment in striatum functioning led to improved declarative memory (Mitchell & Hall, 1988). Moreover, it becomes apparent from Table 1 that larger activation in the MTL, as compared to controls, is a repeated finding in patients suffering from MTL- as well as striatum-related diseases or risk factors. Among the listed aging studies, this relation is much more heterogeneous, with some studies reporting overactivation, others underactivation and some no differences. Finally, reports that could speak to the relation between activation in the hippocampus and memory performance under conditions of adverse physiological brain changes seem contradicting. Whereas some studies show beneficial effects of hippocampus activity (Rieckmann et al., 2010), others speak to the contrary (Bakker et al., 2012).

		Structural		Activity		Memory		
Study	Impairment	MTL	Striatum	MTL	Striatum	Declarative	Procedural	Task
Rodents								
Packard et al., 1989	Lesion	−	0			−	+	8-Arm Maze
McDonald & White, 1994	Lesion	−	0			−		Morris Water Maze
McDonald & White, 1993	Lesion	−	0			−	+	8-Arm Maze
Packard et al., 1989	Lesion	0	−			0	−	8-Arm Maze
Mitchell & Hall, 1988	Lesion	0	−			+	−	Y Maze
McDonald & White, 1993	Lesion	0	−			0	−	8-Arm Maze
Schroeder et al., 2002	Anesthetic	0	0	−		−	+	Cross Maze
Packard & McGaugh, 1996	Anesthetic	0	0	−	0	−	0	Cross Maze
Packard & McGaugh, 1996	Anesthetic	0	0	0	−	0	−	Cross Maze
Wilson et al., 2005	Aging	−	−	+		−		Morris Water Maze
Patients/Risk Populations								
Knowlton et al., 1996	Amnesia	−				−	0	Probabilistic Classification
Bookheimer et al., 2000	APOE $\epsilon 4$	−		+	0	−		Cued Recall
Mormino et al., 2012	Increased Aβ	−		+		−		Subsequent Memory
Bakker et al., 2012	aMCI	−		+		−		Recognition
Bakker et al., 2012	aMCI	−		0		0		Recognition
Voermans et al., 2004	HD		−	+	0		0	Route Learning
Knowlton et al., 1996	PD		−			0	−	Probabilistic Classification
Moody et al., 2004	PD		−	+	0		0	Probabilistic Classification
Shohamy et al., 2004	PD		−			0	−	Probabilistic Classification
Older Adults								
Maguire & Frith, 2003	Aging	−	−	+	0	0		Autobiographic Memory
Dennis & Cabeza, 2011	Aging	−	−	+	0	0	0	SRTT/Recognition
Rieckmann et al., 2010	Aging	−	−	+	0	−	0	SRTT
Moffat et al., 2006	Aging	−	−	−	−	−		Virtual Reality Task
Gutchess et al., 2005	Aging	−	−	−	+	−		Subsequent Memory
Grady et al., 1995	Aging	−	−	−		−		Recognition
Schacter et al., 1996	Aging	−	−	0	0	−		Verbal Recall

Table 1: *Results of studies investigating effects of brain changes on memory performance.*

Note: The table provides only a selection, not an exhaustive overview of studies. '+': greater than normal; '−': less than normal; '0': normal level. Different groups from the same study are listed as own rows, control groups are left out. In light of the uncertainty regarding differences in hippocampal and striatal aging (see section 2.2.1), aging is assumed to result in damage to both structures.

Chapter 3

SUMMARY AND RESEARCH QUESTIONS

The previous chapter outlined evidence for multiple memory systems that process different kinds of information. One system is based primarily on the MTL (section 2.1.1) and subserves declarative memory, which is manifested in the ability to consciously recall past episodes and allocentric spatial memory. The second system, procedural memory, is mainly striatum-dependent (section 2.1.2) and characterized by gradual acquisition, limited accessibility by consciousness and processing of feedback. Both systems can function independently, but research has also indicated that interaction among them might be a common phenomenon (section 2.1.3).

The neurological substrates of procedural and declarative memory are severely affected by aging (see 2.2.1). In addition, many findings indicate that age-related changes in these brain networks are related to decline in their respective memory functions. Moreover, it has been shown that genetic factors that influence aspects of neurological functioning in memory systems play an increasingly large role for cognition in aging.

Interestingly, the pattern of aging memory cannot always be fully explained by the pattern of brain aging. While evidence for an asymmetry in the decline of MTL/striatum function is lacking, some cognitive functions related to procedural memory seem less impaired than declarative memory (see 2.2.4). Currently, it is not yet clear if the observation of spared implicit memory in older adults is also true for tasks that involve different aspects of procedural memory. Moreover, previous research has rarely taken into account the interactions of memory systems, although evidence indicates that aging impairs the ability to switch between memory systems.

Finally, elevated hippocampal activity has repeatedly been reported to co-occur with disease and aging, but the meaning of this phenomenon remains unclear. For example, a study by Bakker *et al.* (Bakker et al., 2012) showed that reducing elevated hippocampus activity in aMCI patients led to improvements in a recognition task. A study by Rieckmann *et al.* (Rieckmann et al., 2010), in contrast, showed that older

adults with more hippocampus activity performed better in an implicit learning task. Note, however, that the latter findings differ with respect to the tested memory function. Hence, it could be that elevated hippocampus activity is associated with impaired declarative and preserved procedural memory. These conclusions, however, are yet to be replicated and confirmed more directly. A better understanding of the properties of the observed hippocampal activity could be an important step for understanding these results.

Here, I argue that the study of human aging might benefit from understanding the relations between structural decline, functional activity, and cognitive impairment in procedural and declarative memory systems. Specifically, the present dissertation aimed to address the following questions:

1. Does the observed relative sparing of procedural memory extend beyond implicit memory to other forms of memory that are striatum-dependent? In particular, it was investigated whether primarily striatum-dependent spatial memory is less affected than primarily MTL-dependent spatial memory.

2. What is the effect of memory system cooperation on observed age-differences in the SRTT? Specifically, do younger adults show improved learning because they engage multiple memory systems in a cooperative manner? Such a 'cooperation' would for example be evident in a successful switching from one system to the other that is associated with better memory performance.

3. How do genetic factors that influence key biological mechanisms in the MTL and striatum impact memory in younger and older adults?

4. What is the impact of aging on memory-related neural *computations* and their localization?

The present dissertation is publication oriented and the above named questions are addressed in different papers. Question 1 is addressed in *Paper III* and *IV*. Question 2 is addressed in *Paper I*. *Papers I* and *III* also speak to Question 3. Question 4 is addressed in *Paper II* and *IV*. The following chapter will describe these papers.

Chapter 4

OVERVIEW OF PUBLICATIONS

The present dissertation includes four articles. *Papers I*, *III* and *IV* are based on work that was conducted within the Neuromodulation of Lifespan Cognition Project, Center for Lifespan Psychology, at the Max Planck Institute for Human Development in Berlin. The project was headed by Prof. Shu-Chen Li and the department is headed by Prof. Dr. Ulman Lindenberger. *Papers I* and *III* included genotyping of a group of younger (aged 20-30 years) and older (aged 60-71 years) adults. Genotyping was done by the group of Dr. Lars Bertram at the Max Planck Institute of Molecular Genetics. Data acquisition reported in *Paper II* was conducted at University of Princeton by Dr. Ben Eppinger and supported by NIA grant AG02436 awarded through the Princeton Center for Health and Wellbeing.

4.1 Paper I

Schuck, N.W., Frensch, P.A., Schjeide, B.M., Schröder, J., Bertram, L. & Li, S.-C. (under revision). Effects of aging and dopamine genotypes on the emergence of explicit memory during incidental sequence learning. Revision invited by *Neuropsychologia* on April 25, 2013, resubmitted June 25, 2013.

The major aim of this paper was to investigate age-differences in the switch between memory systems in younger and older adults and the influence of dopaminergic genes on implicit and explicit memory. To this end, we took an extreme groups approach involving a sample of 70 older adults (aged 60-71 years) and 80 younger adults (20-30) in combination with a candidate gene investigation.

Theoretical background Less age-related losses in implicit as compared to explicit memory have been reported in a number of studies using the SRTT (e.g., D. Howard & Howard, 1989). In line with the proposed link between the striatum and implicit memory, genetic factors that influence dopaminergic signaling have been shown to influence implicit learning in younger adults (Simon et al., 2011). Generally, however,

it has been shown that genetic effects on cognition can be magnified in older adults (Lindenberger et al., 2008). Moreover, the SRTT might involve a switch from implicit to explicit memory, and some evidence indicates that the ability to switch between procedural and declarative memory could be impaired in aging (Dagnas et al., 2013). In line with this, it was previously reported that aging might impair the use of explicit sequence knowledge during implicit learning (Verwey, 2010; Verwey, Abrahamse, Ruitenberg, Jiménez, & Kleine, 2011). Finally, the striatum might play a role in the transition from implicit to explicit sequence knowledge (Rose, Haider, & Büchel, 2010).

Hypotheses In the present study, we investigated the development of explicit knowledge during an incidental learning task and the effect of polymorphisms on the dopamine- and cAMP-regulated neuronal phosphoprotein (*DARPP-32*, rs907094) and dopamine transporter (*DAT*, VNTR) genes on implicit and explicit memory. Based on the above mentioned findings, we hypothesized that learning in the SRTT involves the transition from procedural/implicit to declarative/explicit memory and that older adults might be impaired in this transition. Moreover, the known role of the striatum in implicit learning as well as in the transition to explicit learning suggested that dopamine-related genotypes would be associated with (a) individual differences in implicit learning and (b) the transition to explicit learning. Additionally, based on the reported magnification of genetic effects with age, we also expected the genotype effect to be stronger in older as compared to younger adults.

Major findings Using a method to continuously monitor learning-related RT reductions, we found that younger and older adults showed equivalent learning during the first 70 repetitions of a sequence. With further practice, however, younger adults continued to improve, whereas older adults did not. After training, measures of explicit memory showed that younger adults had larger explicit but comparable implicit memory as compared to older adults, and correlation analysis indicated that the continuing decrease in RTs after 70 repetitions might be related to the emergence of explicit knowledge. Finally, the studied polymorphisms (*DARPP-32*, rs907094 and *DAT*, VNTR) showed effects on overall RTs and verbal recall in older but not in younger adults. This study was the first report that indicated (a) a link between the grad-

ual emergence of age differences in the SRTT and the emergence of explicit memory and (b) age-magnified and interactive effects of polymorphisms on the *DARPP-32* and *DAT* genes on explicit knowledge and RT level. Hence, the study provided further support for an age-related impairment in the interaction of memory systems as well as a magnified effect of DA-related genotypes on explicit sequence memory in older adults. The latter effect was unexpected given previous reports that linked *DAT* to implicit learning in younger adults (Simon et al., 2011). Rather, it could support the idea of changed brain-cognition relations in older adults, or the role of the striatum in the transition between memory systems (Rose et al., 2010).

4.2 Paper II

Eppinger, B., **Schuck, N.W.**, Nystrom, L.E., & Cohen, J.D. (2013) Reduced striatal responses to reward prediction errors in older compared to younger adults. *Journal of Neuroscience*, *33*, 9905–9912. doi:10.1523/JNEUROSCI.2942-12.2013

Paper II was conducted in collaboration with Ben Eppinger, Leigh Nystrom and Jonathan Cohen from Princeton University and involved a sample of 13 older and 13 younger adults. The main goal of this paper was to investigate age-related impairment in neural computations underlying memory subserved by the striatum.

Theoretical background As outlined in the Theoretical Background (2.2.2), it is well known that the DA system deteriorates during the course of aging (Li, Lindenberger, & Bäckman, 2010) and that these impairment likely are related to declined cognitive functioning (Bäckman et al., 2006). Moreover, many studies suggested that the calculation of a prediction error signal is a core computational function of the striatum and provides the basis of its reinforcement-related learning functions (Schultz, 2002). Given the partially spared striatum-related learning functions reported in many studies and replicated in *Paper I*, it seems crucial to investigate effects of aging on this computational function of the striatum. Hence, using a combination of computational modeling and fMRI, *Paper II* investigated age differences in information about prediction errors in brain signals during a reinforcement learning task.

Hypotheses The well known age-related impairment in DA functioning as well as in reinforcement learning clearly point to reduced striatal prediction error signals in

older as compared to younger adults. Additionally, however, age-related impairment in reinforcement learning have been shown to be asymmetric for learning from positive and negative feedback (Frank & Kong, 2008). Finally, based on data indicating potentially different mechanisms for positive and negative reinforcement learning (Yacubian et al., 2006), we expected age differences in positive but not negative prediction error signals.

Major findings In line with our hypothesis, we observed age-related impairment in learning from reward but not in learning from losses. Congruous with these findings, BOLD activity in the ventromedial PFC was reduced in older as compared to younger adults only during positive learning. The model-based fMRI analysis revealed that evidence for avoidance-based reward prediction errors could be found in both age groups, but older adults showed less evidence of prediction errors in the positive condition. Hence, *Paper II* was the first to show partial age impairment in the learning-related computations underlying striatal memory functions in humans using fMRI.

4.3 Paper III

Schuck, N.W., Doeller, C.F., Bisenack, J., Schjeide, B.M., Frensch, P.A., Bertram, L. & Li, S.C. (2013). Aging and KIBRA/WWC1 genotype affect spatial memory processes in a virtual navigation task. *Hippocampus*. Advance online publication. doi:10.1002/hipo.22148.

Paper III investigated whether different forms of spatial memory also exhibit an asymmetry in age-related differences, depending on whether the memory is dependent on the striatum or the MTL in younger adults. Moreover, it investigates the effect of a genetic polymorphism on the *KIBRA* gene (which impacts hippocampal LTP) on these learning forms.

Theoretical background Given the differing definitions and operalizations of striatum - dependent procedural memory, it seems important to investigate the generalizability of the asymmetric age-associated decline. To this end, we utilized a virtual reality task that was previously designed to disentangle hippocampus- and striatum-based spatial navigation (Doeller et al., 2008). Doeller and colleagues showed that learning objects relative to a boundary of the environment was related to hippocampus activation, whereas learning locations relative to an intra-maze landmark (a visual cue) was associated with striatum activation. These findings are well in line with the

known role of boundary distance information in hippocampal place cells (O'Keefe & Burgess, 1996; Burgess & O'Keefe, 1996) and the role of intra-maze cues for striatum-dependent spatial learning (Packard & McGaugh, 1992). Moreover, we used a candidate gene approach to investigate the effects of SNP rs17070145 of the *KIBRA* gene (official name: *WWC1*). The KIBRA protein is known to affect hippocampal LTP via its effect on PKMζ and the utilized SNP has previously been shown to be related to episodic memory (see Milnik et al., 2012, for a review).

Hypotheses In line with previous reports, *Papers I* and *II* indicated that memory functions that are related to the striatum in younger adults, were only partially impaired in older adults. Moreover, insofar a behavioral impairment was observed, a dysfunction on the level of neural computations could also be shown. In the present investigation, we extended the study of age differences in memory functions related to the striatum in younger adults to spatial navigation. We used a task that closely links to the animal studies that gave important insights into memory systems (see section 2.1) and investigated landmark- and boundary-based spatial memory. Following the assumption that the observed phenomenon of asymmetric decline is not confined to single tasks, we predicted a greater reliance on landmark-based spatial navigation in older adults, but a greater reliance on boundary-based navigation in younger adults. Such a finding would indeed be also in line with studies showing that older adults rely more on extrahippocampal strategies as compared to younger adults (Moffat, Kennedy, Rodrigue, & Raz, 2007; Wiener, de Condappa, Harris, & Wolbers, 2013) during spatial navigation.

Major findings All participants performed a virtual reality spatial navigation task in which locations could be learned either relative to a visual cue or to a boundary. The behavioral data showed that learning in older adults was mostly based on processing of landmark information, but in younger adults it was related to processing of boundary information. Moreover, we found an effect of *KIBRA* rs17070145 genotype on learning only among older adults (T-allele carriers were better than C homozygotes). Additional analyses showed that carriers of the beneficial *KIBRA* allele showed improved landmark, but not boundary, processing. These findings show age-related asymmetries

in the role of landmark and boundary information processing during spatial navigation and support the generalizability of the previous findings of less impaired implicit learning. Moreover, this paper was the first to report an age magnification of an effect of *KIBRA* (rs17070145 polymorphism) on spatial memory in humans.

4.4 Paper IV

Schuck, N.W., Doeller, C.F., Polk, T.A., Lindenberger, U. & Li, S.-C. (in preparation). Human aging alters neural representations and computations during spatial navigation.

Paper IV aimed to investigate the underlying neural processes of boundary- and landmark-based learning in older and younger adults. We utilized a model of hippocampal place-cell processes to make trialwise predictions of the BOLD signal that would indicate that a region is involved in this processing. In addition, we defined such predictions for the processing of landmark information. Hence, this experiment enabled us to study the underlying neural computations of spatial memory, their relations to different aspects of performance and their localization in the brain.

Theoretical background Many studies showed that hippocampal place-cell representations are degraded in aged rats (e.g., Barnes et al., 1997; Shen et al., 1997). As already outlined in the description of *Paper III*, models and data of place-cell firing (O'Keefe & Burgess, 1996) highlight a dominant role of information about the distance to boundaries for place-cell representations (Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009). At the same time, place-cells are less sensitive to visual cues. Moreover, animal research has shown the current state of place-cells retains a stable relation to memory (O'Keefe & Speakman, 1987), such that models of place-cells can be used to make behavioral predictions (Hartley, Trinkler, & Burgess, 2004). Hence, *Paper IV* investigated the match between predictions made by a place-cell model and behavior and neural activity observed in younger and older adults. This place-cell model was contrasted with a simple model that emphasized the processing of landmark information.

Hypotheses In replication and extension of the findings from *Paper III*, it was expected that younger adults' behavior would fit better with the place-cell model as

compared to the landmark model, but in older adults, a greater match with the landmark model was anticipated. Moreover, given these differences on the level of behavior and their proposed links to brain processes, we anticipated greater MTL activation in younger adults, but greater striatum activation in older adults. In addition, in light of reports of additional MTL activation in older adults performing a task that is striatum-dependent, and the results from *Paper III* that showed an involvement of *KIBRA* genotype on spatial navigation in older adults, additional MTL activation was also expected in older adults. Finally, with respect to the brain activation that reflects the model's predictions, we expected correlations of brain activity in the MTL with predictions from the place-cell model in younger adults. Likewise, it was expected that activity in the striatum would be correlated with the predictions from the landmark model in older adults. Finally, the finding that *KIBRA* polymorphism rs17070145 had an influence on landmark-based learning in older adults, suggested that BOLD activity related to landmark processing might be found in the MTL.

Major findings During a transfer phase with modified spatial information, younger adults' behavior was consistent with a model of place cell firing, whereas older adults behaved consistently with landmark information processing. In line with these findings, younger adults showed recruitment of the hippocampus, but older adults showed activations in the caudate nucleus during learning. Results from model-based analyses indicated that the activity in the parahippocampal gyrus was related to the processing of boundary information in younger adults, but activity in the hippocampus to landmark learning in older adults. Using a more lenient statistical threshold ($p < .005$, clustersize = 20), older adults' activity in the caudate nucleus also showed indications of landmark information processing. These results suggest differences in the neural computations and representations underlying spatial memory and show a fundamental change in the neural computations characterizing different memory systems in younger and older adults.

Chapter 5

DISCUSSION

In the following chapter, I will summarize the findings of all studies and integrate these into existing knowledge and the debate about aging of memory systems. In addition, I will consider the most significant limitations and outline potential avenues for future research based on the conclusions that can be drawn from the presented experiments.

5.1 Summary and Evaluation

5.1.1 Procedural memory is partially intact in older adults

Previous studies indicated that older adults are less impaired in implicit memory (D. Howard & Howard, 1989; Rieckmann et al., 2010), but it is an open question whether it can be inferred from these studies that on a general level, aging does impair procedural memory less than declarative memory. *Paper I* showed that learning in the SRTT is initially comparable in younger and older adults. After extended training, however, a disadvantage of older adults became evident. *Paper II* indicated that reinforcement learning from negative outcomes, but not from positive outcomes, was unimpaired in older adults. In *Papers III* and *IV*, the generalizability of the relative sparing of procedural memory functions was further corroborated. In particular, this research showed that older adults' memory performance was relatively more intact for landmark as opposed to boundary-based spatial memory, two phenomena that in younger adults are related to procedural and declarative memory (Doeller & Burgess, 2008) and to striatal and hippocampal activity (Doeller et al., 2008), respectively. These papers indicated that in a situation in which both memory systems could be used, older and younger adults showed qualitatively different memory representations that incorporated different aspects of the spatial environment. In addition to experimental manipulations and mean differences, the findings of *Paper IV* used quantitative predictions about memory and neural responses and provided strong support for the

findings of *Paper III*.

5.1.2 Interaction of memory systems

Another important question is whether aging changes the interaction of procedural and declarative memory. Few previous studies in animals have indicated that aging might impair the ability of switching between the two memory systems (Dagnas et al., 2013). To investigate this question in humans, *Paper I* utilized an incidental sequence learning task in which learning is initially implicit/procedural but can become increasingly more explicit/declarative over the course of training. In this study it was shown that age differences, as measured by differences in RT gains, gradually emerged over the course of training. Moreover, at the end of training younger adults had more explicit and equivalent implicit memory about the sequence. Correlational analyses indicated that the emergence of explicit memory had been related to the memory benefits of younger adults. Hence, younger adults showed successful cooperation of memory systems, whereas older adults did not show this pattern. Given similar previous observation about an specific impairment in explicit memory (D. Howard & Howard, 1989), this finding was not surprising. In contrast to previous studies, however, it showed that within the SRTT, age differences in RTs might have been a function of the development of explicit knowledge. Although these results were not conclusive, they were in line with animal studies showing that not only declarative memory performance is impaired in aging, but that a reduced switching between memory systems might be an additional consequence.

5.1.3 Magnification of genetic effects in older adults

Another important topic in the study of cognitive aging is the possibility that a nonlinear relationship between brain resources and cognition leads to magnification of genetic effects with aging (Lindenberger et al., 2008). In line with this proposal, several studies have shown that DA-related genotypes played an larger role in older as compared to younger adults (Li et al., 2013; Papenberg et al., 2013; Hämmerer et al., 2013, see also Störmer et al., 2012). Moreover, the pattern of age selective or age-magnified effects on cognitive variables has been extended to BDNF genotypes (Nagel et al.,

2008; Li, Chicherio, et al., 2010). *Papers I* and *III* of the present dissertation further corroborated these findings. Specifically, *Paper I* showed that a combination of two non-beneficial DA-related genotypes (see also Papenberg et al., 2013; Bertolino et al., 2009) was associated with slower RTs and less explicit sequence knowledge in older but not younger adults. In *Paper III* it was observed that the SNP rs17070145 on KIBRA/WWC1 was associated with better spatial memory performance and more landmark processing in older but not younger adults. Both of these findings showed an age-related magnification of genetic effects on memory and hence are in line with the resource modulation hypothesis.

Interestingly, while genetic effects in both cases were expected, the observed relations to the procedural and declarative aspects of memory were surprising. In fact, these seemed to contradict the known relation of the genetic factors to brain processes on the one hand and the known relation of brain processes to memory performance on the other hand. In particular, the dependence of implicit/procedural memory on the striatum would have predicted an effect of DA-related genes on implicit, but not explicit memory. Likewise, the link between the *KIBRA* protein and hippocampal LTP would suggests that *KIBRA* has an effect on boundary-based learning. Instead, we found that in older adults *KIBRA* had an effect on landmark-based learning. These findings are clearly surprising at first, but at second sight they might be reflections of the changes in brain-cognition relations that have been a topic of this thesis. This idea is most clearly supported by our findings in *Paper IV*, in which landmark-related processes in older adults were indeed linked to hippocampal activity, and hence provided support for the interpretation offered above. Moreover, the effect of DA-related genotypes on implicit learning could be related to an increased role of the MTL in implicit learning (Rieckmann et al., 2010).

5.1.4 Impairment of neural computations related to the procedural and the declarative memory systems

While lesion-based animal studies only offered global insights into links between brain areas and cognitive function, neurophysiological research has offered insights into some of the neural mechanisms underlying declarative and procedural memory. In particular, numerous studies have shown that the striatum engages in the computation of

prediction errors during reinforcement learning (Schultz, 2002). Moreover, it has been reported that hippocampal neurons use boundary distance information in the computations underlying place cell firing (Burgess & O'Keefe, 1996). Model-based fMRI was utilized in *Papers II* and *IV* to investigate these computations in older and younger humans. *Paper II* utilized a reinforcement learning paradigm and showed that younger and older adults learned equivalently well from negative outcomes, but younger outperformed older adults in learning from positive outcomes. Consistent with this picture, younger adults had greater prediction error-related activity in the nucleus accumbens during positive but not negative learning, indicating a partial age-related impairment in these neural computations. *Paper IV* investigated the brain activity related to boundary-based learning during a spatial navigation task. As mentioned above, the analysis of memory performance indicated that younger adults used boundary distance information to support memory of spatial locations, whereas older adults primarily relied on a visual cue. Younger adults' neural activity in the parahippocampal gyrus during spatial learning was also greater for locations that were linked more strongly to the boundary distance, but correlations between hippocampal activity and landmark processing were evident in older adults. These results are in line with changed neural computations during spatial learning in older as compared to younger adults, and might indicate a deficit in older adults' neural implementation of a cognitive map. *Studies II* and *IV* were the first to investigate age-related memory deficits on a level of neural computations.

Neural dedifferentiation

In addition to this degradation on the level of neural computations, *Paper IV* observed a changed pattern of brain activation in older adults. In terms of mean activation, older adults showed hippocampal as well as striatal activation, whereas younger adults showed activity only in the hippocampus and deactivation in the caudate nucleus. Interestingly, the analysis of activity related to landmark processing showed that in older adults hippocampus activity was associated with processes that in younger adults have been shown to reside in the caudate nucleus. Using a more lenient statistical threshold additionally revealed that activity in a striatal-hippocampal network was related to cue-related spatial information processing. These results demonstrated that

neural computations related to the striatum in younger adults can be found in the MTL in older adults. This was also in line with the effect of *KIBRA* genotype on landmark-based spatial learning in older adults found in *Paper III*. At the same time, older adults exhibited grave performance impairment. To clarify whether this finding can be interpreted as dedifferentiation or compensation, however, detailed analyses linking the performance to an indicator of neural dedifferentiation will be necessary (see section 2.2.6).

5.2 Limitations

5.2.1 Procedural and declarative memory systems

Despite many animal and patient studies showing dissociations between procedural and declarative memory, the definitions of and the border between these two concepts are often fuzzy. Different tasks that are assumed to be indicative of procedural memory can vary with respect to cognitive factors such as the involvement of external rewards (compare the reinforcement learning task used in *Paper II* and the implicit serial learning task in *Paper I*) and the accessibility by consciousness (compare the SRTT to the spatial navigation task, where the aspect of consciousness is not clear). Moreover, there is a continuing debate about the relation of episodic memory and spatial memory based on a cognitive map (Eichenbaum et al., 1999; Kumaran & Maguire, 2005). Hence, some uncertainty with respect to the precise definitions of these concept remains. In addition, the neural bases of either memory system are also not as clear as some literature suggests. Neuroimaging studies rarely show isolated activations of the striatum or the MTL during procedural or episodic memory, respectively, and often indicate a prominent role of the frontal cortex in association with episodic memory and a prominent role of the cerebellum during procedural learning. Lesion studies offer a firmer basis for inference about the necessity of a brain region for a cognitive function, but lesions might also induce (reorganizational) changes in other brain areas or their connectivity – a possibility that is rarely accounted for. Patient studies suffer from the same disadvantage and additionally cannot offer precise information about the location of the distribution of the damages in the used sample. Additionally, some studies have challenged the links between procedural and declarative memory functions and their

proposed neural bases by showing that amnesic patients are impaired in implicit memory (Chun & Phelps, 1999), or hippocampal activation can be found during implicit learning (Degonda et al., 2005; Schendan, Searl, Melrose, & Stern, 2003).

Many of the above-mentioned complications about the heterogeneity of the cognitive constructs and their neural bases apply to this dissertation. To circumvent some of these problems, the present dissertation sought to generalize some phenomena by combining data from different paradigms. To establish definitions of the concept, the functional neurobiology of younger adults was taken as a reference point for the terms procedural and declarative memory. At the same time, this dissertation tried to alleviate some of these concerns by focusing on computational mechanisms that offer a relatively precise definition of cognitive function.

5.2.2 Cross-sectional design

The aim of the present research was to provide further information about changes in behavior and brain-behavior relations that occur during the course of aging. Strictly speaking, however, these questions cannot be answered with a cross-sectional design, because differences between age groups do not necessarily reflect longitudinal changes (Hofer & Sliwinski, 2001) and hence the inference about longitudinal changes that can be drawn from any cross-sectional study is limited. One particular relevant factor are cohort effects – mean differences between different birth cohorts – which often appear in the form of educational differences and bias cross-sectional designs (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Likewise, in the present research on spatial navigation (*Papers III* and *IV*), cohort differences stemming from the vastly changed environmental demands on mobility could be a contributing factor to the obtained results. This assumption is for instance supported by data from the Seattle Longitudinal Study that showed cohort effects in spatial orienting (Schaie, 1996). Moreover, Nyberg and colleagues (Nyberg et al., 2010) showed that even changed brain patterns (overrecruitment) can be a result that appears only in cross-sectional but not in longitudinal analyses and might be a reflection of selective age samples. Accordingly, the here presented findings about changed brain activity and changed neural representations can only be interpreted with caution and eventually will need confirmation from longitudinal studies.

5.2.3 Neurogenetic approach

The many contradicting results of studies that combined cognitive neuroscience with genetic data undoubtedly witness the methodological problems of the field (Payton, 2009; Green et al., 2008). The most prominent shortcoming of the present dissertation in this regard is its small sample size, which – although not unusual in the literature – does not meet the recommended criteria for neurogenetic studies. Previous studies have shown that to-be-expected effect sizes are very small, often well below 1%, and given an average power of 80% this would require a sample size of greater than 800 (Payton, 2009). Hence, a replication of the effects reported in *Studies I* and *III* will be necessary, preferably using independent and much larger samples. A further criticism concerns the investigated psycho- or neurological traits, which are relatively ill-defined and suffer from measurement problems such as ceiling effects. As I outlined above (section 5.2.1), the present dissertation also suffers from these limitations of imprecise definitions of psychological traits. At the same time, however, the used measures of memory might have been in the right range of difficulty and at the same time sensible enough to pick up the reported associations. Previous research has indicated that genetic effects might only be found at the right level of demand (Li, Chicherio, et al., 2010). In addition, the potential value of the genetic findings presented here is increased by the investigations of gene-gene as well as gene-age interactions. Given that proteins encoded by genes often have many interaction partners, which in turn are influenced by different genes as well as other biological factors such as age, studying such interactions might be crucial for finding larger effects (Payton, 2009).

5.3 Future Directions and Conclusions

Memory is expressed in many ways, ranging from being able to drive a bicycle to the ability to vividly re-experience past events. The neurobiology of memory reflects this diversity. Accordingly, memory has been classified into different memory systems, which are characterized by the kind of information that is stored and the systems of neural structures that support these functions. The resulting taxonomy has proven to be a greatly successful approach for describing and understanding the effects of many neurological diseases on cognitive functioning. In many cases, isolated neural damage

has been described to result in isolated impairment for one but not the other memory system. Yet, the assumption that these memory systems are independent does not seem to fully suffice to explain all evidence. Data on human memory and brain aging is one interesting case that underlines this difficulty: the apparently equivalent age-related impairment in the neurological bases of declarative and procedural memory do not induce equivalent impairment in these memory functions.

A review of the literature suggested that the assumption of independence is countered by many available sources of evidence. Animal, patient and aging studies have consistently shown that adverse effects on the neural substrate of one memory system can have implications for the cognitive functioning of another system. Taken together, the reviewed findings suggested that in a healthy brain, MTL- and striatum-based memory are balanced. This balance is on the one hand stabilized by inhibitory connectivity and on the other hand flexible enough to allow for shifts between the memory systems with ongoing training, changed environmental or neurochemical conditions. The underlying mechanisms of these observations are unclear, and the diversity of findings suggests that they are probably caused by multiple factors.

Based on these insights, the question arises how the asymmetry in the cognitive decline of procedural and declarative memory can be explained. The present dissertation was devoted to provide a starting point that could help to understand these issues better. *Paper I* showed that age-differences in an implicit/procedural learning task emerged because younger adults developed explicit/declarative memory and increasingly used this memory. *Paper II* indicated that aspects of procedural memory which were preserved in older adults were linked to preserved neural processes in the striatum. It was demonstrated in *Paper III* that the asymmetric impact of aging of memory could also be found in a spatial navigation paradigm that tested novel aspects of procedural and declarative memory. *Paper IV* showed that in younger adults, neural computations related to declarative memory were reflected in behavior and neural activity within the MTL. In older adults, in contrast, behavior and neural activity within the striatum reflected procedural memory. Interestingly, however, older adults also showed elevated MTL activity that was related to procedural memory. Hence, these results indicated

- partially intact procedural memory-related cognitive functions in older adults
- partially intact procedural memory-related neural processes in older adults
- the impact of memory system interaction on observable age-differences
- procedural memory-related neural processes in the MTL and the striatum of older adults.

To further investigate the effect of factors that differentially influence neural processes in the declarative and procedural memory system, *Papers I* and *III* utilized a neurogenetic approach. In line with the resource modulation hypothesis, both studies found that genetic effects were only evident in older adults. Moreover, in both studies the effect of the genotypes related to memory functions that in younger adults are ascribed to the 'opposing' memory system. Specifically, genotypes related to DA processes in the striatum affected declarative memory in *Paper I* and the polymorphism rs17070145 on the hippocampus-related gene *KIBRA/WWC1* affected procedural memory in *Paper III*.

In conclusion, these results suggest that preserved performance in procedural memory tasks was related to preserved neural computations in the striatum. Moreover, however, procedural memory functioning was also affected by *KIBRA* rs17070145 and procedural memory related neural computations could be found in the MTL. Hence, in addition to striatal functioning, the MTL was also related to procedural memory in older adults. The exact reason for the latter findings remains unclear. In principle these results are in line with the computational theory of neuromodulation (e.g., Li et al., 2001) which predicts *dedifferentiated* neural activation. As outlined above, one interesting possibility concerns a changed balance between the MTL- and striatum-based system that could for example result from less inhibition between the two systems. From a different perspective, the findings could also indicate a compensatory mechanism (Rieckmann et al., 2010). The present results extended beyond previous reports as they showed activity related to neural computations rather than just elevated mean activity. Because from *Paper IV* it appears that the additional MTL activation was indeed carrying out computations that are localized in the striatum in younger adults, this result was consistent with one of the key properties of compensation.

These conclusions provide avenues for future research. Firstly, analyzing the functional and structural connectivity between the MTL and the striatum will be an important endeavor to understand the possibility of a changed balance between the declarative and procedural memory systems. Secondly, detailed analyses that quantify the match between the localization of neural computations in younger and older adults will be necessary to understand the link between the changed localization and memory performance. Thirdly, relating age-related changes in the structural and neurochemical state of the procedural and declarative memory systems to the localization of neural processes and the performance will give further important insights. Finally, a longitudinal approach to all these research enterprises will be of crucial importance to understand the effect of age-related *changes* on *changes* in memory performance and its underlying neural mechanisms.

REFERENCES

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., et al. (2008). Both the hippocampus and striatum are involved in consolidation of motor sequence memory. *Neuron*, *58*(2), 261–72.

Aosaki, T., Kimura, M., & Graybiel, A. M. (1995). Temporal and spatial characteristics of tonically active neurons of the primate's striatum. *Journal of Neurophysiology*, *73*(3), 1234–52.

Bach, M. E., Barad, M., Son, H., Zhuo, M., Lu, Y. F., Shih, R., et al. (1999). Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(9), 5280–5.

Bäckman, L., & Farde, L. (2001). Dopamine and cognitive functioning: Brain imaging findings in Huntington's disease and normal aging. *Scandinavian Journal of Psychology*, *42*(3), 287–296.

Bäckman, L., & Farde, L. (2005). The role of dopamine systems in cognitive aging. In R. Cabeza & L. Nyberg (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 58–84). New York: Oxford University Press.

Bäckman, L., Lindenberger, U., Li, S.-C., & Nyberg, L. (2010). Linking cognitive aging to alterations in dopamine neurotransmitter functioning: Recent data and future avenues. *Neuroscience and Biobehavioral Reviews*, *34*(5), 670–7.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience and Biobehavioral Reviews*, *30*(6), 791–807.

Bäckman, L., Small, B. J., & Wahlin, A. (2001). Aging and memory. Cognitive and biological perspectives. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (pp. 349–377). San Diego, USA: Academic Press.

Baddeley, A., & Warrington, E. K. (1970). Amnesia and the distinction between long-

and short-term memory. *Journal of Verbal Learning and Verbal Behavior*, *9*(2), 176–189.

Bakker, A., Krauss, G. L., Albert, M. S., Speck, C. L., Jones, L. R., Stark, C. E., et al. (2012). Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. *Neuron*, *74*(3), 467–74.

Baltes, P. B., Cornelius, S. W., Spiro, A., Nesselroade, J. R., & Willis, S. L. (1980). Integration versus differentiation of fluid/crytallized intelligence in old age. *Developmental Psychology*, *16*(6), 625–635.

Banner, H., Bhat, V., Etchamendy, N., Joober, R., & Bohbot, V. D. (2011). The brain-derived neurotrophic factor Val66Met polymorphism is associated with reduced functional magnetic resonance imaging activity in the hippocampus and increased use of caudate nucleus-dependent strategies in a human virtual navigation task. *The European Journal of Neuroscience*, *33*(5), 968–77.

Barnes, C. A., Suster, M. S., Shen, J., & McNaughton, B. L. (1997). Multistability of cognitive maps in the hippocampus of old rats. *Nature*, *388*(6639), 272–5.

Bennett, I. J., Howard, J. H., & Howard, D. V. (2007). Age-related differences in implicit learning of subtle third-order sequential structure. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62*(2), P98–103.

Bertolino, A., Fazio, L., Di Giorgio, A., Blasi, G., Romano, R., Taurisano, P., et al. (2009). Genetically determined interaction between the dopamine transporter and the D2 receptor on prefronto-striatal activity and volume in humans. *Journal of Neuroscience*, *29*(4), 1224–34.

Bliss, T. V., & Lomø, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331–56.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., et al. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *The New England Journal of Medicine*, *343*(7), 450–6.

Boyd, L. A., & Winstein, C. J. (2004). Providing explicit information disrupts implicit motor learning after basal ganglia stroke. *Learning & Memory*, *11*(4), 388–96.

Burgess, N. (2008). Spatial cognition and the brain. *Annals of the New York Academy*

of Sciences, *1124*, 77–97.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625–41.

Burgess, N., & O'Keefe, J. (1996). Neuronal computations underlying the firing of place cells and their role in navigation. *Hippocampus*, *762*(1996), 749–762.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage*, *17*(3), 1394–1402.

Carp, J., Park, J., Hebrank, A., Park, D. C., & Polk, T. A. (2011). Age-related neural dedifferentiation in the motor system. *PloS One*, *6*(12), e29411.

Carp, J., Park, J., Polk, T. A., & Park, D. C. (2011). Age differences in neural distinctiveness revealed by multi-voxel pattern analysis. *NeuroImage*, *56*(2), 736–43.

Chun, M. M., & Phelps, E. A. (1999). Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. *Nature Neuroscience*, *2*(9), 844–7.

Cohen, N. J., & Eichenbaum, H. (1993). *Memory, amnesia, and the hippocampal system*. Cambridge, MA: MIT Press.

Cohen, N. J., Poldrack, R. A., & Eichenbaum, H. (1997). Memory for items and memory for relations in the procedural/declarative memory framework. *Memory*, *5*(1-2), 131–78.

Cohen, N. J., & Squire, L. R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, *210*(4466), 207–10.

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. *Brain*, *129*, 1659–73.

Corkin, S. (1965). Tactually-guided maze learning in man: Effects of unilateral cortical excisions and bilateral hippocampal lesions. *Neuropsychologia*, *3*(4), 339–351.

Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia*, *6*(3), 255–265.

Dagnas, M., Guillou, J.-L., Prévôt, T., & Mons, N. (2013). HDAC inhibition facilitates the switch between memory systems in young but not aged mice. *Journal of*

Neuroscience, *33*(5), 1954–63.

Dayan, P., & Niv, Y. (2008). Reinforcement learning: The good, the bad and the ugly. *Current Opinion in Neurobiology*, *18*(2), 185–96.

Degonda, N., Mondadori, C. R. A., Bosshardt, S., Schmidt, C. F., Boesiger, P., Nitsch, R. M., et al. (2005). Implicit associative learning engages the hippocampus and interacts with explicit associative learning. *Current Opinion in Neurobiology*, *46*(3), 505–20.

Dennis, N. A., & Cabeza, R. (2011). Age-related dedifferentiation of learning systems: An fMRI study of implicit and explicit learning. *Neurobiology of Aging*, *32*(12), 2318.e17–30.

Destrebecqz, A., Peigneux, P., Laureys, S., Degueldre, C., Del Fiore, G., Aerts, J., et al. (2005). The neural correlates of implicit and explicit sequence learning: Interacting networks revealed by the process dissociation procedure. *Learning & Memory*, *12*(5), 480–90.

Doeller, C. F., Barry, C., & Burgess, N. (2010). Evidence for grid cells in a human memory network. *Nature*, *463*(7281), 657–61.

Doeller, C. F., & Burgess, N. (2008). Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(15), 5909–14.

Doeller, C. F., King, J. A., & Burgess, N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(15), 5915–20.

Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Current Opinion in Neurobiology*, *15*(2), 161–7.

Doyon, J., Gaudreau, D., Laforce, R., Castonguay, M., Bédard, P. J., Bédard, F., et al. (1997). Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain and Cognition*, *34*(2), 218–45.

Düzel, E., Schütze, H., Yonelinas, A. P., & Heinze, H.-J. (2011). Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation. *Hippocampus*, *21*(8), 803–14.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature*

Reviews Neuroscience, *1*(1), 41–50.

Eichenbaum, H. (2004). An information processing framework for memory representation by the hippocampus. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (3rd ed., pp. 679–690). Cambridge, MA: MIT Press.

Eichenbaum, H., & Cohen, N. J. (2001). *From conditioning to conscious recollection: Memory systems of the brain.* Oxford: Oxford University Press.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., & Tanila, H. (1999). The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron*, *23*(2), 209–26.

Ekstrom, A., Kahana, M., & Caplan, J. (2003). Cellular networks underlying human spatial navigation. *Nature*, *425*, 184–8.

Erixon-Lindroth, N., Farde, L., Wahlin, T.-B. R., Sovago, J., Halldin, C., & Bäckman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research*, *138*(1), 1–12.

Ewers, M., Sperling, R. A., Klunk, W. E., Weiner, M. W., & Hampel, H. (2011). Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends in Neurosciences*, *34*(8), 430–42.

Eyler, L. T., Sherzai, A., Kaup, A. R., & Jeste, D. V. (2011). A review of functional brain imaging correlates of successful cognitive aging. *Biological Psychiatry*, *70*(2), 115–22.

Ferraro, F. R., Balota, D. A., & Connor, L. T. (1993). Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: A serial reaction time (SRT) investigation. *Brain and Cognition*, *21*(2), 163–80.

Flagel, S. B., Clark, J. J., Robinson, T. E., Mayo, L., Czuj, A., Willuhn, I., et al. (2011). A selective role for dopamine in stimulus-reward learning. *Nature*, *469*(7328), 53–7.

Fleischman, D. A., & Gabrieli, J. D. E. (1998). Repetition priming in normal aging and Alzheimer's disease: A review of findings and theories. *Psychology and Aging*, *13*(1), 88–119.

Foerde, K., Knowlton, B. J., & Poldrack, R. A. (2006). Modulation of competing memory systems by distraction. *Proceedings of the National Academy of Sciences*

of the United States of America, *103*(31), 11778–83.

Frank, M. J., & Kong, L. (2008). Learning to avoid in older age. *Psychology and Aging*, *23*(2), 392–8.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: Cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–3.

Frey, U., Schroeder, H., & Matthies, H. (1990). Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. *Brain Research*, *522*(1), 69–75.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science*, *269*(5221), 218–21.

Graybiel, A. M., & Kimura, M. (1995). Adaptive neural networks in the basal ganglia. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 103–116). Cambridge, MA: MIT Press.

Green, A. A. E., Munafò, M. R., DeYoung, C. G. C., Fossella, J. A. J., Fan, J., & Gray, J. R. (2008). Using genetic data in cognitive neuroscience: From growing pains to genuine insights. *Nature Reviews Neuroscience*, *9*(9), 710–20.

Gupta, P., & Cohen, N. J. (2002). Theoretical and computational analysis of skill learning, repetition priming, and procedural memory. *Psychological Review*, *109*(2), 401–448.

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., et al. (2005). Aging and the neural correlates of successful picture encoding: Frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, *17*(1), 84–96.

Hafting, T., Fyhn, M., Molden, S., Moser, M.-B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, *436*(7052), 801–6.

Haider, H., & Frensch, P. A. (2005). The generation of conscious awareness in an incidental learning situation. *Psychological Research*, *59*(6), 399–411.

Hämmerer, D., Biele, G., Müller, V., Thiele, H., Nürnberg, P., Heekeren, H. R., et al. (2013). Effects of PPP1R1B (DARPP-32) polymorphism on feedback-related brain potentials across the life span. *Frontiers in Psychology*, *4*, 89.

Harris, M. A., Wiener, J. M., & Wolbers, T. (2012). Aging specifically impairs switching

to an allocentric navigational strategy. *Frontiers in Aging Neuroscience*, *4*, 29.

Hartley, T., Trinkler, I., & Burgess, N. (2004). Geometric determinants of human spatial memory. *Cognition*, *94*(1), 39–75.

Head, D., & Isom, M. (2010). Age effects on wayfinding and route learning skills. *Behavioural Brain Research*, *209*(1), 49–58.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature reviews. Neuroscience*, *5*(2), 87–96.

Hein, G., & Schubert, T. (2004). Aging and input processing in dual-task situations. *Psychology and Aging*, *19*(3), 416–32.

Hof, P. R., & Mobbs, C. V. (Eds.). (2009). *Handbook of the neuroscience of aging.* London: Academic Press.

Hofer, S. M., & Sliwinski, M. J. (2001). Understanding ageing. *Gerontology*, *47*(6), 341–352.

Howard, D., & Howard, J. (1989). Age differences in learning serial patterns: Direct versus indirect measures. *Psychology and Aging*, *4*(3), 357–64.

Howard, D., Howard, J., Japikse, K., DiYanni, C., Thompson, A., & Somberg, R. (2004). Implicit sequence learning: Effects of level of structure, adult age, and extended practice. *Psychology and Aging*, *19*(1), 79–92.

Howard, D. V., Howard, J. H., Dennis, N. A., LaVine, S., & Valentino, K. (2008). Aging and implicit learning of an invariant association. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *63*(2), P100–5.

Hoyer, W. J., & Verhaeghen, P. (2006). Memory aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (6th ed., pp. 209–224). Waltham, MA: Academic Press.

Jog, M. S., Kubota, Y., Connolly, C. I., Hillegaart, V., & Graybiel, A. M. (1999). Building neural representations of habits. *Science*, *286*(5445), 1745–9.

Kaasinen, V., Vilkman, H., Hietala, J., Någren, K., Helenius, H., Olsson, H., et al. (2000). Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiology of Aging*, *21*(5), 683–8.

Karabanov, A., Cervenka, S., de Manzano, O., Forssberg, H., Farde, L., & Ullén, F. (2010). Dopamine D2 receptor density in the limbic striatum is related to implicit but not explicit movement sequence learning. *Proceedings of the National*

Academy of Sciences of the United States of America, *107*(16), 7574–9.

Keane, M. M., Gabrieli, J. D., Mapstone, H. C., Johnson, K. A., & Corkin, S. (1995). Double dissociation of memory capacities after bilateral occipital-lobe or medial temporal-lobe lesions. *Brain*, *118*, 1129–48.

Kempermann, G., Gast, D., & Gage, F. H. (2002). Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Annals of Neurology*, *52*(2), 135–43.

Knowlton, B. J., Mangels, J. a., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science*, *273*(5280), 1399–402.

Knowlton, B. J., & Moody, T. D. (2008). Procedural learning in humans. In J. H. Byrne & H. Eichenbaum (Eds.), *Learning & memory: A comprehensive reference (vol. 3: Memory systems)* (pp. 321–340). Amsterdam: Elsevier Ltd.

Kumaran, D., & Maguire, E. a. (2005). The human hippocampus: cognitive maps or relational memory? *Journal of Neuroscience*, *25*(31), 7254–9.

Lee, S.-H. S., Kwan, A. C. A., Zhang, S., Phoumthipphavong, V., Flannery, J. G., Masmanidis, S. C., et al. (2012). Activation of specific interneurons improves V1 feature selectivity and visual perception. *Nature*, *488*(7411), 379–383.

Leventhal, A. G., Wang, Y., Pu, M., Zhou, Y., & Ma, Y. (2003). GABA and its agonists improved visual cortical function in senescent monkeys. *Science*, *300*(5620), 812–5.

Lever, C., Burton, S., Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary vector cells in the subiculum of the hippocampal formation. *Journal of Neuroscience*, *29*(31), 9771–7.

Li, S.-C., Chicherio, C., Nyberg, L., von Oertzen, T., Nagel, I. E., Papenberg, G., et al. (2010). Ebbinghaus revisited: Influences of the BDNF Val66Met polymorphism on backward serial recall are modulated by human aging. *Journal of Cognitive Neuroscience*, *22*(10), 2164–2173.

Li, S.-C., Lindenberger, U., & Bäckman, L. (2010). Dopaminergic modulation of cognition across the life span. *Neuroscience and Biobehavioral Reviews*, *34*(5), 625–30.

Li, S.-C., Lindenberger, U., & Frensch, P. A. (2000). Unifying cognitive aging: From neuromodulation to representation to cognition. *Neurocomputing*, *32-33*(1-4),

879–890.

Li, S.-C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W., & Baltes, P. B. (2004). Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. *Psychological Science*, *15*(3), 155–63.

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: From neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479–486.

Li, S.-C., Naveh-Benjamin, M., & Lindenberger, U. (2005). Aging neuromodulation impairs associative binding: A neurocomputational account. *Psychological Science*, *16*(6), 445–50.

Li, S.-C., Papenberg, G., Nagel, I. E., Preuschhof, C., Schröder, J., Nietfeld, W., et al. (2013). Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory. *Neurobiology of Aging*, *34*(1), 358.e1–358.e10.

Li, S.-C., & Sikström, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neuroscience and Biobehavioral Reviews*, *26*(7), 795–808.

Li, S.-C., von Oertzen, T., & Lindenberger, U. (2006). A neurocomputational model of stochastic resonance and aging. *Neurocomputing*, *69*(13-15), 1553–1560.

Lieberman, M. D., Chang, G. Y., Chiao, J., Bookheimer, S. Y., & Knowlton, B. J. (2004). An event-related fMRI study of artificial grammar learning in a balanced chunk strength design. *Journal of Cognitive Neuroscience*, *16*(3), 427–38.

Light, L. L., & Singh, A. (1987). Implicit and explicit memory in young and older adults. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *13*(4), 531–41.

Lindenberger, U., Nagel, I. E., Chicherio, C., Li, S.-C., Heekeren, H. R., & Bäckman, L. (2008). Age-related decline in brain resources modulates genetic effects on cognitive functioning. *Frontiers in Neuroscience*, *2*(2), 234–44.

Lindenberger, U., Smith, J., Mayer, K. U., & Baltes, P. B. (2010). *Die Berliner Altersstudie*. Berlin: Akademie Verlag.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron*, *46*(5), 703–13.

Lisman, J. E., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic

memory; role of dopamine-dependent late LTP. *Trends in neurosciences*, *34*(10), 536–47.

Lynch, M. (2004). Long-term potentiation and memory. *Physiological Reviews*, 87–136.

MacDonald, S. W. S., Li, S.-C., & Bäckman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychology and Aging*, *24*(4), 792–808.

Maguire, E. A., & Frith, C. D. (2003). Aging affects the engagement of the hippocampus during autobiographical memory retrieval. *Brain*, *126*(7), 1511–23.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience*, *107*(1), 3–22.

McDonald, R. J., & White, N. M. (1994). Parallel information processing in the water maze: Evidence for independent memory systems involving dorsal striatum and hippocampus. *Behavioral and Neural Biology*, *61*(3), 260–70.

Milner, B. (1966). Amnesia following operation on the temporal lobes. In C. Whitty & O. Zangwill (Eds.), *Amnesia* (pp. 109–133). London: Butterworths.

Milner, B., Corkin, S., & Teuber, H.-L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia*, *6*(3), 215–234.

Milnik, A., Heck, A., Vogler, C., Heinze, H.-J., de Quervain, D. J.-F., & Papassotiropoulos, A. (2012). Association of KIBRA with episodic and working memory: a meta-analysis. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *159B*(8), 958–69.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984). Memories and habits: Two neural systems. In G. Lynch, J. McGaugh, & N. Weinberger (Eds.), *Neurobiology of learning and memory* (pp. 65–77). New York: Guilford Press.

Mitchell, J. A., & Hall, G. (1988). Caudate-putamen lesions in the rat may impair or potentiate maze learning depending upon availability of stimulus cues and relevance of response cues. *The Quarterly Journal of Experimental Psychology B: Comparative and Physiological Psychology*, *40*(3), 243–58.

Moffat, S. D. (2009). Aging and spatial navigation: What do we know and where do

we go? *Neuropsychology Review*, *19*(4), 478–89.

Moffat, S. D., Elkins, W., & Resnick, S. M. (2006). Age differences in the neural systems supporting human allocentric spatial navigation. *Neurobiology of Aging*, *27*(7), 965–72.

Moffat, S. D., Kennedy, K. M., Rodrigue, K. M., & Raz, N. (2007). Extrahippocampal contributions to age differences in human spatial navigation. *Cerebral Cortex*, *17*(6), 1274–82.

Molina-Luna, K., Pekanovic, A., Röhrich, S., Hertler, B., Schubring-Giese, M., Rioult-Pedotti, M.-S., et al. (2009). Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PLoS One*, *4*(9), e7082.

Moody, T. D., Bookheimer, S. Y., Vanek, Z., & Knowlton, B. J. (2004). An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. *Behavioral Neuroscience*, *118*(2), 438–42.

Mora, F., Segovia, G., & Arco, A. del. (2007). Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Research Reviews*, *55*(1), 78–88.

Mormino, E. C., Brandel, M. G., Madison, C. M., Marks, S., Baker, S. L., & Jagust, W. J. (2012). Aβ Deposition in aging is associated with increases in brain activation during successful memory encoding. *Cerebral Cortex*, *22*(8), 1813–23.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, *297*(5868), 681–683.

Moustafa, A. A., & Gluck, M. A. (2011). A neurocomputational model of dopamine and prefrontal-striatal interactions during multicue category learning by Parkinson patients. *Journal of Cognitive Neuroscience*, *23*(1), 151–67.

Nagel, I. E., Chicherio, C., Li, S.-C., von Oertzen, T., Sander, T., Villringer, A., et al. (2008). Human aging magnifies genetic effects on executive functioning and working memory. *Frontiers in Human Neuroscience*, *2*, 1.

Nilsson, L.-G., Bäckman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, G., et al. (1997). The betula prospective cohort study: Memory, health, and aging. *Aging, Neuropsychology, and Cognition*, *4*(1), 1–32.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence

from performance measures. *Cognitive Psychology*, *19*(1), 1–32.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305.

Nyberg, L., Salami, A., Andersson, M., Eriksson, J., Kalpouzos, G., Kauppi, K., et al. (2010). Longitudinal evidence for diminished frontal cortex function in aging. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(52), 22682–6.

O'Doherty, J. P., Dayan, P., Friston, K., Critchley, H., Dolan, R. J., & Doherty, J. P. O. (2003). Temporal difference models and reward-related learning in the human brain. *Neuron*, *38*(2), 329–37.

O'Keefe, J., & Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature*, *381*(6581), 425–8.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, *34*(1), 171–175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford: Oxford University Press.

O'Keefe, J., & Speakman, A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation cérébrale*, *68*(1), 1–27.

Packard, M. G. (1999). Glutamate infused posttraining into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(22), 12881–6.

Packard, M. G., Hirsh, R., & White, N. M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *Journal of Neuroscience*, *9*(5), 1465–72.

Packard, M. G., & McGaugh, J. L. (1992). Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: Further evidence for multiple memory systems. *Behavioral Neuroscience*, *106*(3), 439–46.

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response

learning. *Neurobiology of Learning and Memory*, *65*(1), 65–72.

Papenberg, G., Bäckman, L., Nagel, I. E., Nietfeld, W., Schröder, J., Bertram, L., et al. (2013). Dopaminergic gene polymorphisms affect long-term forgetting in old age: further support for the magnification hypothesis. *Journal of Cognitive Neuroscience*, *25*(4), 571–9.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*, *17*(2), 299–320.

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–5.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–96.

Park, J., Carp, J., Hebrank, A., Park, D. C., & Polk, T. A. (2010). Neural specificity predicts fluid processing ability in older adults. *Journal of Neuroscience*, *30*(27), 9253–9.

Park, J., Carp, J., Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Huang, C.-M., et al. (2012). Neural broadening or neural attenuation? Investigating age-related dedifferentiation in the face network in a large lifespan sample. *Journal of Neuroscience*, *32*(6), 2154–8.

Payton, A. (2009). The impact of genetic research on our understanding of normal cognitive ageing: 1995 to 2009. *Neuropsychology Review*, *19*(4), 451–77.

Peigneux, P., Maquet, P., Meulemans, T., Destrebecqz, A., Laureys, S., Degueldre, C., et al. (2000). Striatum forever, despite sequence learning variability: a random effect analysis of PET data. *Human Brain Mapping*, *10*(4), 179–94.

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.-G., Ingvar, M., et al. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex*, *16*(7), 907–15.

Persson, J., Pudas, S., Lind, J., Kauppi, K., Nilsson, L.-G., & Nyberg, L. (2012). Longitudinal structure-function correlates in elderly reveal MTL dysfunction with cognitive decline. *Cerebral Cortex*, *22*(10), 2297–304.

Poldrack, R. A., Clark, J., Paré-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., et al. (2001). Interactive memory systems in the human brain. *Nature*, *414*(6863), 546–50.

Poldrack, R. A., & Gabrieli, J. D. E. (2001). Characterizing the neural mechanisms of skill learning and repetition priming: Evidence from mirror reading. *Brain*, *124*(1), 67–82.

Poldrack, R. A., & Packard, M. G. (2003). Competition among multiple memory systems: Converging evidence from animal and human brain studies. *Neuropsychologia*, *41*(3), 245–51.

Poldrack, R. A., Prabhakaran, V., Seger, C. a., & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology*, *13*(4), 564–74.

Price, A. L. (2005). Cortico-striatal contributions to category learning: dissociating the verbal and implicit systems. *Behavioral Neuroscience*, *119*(6), 1438–47.

Putcha, D., Brickhouse, M., O'Keefe, K., Sullivan, C., Rentz, D., Marshall, G., et al. (2011). Hippocampal hyperactivation associated with cortical thinning in Alzheimer's disease signature regions in non-demented elderly adults. *Journal of Neuroscience*, *31*(48), 17680–8.

Rauch, S. L., Whalen, P. J., Savage, C. R., Curran, T., Kendrick, A., Brown, H. D., et al. (1997). Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping*, *5*(2), 124–32.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–89.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews*, *30*(6), 730–48.

Raz, N., Rodrigue, K. M., Kennedy, K. M., Head, D., Gunning-Dixon, F., & Acker, J. D. (2003). Differential aging of the human striatum: Longitudinal evidence. *American Journal of Neuroradiology*, *24*(9), 1849–56.

Redish, A. D., & Touretzky, D. S. (1998). The role of the hippocampus in solving the

Morris water maze. *Neural Computation*, *10*(1), 73–111.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical conditioning ii: current research and theory* (pp. 64–99). New York: Appleton-Century-Crofts.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, *17*(3), 177–182.

Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: Reorganizing discoveries about the aging mind. *Current Opinion in Neurobiology*, *15*(2), 245–51.

Rieckmann, A., & Bäckman, L. (2009). Implicit learning in aging: Extant patterns and new directions. *Neuropsychology Review*, *19*(4), 490–503.

Rieckmann, A., Fischer, H. k., & Bäckman, L. (2010). Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: Relations to performance. *NeuroImage*, *50*(3), 1303–12.

Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., et al. (2011). Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: links to cognitive performance. *Cerebral Cortex*, *21*(9), 2023–32.

Rinne, J. O., Hietala, J., Ruotsalainen, U., Säkö, E., Laihinen, A., Någren, K., et al. (1993). Decrease in human striatal dopamine D2 receptor density with age: A PET study with [11C]raclopride. *Journal of Cerebral Blood Flow and Metabolism*, *13*(2), 310–4.

Rolls, E. T. (2000). Memory systems in the brain. *Annual Review of Psychology*, *51*(1), 599–630.

Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L.-G. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychology and Aging*, *20*(1), 3–18.

Rose, M., Haider, H., & Büchel, C. (2010). The emergence of explicit memory during learning. *Cerebral Cortex*, *20*(12), 2787–97.

Rünger, D., & Frensch, P. A. (2008). How incidental sequence learning creates reportable knowledge: The role of unexpected events. *Journal of Experimental*

Psychology: Learning, Memory, and Cognition, *34*(5), 1011–26.

Rushton, J. P., & Ankney, C. D. (2009). Whole brain size and general mental ability: A review. *The International Journal of Neuroscience*, *119*(5), 691–731.

Saito, S., Kobayashi, S., Ohashi, Y., Igarashi, M., Komiya, Y., & Ando, S. (1994). Decreased synaptic density in aged brains and its prevention by rearing under enriched environment as revealed by synaptophysin contents. *Journal of Neuroscience Research*, *39*(1), 57–62.

Salthouse, T. A. (1998). Independence of age-related influences on cognitive abilities across the life span. *Developmental Psychology*, *34*(5), 851–64.

Salthouse, T. A. (2003). Memory aging from 18 to 80. *Alzheimer Disease & Associated Disorders*, *17*(3), 162–167.

Schacter, D. L. (2009). Introduction to memory. In M. Gazzaniga (Ed.), *The cognitive neurosciences* (3rd ed., pp. 655–659). Cambridge, MA: MIT Press.

Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L., & Albert, M. S. (1996). The role of hippocampus and frontal cortex in age-related memory changes: A PET study. *Neuroreport*, *7*(6), 1165–9.

Schaie, K. W. (1996). *Intellectual development in adulthood: The seattle longitudinal studies*. Cambridge: Cambridge University Press.

Schendan, H. E., Searl, M. M., Melrose, R. J., & Stern, C. E. (2003). An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron*, *37*(6), 1013–1025.

Schmolesky, M. T., Wang, Y., Pu, M., & Leventhal, A. G. (2000). Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. *Nature Neuroscience*, *3*(4), 384–90.

Schroeder, J. P., Wingard, J. C., & Packard, M. G. (2002). Post-training reversible inactivation of hippocampus reveals interference between memory systems. *Hippocampus*, *12*(2), 280–4.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*(1), 1–27.

Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron*, *36*(2), 241–63.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A Neural Substrate of Prediction

and Reward. *Science*, *275*(5306), 1593–1599.

Scoville, W., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, *20*(1), 11–21.

Seeman, P., Bzowej, N. H., Guan, H. C., Bergeron, C., Becker, L. E., Reynolds, G. P., et al. (1987). Human brain dopamine receptors in children and aging adults. *Synapse*, *1*(5), 399–404.

Seidler, R. D. (2006). Differential effects of age on sequence learning and sensorimotor adaptation. *Brain Research Bulletin*, *70*(4-6), 337–46.

Seidler, R. D., Purushotham, A., Kim, S.-G., Ugurbil, K., Willingham, D., & Ashe, J. (2005). Neural correlates of encoding and expression in implicit sequence learning. *Experimental Brain Research*, *165*(1), 114–124.

Shen, J., Barnes, C. A., McNaughton, B. L., Skaggs, W. E., & Weaver, K. L. (1997). The effect of aging on experience-dependent plasticity of hippocampal place cells. *Journal of Neuroscience*, *17*(17), 6769–82.

Shing, Y. L., Rodrigue, K. M., Kennedy, K. M., Fandakova, Y., Bodammer, N., Werkle-Bergner, M., et al. (2011). Hippocampal subfield volumes: age, vascular risk, and correlation with associative memory. *Frontiers in Aging Neuroscience*, *3*, 2.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., & Gluck, M. A. (2005). The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease. *Behavioural Brain Research*, *156*(2), 191–199.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. a., & Poldrack, R. a. (2004). Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. *Brain*, *127*(4), 851–9.

Shohamy, D., Myers, C. E., Kalanithi, J., & Gluck, M. a. (2008). Basal ganglia and dopamine contributions to probabilistic category learning. *Neuroscience and Biobehavioral Reviews*, *32*(2), 219–36.

Simon, J. R., Stollstorff, M., Westbay, L. C., Vaidya, C. J., Howard, J., & Howard, D. (2011). Dopamine transporter genotype predicts implicit sequence learning. *Behavioural Brain Research*, *216*(1), 452–7.

Smith, J., Siegert, R. J., McDowall, J., & Abernethy, D. (2001). Preserved implicit learning on both the serial reaction time task and artificial grammar in patients with Parkinson's disease. *Brain and Cognition*, *45*(3), 378–91.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–7.

Squire, L. R., & Zola-Morgan, S. (1991). The Medial temporal lobe memory system. *Science*, *253*(5026), 1380.

Störmer, V. S., Passow, S., Biesenack, J., & Li, S.-C. (2012). Dopaminergic and cholinergic modulations of visual-spatial attention and working memory: insights from molecular genetic research and implications for adult cognitive development. *Developmental Psychology*, *48*(3), 875–89.

Strobach, T., Frensch, P., Müller, H., & Schubert, T. (2012). Age- and practice-related influences on dual-task costs and compensation mechanisms under optimal conditions of dual-task performance. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *19*(1-2), 222–47.

Sutton, R. S., & Barto, A. G. (1998). *Reinforcement learning: An introduction*. Cambridge: Cambridge University Press.

Takahashi, H., Kato, M., Hayashi, M., Okubo, Y., Takano, A., Ito, H., et al. (2007). Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. *NeuroImage*, *34*(4), 1643–9.

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review*, *55*(4), 189–208.

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1946). Studies in spatial learning; place learning versus response learning. *Journal of Experimental Psychology*, *36*, 221–9.

Tulving, E. (1983). *Elements of Episodic Memory*. Oxford: Clarendon Press.

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology*.

Tulving, E., & Markowitsch, H. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus*, *204*, 198–204.

van Dyck, C. H., Seibyl, J. P., Malison, R. T., Laruelle, M., Zoghbi, S. S., Baldwin, R. M., et al. (2002). Age-related decline in dopamine transporters: Analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. *The American Journal of Geriatric Psychiatry*, *10*(1), 36–43.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability

in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394–413.

Verhaeghen, P., Marcoen, A., & Goossens, L. (1993). Facts and fiction about memory aging: a quantitative integration of research findings. *Journal of Gerontology*, *48*(4), P157–71.

Verwey, W. B. (2010). Diminished motor skill development in elderly: Indications for limited motor chunk use. *Acta Psychologica*, *134*(2), 206–14.

Verwey, W. B., Abrahamse, E. L., Ruitenberg, M. F. L., Jiménez, L., & Kleine, E. de. (2011). Motor skill learning in the middle-aged: Limited development of motor chunks and explicit sequence knowledge. *Psychological Research*, *75*(5), 406–22.

Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V., & Arnsten, A. F. T. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience*, *10*(3), 376–84.

Voermans, N. C., Petersson, K. M., Daudey, L., Weber, B., Van Spaendonck, K. P., Kremer, H. P. H., et al. (2004). Interaction between the human hippocampus and the caudate nucleus during route recognition. *Neuron*, *43*(3), 427–35.

Walhovd, K. B., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., et al. (2011). Consistent neuroanatomical age-related volume differences across multiple samples. *Neurobiology of Aging*, *32*(5), 916–32.

Wang, Y. (2008). Differential effect of aging on synaptic plasticity in the ventral and dorsal striatum. *Neurobiology of learning and memory*, *89*(1), 70–5.

Wang, Y., Chan, G. L., Holden, J. E., Dobko, T., Mak, E., Schulzer, M., et al. (1998). Age-dependent decline of dopamine D1 receptors in human brain: A PET study. *Synapse*, *30*(1), 56–61.

West, M., Coleman, P., Flood, D., & Troncoso, J. (1994). Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *The Lancet*, *344*(8925), 769–772.

White, N. (2007). Multiple memory systems. *Scholarpedia*, *2*(7), 2663.

Wiener, J. M., de Condappa, O., Harris, M. A., & Wolbers, T. (2013). Maladaptive bias for extrahippocampal navigation strategies in aging humans. *Journal of Neuroscience*, *33*(14), 6012–6017.

Willingham, D. B. (1998). What differentiates declarative and procedural memories: Reply to Cohen, Poldrack, and Eichenbaum (1997). *Memory*, *6*(6), 689–99.

Wilson, I. A., Ikonen, S., Gallagher, M., Eichenbaum, H., & Tanila, H. (2005). Age-associated alterations of hippocampal place cells are subregion specific. *Journal of Neuroscience*, *25*(29), 6877–86.

Wittmann, B. C., Schott, B. H., Guderian, S., Frey, J. U., Heinze, H.-J., & Düzel, E. (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron*, *45*(3), 459–67.

Yacubian, J., Gläscher, J., Schroeder, K., Sommer, T., Braus, D. F., & Büchel, C. (2006). Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. *Journal of Neuroscience*, *26*(37), 9530–7.

Yeoman, M., Scutt, G., & Faragher, R. (2012). Insights into CNS ageing from animal models of senescence. *Nature Reviews Neuroscience*, *13*(6), 435–45.