Behavioural and Structural Adaptation to Hippocampal Dysfunction in Humans

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Zusammenfassung

Die flexible Anwendung von Wissen in neuen Situationen im Alltag ist eine notwendige kognitive Fähigkeit. Bisherige Studien betonen die zentrale Rolle des Hippocampus beim Lernen und Verknüpfen neuer Informationen mit bereits vorhandenem Wissen. Die funktionelle Integrität des Hippocampus ändert sich jedoch im Laufe des Lebens bzw. wird durch neuropsychiatrische Erkrankungen häufig beeinflusst. Die betroffenen Personen müssen deswegen adaptive Strategien entwickeln, um behaviorale Ziele weiter zu erreichen.

Vor diesem Hintergrund befasst sich meine Doktorarbeit mit Adaptationsprozessen im sich entwickelnden Gehirn und im vollständig entwickelten Gehirn mit einer hippocampalen Dysfunktion. Diese Synopsis umfasst dazu drei Studien: (1) zu behavioralen Strategien im sich entwickelnden Gehirn, (2) zu behavioralen Strategien im vollständig entwickelten Gehirn nach einer Läsion und (3) zu strukturellen Veränderungen im vollständig entwickelten Gehirn nach einer Läsion.

In Studie 1 lösten die in drei Altersgruppen zusammengestellten Teilnehmer eine Aufgabe, für deren Bewältigung Interferenzen (AC) zwischen überlappenden Paaren (AB, BC) gebildet werden mussten. Nach jedem der vier Durchgänge wurden jeweils die inferentiellen Paare (indirekten Trials) und die direkten assoziativen Paare (direkten Trials) in einem Test abgefragt. Junge Erwachsene (19-25 Jahre) erzielten bessere Ergebnisse als Teenager (12-13 Jahre) und Teenager wiederum erzielten eine signifikant bessere Leistung als Kinder (9-10 Jahre) in beiden Trial-Typen. Bezüglich der Reaktionszeiten wurden bei den Kindern größere Unterschiede zwischen indirekten und direkten Trials beobachtet als bei Teenagern und jungen Erwachsenen. Weitere Analysen ergaben, dass junge Erwachsene höhere Korrelationen zwischen den korrekten Antworten in direkten und indirekten Trials als Kinder aufwiesen. Dies lässt auf einen altersgebundenen Wechsel bei der Integration von Informationen schließen: Kinder führen die inferentiellen Prozesse in der Abrufphase durch, wohingegen junge Erwachsene integrative Repräsentationen während verschiedener Gedächtnisverarbeitungsstufen formen.

In Studie 2 untersuchten wir mit derselben assoziativen Aufgabe wie in Studie 1 Patienten mit hippocampalen Läsionen und gesunde Kontrollprobanden. Während die Kontrollprobanden bei der experimentellen Aufgabe ihre Leistung steigern konnten, sank die Gedächtnisleistung von Patienten auf Zufallsniveau. Die Datenanalyse deutete darauf hin, dass die Defizite nicht allein Folge eines beeinträchtigten assoziativen Gedächtnisses waren, sondern auf einen zusätzlichen hippocampalen Beitrag zur Gedächtnisintegration zurückzuführen waren. Zusätzlich wiesen unsere Daten auf kontextuelle Faktoren hin, die diesen Mechanismus modulieren. Die Patienten waren in der Lage, ihre behavioralen Ziele zu erreichen, solange sie eine erfolgreiche behaviorale Strategie zur Kompensation der hippocampalen Defizite anwendeten.

In Studie 3 wurden frühe Volumenveränderungen nach einer Resektion des medialen Temporallappens analysiert. Die strukturelle Datenanalyse zeigte einen signifikanten Zuwachs im rechten Hippocampus sowie einen Zuwachs der grauen Substanz im medialen präfrontalen Kortex nach linksseitiger Resektion. Die Ergebnisse legen nahe, dass eine signifikante plastische Veränderung des kontralateralen Hippocampus stattfand – sogar bei Patienten mit einer länger bestehenden unilateralen hippocampalen Dysfunktion. Diese Reorganisationsprozesse wurden in weit entfernt gelegenen, aber funktionell verbundenen Gehirnarealen beobachtet.

Zusammenfassend zeigen die Ergebnisse der drei Studien, dass eine hippocampale Dysfunktion Adaptationsprozesse sowohl auf der behavioralen als auch auf der strukturellen Ebene auslöst. Aus diesem Grund sollten zukünftige Lern- und Rehabilitationsprogramme auf die Förderung dieser Prozesse ausgerichtet werden.

Abstract

Applying knowledge flexibly to new situations is a cognitive faculty that is necessary in everyday life. Previous findings emphasise the crucial role the hippocampus plays in learning and linking new information with pre-existing knowledge. However, the functional integrity of the hippocampus changes over the lifespan and is frequently affected by neuropsychiatric disorders. The affected subjects must, therefore, develop adaptive strategies to achieve behavioural goals.

Against that background, my doctoral thesis deals with adaptation processes in the developing brain and in adult brains with a hippocampal dysfunction. This synopsis encompasses three studies on: (1) behavioural strategies in the developing brain, (2) behavioural strategies in the lesioned fully developed brain, and (3) structural changes in the lesioned fully developed brain.

In Study 1, participants of three different age groups solved a task for which inferences (AC) between overlapping pairs (AB, BC) had to be formed. After each of the four cycles the inferential pairs (indirect trials) and the direct associative pairs (direct trials) were assessed in a test. Young adults (19-25 years) outperformed teenagers (12-13 years), who for their part outperformed children (9-10 years) in both trial types. Additionally, children showed a greater difference in the reaction time between indirect and direct trials compared to teenagers and young adults. Further analyses revealed that young adults showed a higher correlation between accuracy in direct and indirect trials than children. These findings suggest an age-related shift in information integration: While children may rely more on making inferences at retrieval, young adults may form integrated representations at different memory processing stages.

In Study 2, patients with hippocampal lesions and healthy control subjects completed the same associative task that was used in Study 1. However, across the experimental tasks, the participants in the control group increased their performance in indirect trials, while the performance of patients decreased to the chance level. Analysis suggests that this deficit was not merely a consequence of an impaired associative memory but rather resulted from an additional hippocampal contribution to the memory integration. Furthermore, our data indicate that contextual factors alter this contribution and that patients may still achieve behavioural goals as long as they use appropriate behavioural strategies to compensate for their hippocampal dysfunction.

In Study 3, we analysed early volumetric changes following medial temporal lobe resection. The structural analysis revealed a significant increase of the right hippocampal volume and an increase of grey matter volume in the medial prefrontal cortex, following left-sided resections. These results demonstrate that there is significant structural plasticity of the contralateral hippocampus, even in patients with a long-standing unilateral hippocampal dysfunction, and that these structural reorganisation processes extend to include distant but functionally connected brain regions.

In conclusion, findings from these three studies show that hippocampal dysfunction leads to adaptation processes on both the behavioural and the structural level. Therefore, future learning and rehabilitative programmes should be directed at boosting these processes.

1. Introduction

Traditionally, the hippocampus has mainly been seen as a gateway to memory, and hippocampal dysfunction has predominantly been associated with memory impairments. Yet in the last decades, research has broadened our understanding of the role of the hippocampus in memory, emotion regulation, and other cognitive functions. The extent of deficits after hippocampal lesions, however, varies considerably across patients, with some only showing minor deficits in cognitive performance. This implies compensatory processes that occur with differing efficacy in distinct patient groups. In addition, there are differences between children and adults in the structure and function of the hippocampus as well as significant changes in memory performance during the development that suggest an age-related shift in information processing. Against that background, this doctoral thesis deals with adaptation processes in the developing brains of children as well as with adaptation processes in the adult brain with hippocampal dysfunction. In three experimental studies, I have explored the behavioural and structural factors underlying compensation.

1.1. Anatomy of the Hippocampus

Due to its distinctive sea-horse shape, the 16th century Bolognese anatomist Giulio Cesare Aranzi named this structure of the brain 'hippocampus', a term originating from Greek mythology (Greek: ἱππόκαμπος) and referring to a creature that was imagined to be half horse (Greek: ἵππος) and half sea monster (Greek: κάμπος). Almost 200 years later, René-Jacques Croissant de Garengeot coined the term 'Cornu Ammonis' for the same structure. The curved shape of the hippocampus reminded him of the horn of a ram's head, as can be seen in the ancient Egyptian god Amun (Lewis, 1923). Nowadays, the term 'hippocampus' is generally accepted and applied, while 'Cornu Ammonis' has survived in its abbreviated form 'CA', referring to the subfields of the hippocampus.

The terms 'hippocampal formation' and 'hippocampus' are often used as synonyms. Yet hippocampal formation usually refers to a group of adjacent cortical structures in the

medial temporal lobe (MTL). This group consists of the dentate gyrus, hippocampus, subiculum, presubiculum, parasubiculum, and entorhinal cortex (Per, Morris, Amaral, Bliss, & O'Keefe, 2006). Within the temporal lobe, the hippocampus is densely connected with the entorhinal cortex, perirhinal cortex, and parahippocampal cortex. These surrounding structures receive inputs from association areas in the frontal, parietal, temporal, and cingulate cortices. In humans, the perirhinal and parahippocampal cortices provide the major input to the entorhinal cortex, which then projects to the hippocampus. Although the signal that flows through the hippocampus is unidirectional, there are many recurrent connections between the entorhinal cortex and all of the hippocampal subdivisions: CA1, CA2, and CA3. The main projections from the hippocampus run to the fornix and further to the mammillary bodies and to the thalamus (Amaral, 1999; Amaral & Lavenex, 2006; Lavenex & Amaral, 2000).

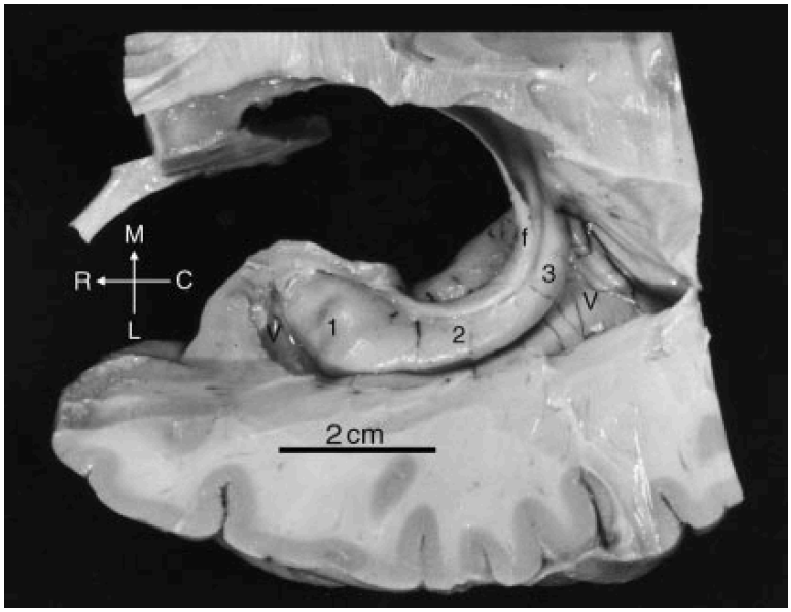

Fig.: Intraventricular hippocampal formation from above showing the anterior (1), middle (2), and posterior (3) portions of the hippocampal formation. The fimbrial fornix (f) and the temporal horn of the lateral ventricle (V) can be found near the posterior hippocampus. Bars indicate rostral (R), caudal (C), medial (M), and lateral (L) directions (from Amaral, 1999).

1.2. The Role of the Hippocampus for Learning, Memory, and Other Behaviours

The key role of the hippocampus for declarative, i.e. conscious, memory processes is well-investigated. Over the years, numerous studies have demonstrated that the hippocampus is crucial for encoding new information (Kee, Teixeira, Wang, & Frankland, 2007; Ramírez-Amaya, Balderas, Sandoval, Escobar, & Bermúdez-Rattoni, 2001; Stone et al., 2011; Tashiro, Makino, & Gage, 2007; Trouche, Bontempi, Roullet, & Rampon, 2009; van Praag et al., 2002) and for retrieving memories (Milner, Corkin, & Teuber, 1968; Vargha-Khadem et al., 1997). Additionally, the hippocampus appears to contribute to the memory consolidation (Diekelmann & Born, 2010; Gais et al., 2007; Kreutzmann, Havekes, Abel, & Meerlo, 2015; Lahl, Wispel, Willigens, & Pietrowsky, 2008). These processes may occur predominantly during sleep (Rasch & Born, 2013) and may be related to default mode network (DMN) activity (Huo, Li, Wang, Zheng, & Li, 2018; Sestieri, Corbetta, Romani, & Shulman, 2011).

Nowadays, the hippocampus is not primarily considered as a long-term repository for memories. Rather, it is regarded as a structure binding together relations among different elements of experience that are represented in cortices outside the hippocampus (Eichenbaum, 2001). Furthermore, during the acquisition of new information the hippocampus is involved in integrating new memories to related knowledge, and simultaneously prevents interference with similar information (Kesner, Lee, & Gilbert, 2004).

The hippocampus also maintains pattern separation and pattern completion processes, which are involved in the differentiation between similar experiences (Bakker, Kirwan, Miller, & Stark, 2008; Gilbert, Kesner, & Lee, 2001; Rolls, 2013). The hippocampus supports the formation of new associative memories to facilitate a flexible knowledge system, which may be used for decision making in novel and uncertain situations (Eichenbaum, 2001; O'Neil et al., 2015; Zeithamova, Schlichting, & Preston, 2012). Additionally, the hippocampus contributes to autobiographical memories (Addis, Moscovitch, & McAndrews, 2007; Scoville & Milner, 1957), imagination, and thinking about the future (Schacter et al., 2012).

The hippocampus also plays a key role in spatial behaviour, including orientation and navigation (O'Keefe & Nadel, 1978). The hippocampal place cells reflect the topography of environmental cues (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; O'Keefe, 1979) and represent spatial dimensions (O'Keefe & Burgess, 1996). Furthermore, these cells interact with grid cells, which respond to the location in the environment, and with border cells expressing the proximity to geometric borders (Rowland, Roudi, Moser, & Moser, 2016). Additionally, the hippocampus is necessary for the use of allocentric representations but not for egocentric spatial representations (Banta Lavenex, Amaral, & Lavenex, 2006).

Although the hippocampus has been in the focus of neuroscience for decades, we are still missing a comprehensive theory about its function. For example, the cognitive map theory (O'Keefe & Nadel, 1978) focuses on the role of the hippocampus for spatial relations in the environment. The relational memory theory (Eichenbaum, 2004), on the other hand, emphasises hippocampal activity as critical for relational memory binding. The multiple trace theory argues that the hippocampus supports the storage and retrieval of information, while semantic information is represented in the neocortex (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). And a last example: The episodic memory theory focuses on human memory processes and stresses the importance of the hippocampus for episodic memory but not for semantic memory (Tulving & Markowitsch, 1998).

While these theories focus on memory processes, they do not address the role of the hippocampus for other cognitive functions. For example, recent studies reported that the hippocampus supports higher-order perception (Graham, Barense, & Lee, 2010; Lee, Yeung, & Barense, 2012; Yonelinas, 2013) and language processing (Duff & Brown-Schmidt, 2012). Moreover, the hippocampus influences the awareness and perception of the self (Lu, Li, Wang, Song, & Liu, 2018). As part of the limbic system, this structure is also involved in stress and emotion regulation (Bannerman et al., 2004; Dong, Swanson, Chen, Fanselow, & Toga, 2009; Fanselow & Dong, 2010).

The hippocampal structure changes over the lifespan and these structural changes may influence hippocampus-dependent functions. For example, episodic memory performance (Newcombe, Balcomb, Ferrara, Hansen, & Koski, 2014; Sluzenski, Newcombe, & Ottinger, 2004) and relational flexibility increase gradually during development (Edgin, Spanò, Kawa, & Nadel, 2014). In this period, the hippocampus also undergoes structural and functional changes (Lavenex & Banta Lavenex, 2013). These developmental changes are associated with an increase in the performance of tasks that demand representational flexibility (DeMaster, Coughlin, & Ghetti, 2016; Schlichting, Guarino, Schapiro, Turk-Browne, & Preston, 2017).

The hippocampus-dependent memory functions develop throughout childhood and again change significantly during ageing. A growing number of studies has focused on age-related memory decline (Ghisletta, Rabbitt, Lunn, & Lindenberger, 2012; Spencer & Raz, 1995) as well as on the regional loss of neurons and synapses (Lister & Barnes, 2009). However, different memory functions are affected differently by ageing. For example, the memory for content shows a smaller age-related decrease compared to the memory for context (Spencer & Raz, 1995). Moreover, creating and retrieving intra-item and inter-item associations seem also to be impaired in older adults (Old & Naveh-Benjamin, 2008). Last but not least, neuroimaging studies also underline the difference between healthy ageing and pathological processes in old age such as in Alzheimer's disease (Lister & Barnes, 2009; West, 1993).

1.3. Behavioural Consequences of Hippocampal Dysfunction

Studies on brains with hippocampal lesions contribute profoundly to understanding the hippocampal function. As the hippocampus is vulnerable to a variety of neurological and psychiatric disorders, clinical studies allow assessing its role for human cognitive processes.

The results of human lesion studies have been highly influential in linking the hippocampal structure to cognitive functions. Ever since the first study that identified the hippocampus as a crucial structure for memory (Scoville & Milner, 1957), numerous patient studies have con-

firmed the pivotal role of the hippocampus for declarative memory processes. In particular, hippocampal lesions in animals and humans lead to impairments in visuospatial memory and orientation, especially when allocentric spatial representations need to be established (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Banta Lavenex et al., 2006; Bohbot et al., 1998). Furthermore, patients with hippocampal damage are unable to learn spatial information about new environment but can recall remotely learned spatial memories (Clark & Maguire, 2016).

A number of neurological and psychiatric disorders also affect the hippocampus. For example, hippocampal sclerosis is the most common pathology underlying MTL epilepsy (Gates & Cruz-Rodriguez, 1990). Hippocampal sclerosis is characterised by an extensive cell loss (Blümcke et al., 2000) and atrophy (Düzel et al., 2006), and typically involves significant memory impairments (Helmstaedter, 2002). Alzheimer's disease, which is the most frequent form of dementia worldwide (World Health Organization, 2009), is another well-known and socially relevant disease resulting from hippocampal pathology. Hippocampal atrophy and memory deficits are core symptoms of Alzheimer's disease and may result in amnesia (Halliday, 2017). Hippocampal lesions are also observed in limbic encephalitis and multiple sclerosis due to inflammatory responses and immunologically mediated mechanisms (Dalmau & Bataller, 2006; Geurts et al., 2007). Recent studies have linked hippocampal pathology in these diseases with deficits in long-term memory (Hansen, 2019; Planche et al., 2017). Pathological hippocampal changes and memory deficits in hippocampus-dependent memory tasks have also been observed in chronic stress (Kim, Pellman, & Kim, 2015) as well as in disorders such as depression (Sapolsky, 2002) and schizophrenia (Heckers & Konradi, 2010; Lieberman et al., 2018).

1.4. Structural and Functional Plasticity of the Hippocampus in Animal Experiments

Animal experiments have broadened our understanding of the hippocampus. Altman and Das (1965) demonstrated, for the first time, that hippocampal plasticity occurs postnatally in the rat dentate gyrus. About 40% of the granule cells in mature 5–10 year-old monkeys are

added to the granule cell layer after birth (Jabès, Banta Lavenex, Amaral, & Lavenex, 2010). Neurotransmitters, growth factors, hormones, and pharmacological substances modulate the hippocampal plasticity (Kempermann, 2011). Interestingly, also external factors like exercise, enriched environment, or stress may influence plasticity processes (Kempermann, 2011). For example, increased hippocampal neurogenesis due to physical exercise has been linked to an enhanced formation of new memories (Creer, Romberg, Saksida, van Praag, & Bussey, 2010). Moreover, external factors may have an additive effect: running and enriched housing conditions have both been shown to enhance hippocampal neurogenesis, but only the mice housed in an enriched environment presented an increased survival rate of new hippocampal cells (Curlik & Shors, 2013).

Hippocampal functions may also be taken over by other brain areas. A previous study (Lavenex, Banta Lavenex, & Amaral, 2007) reported that monkeys that had received hippocampal lesions early in life presented intact spatial relational learning. Conversely, adult animals with similar lesions showed impairments in this cognitive domain (Banta Lavenex et al., 2006). Further exploration of the functional organisation of the MTL memory system after neonatal hippocampal damage revealed that – depending on the presence or absence of the hippocampus – different structures support spatial learning (Chareyron, Banta Lavenex, Amaral, & Lavenex, 2017).

1.5. Structural and Functional Plasticity of the Hippocampus in Healthy Humans and in Human Patients

Although there are striking differences in its cytoarchitecture and connectivity across species, the hippocampus has a similar appearance and basic structure among all mammals (West, 1990). Correspondingly, findings from human studies – similarly as in animal studies – also suggest the existence of both local hippocampal and extrahippocampal neocortical mechanisms that compensate for hippocampal immaturity and dysfunction.

The crucial finding came many years after the first demonstration of neurogenesis in animals. Eriksson et al. (1998) investigated the brain tissue post-mortem of patients who had suffered

from tumours and who had received a marker determining the cell proliferation rates. That way, Eriksson and his team showed, for the first time, neurogenesis in the adult human hippocampus. Moreover, a study using carbon-14 dating as a parameter for dividing cells reported that hippocampal neurogenesis persists throughout adulthood (Spalding et al., 2013). Only a modest decline in the number of new cells per day was observed during ageing (Spalding et al., 2013), and hippocampal neurogenesis seems to continue to some extent even in persons of up to an age of 100 years (Knoth et al., 2010). External factors such as physical exercise (Fotuhi, Do, & Jack, 2012; Voss, Vivar, Kramer, & van Praag, 2013), learning (Draganski et al., 2006; Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014; Maguire et al., 2000; Woollett & Maguire, 2011), and environment (Kempermann, 2011) have been demonstrated to influence the hippocampal volume.

Many studies reported a link between the increased hippocampal volume and memory performance in humans. Increased hippocampal volume correlated positively with memory performance (Erickson et al., 2011), even at an old age (Düzel, Van Praag, & Sendtner, 2016). Interestingly, volume changes may also serve as a predictor of successful learning (Woollett & Maguire, 2011). Moreover, structural hippocampal plasticity was even observed in patients suffering from Alzheimer's disease (Mufson et al., 2015; Rosen, Sugiura, Kramer, Whitfield-Gabrieli, & Gabrieli, 2011; ten Brinke et al., 2015) and schizophrenia (Pajonk et al., 2010).

In addition to local hippocampal mechanisms, hippocampal dysfunction may induce compensatory processes in extrahippocampal brain regions that operate with distinct efficacy in different patient groups. For example, bilateral lesions of the hippocampus in children severely affect their episodic memory, while their semantic memory is not affected (Vargha-Khadem et al., 1997). Similar lesions in adults, however, affect both memory systems (Squire & Zola, 1996). Children who had been operated due to MTL epilepsy regained preoperative memory performance within 12 months after the surgical treatment. In contrast, adults, after similar resection, showed a reduced verbal memory performance after 12 months compared to their baseline level (Gleissner, Sassen, Schramm, Elger, & Helmstaedter, 2005). Adult patients with MTL epilepsy only suffered postoperatively from

memory deficits when the resected area had just a few pathological changes (Hermann & Whitman, 1992; Seidenberg et al., 1998). Additionally, a recent study (Finke, Bruehl, Düzel, Heekeren, & Ploner, 2013) reported that patients with a long disease duration showed increased activity in the contralateral hippocampus and in an extensive bi-hemispherical neocortical network. This increased activity correlated positively with the memory performance.

Taken together, human studies suggest the existence of hippocampal and extrahippocampal compensation mechanisms. However, the temporal course of hippocampal changes during development and after the acquired hippocampal dysfunction is still largely unclear. Closing this gap is crucial: a better understanding of the functional and structural hippocampal plasticity is a critical precondition for the development of supportive interventions in humans with hippocampal dysfunction.

2. Research Questions and Experimental Approach

My doctoral thesis investigates how the developing brain and the adult brain with acquired hippocampal dysfunction adapt both strategically and structurally to behavioural contexts that require hippocampal integrity. This dissertation encompasses three studies: Study 1 on behavioural strategies in the developing brain (Shing et al., 2019); Study 2 on behavioural strategies in the lesioned mature brain (Pajkert et al., 2017); and Study 3 on structural changes in the lesioned mature brain (Pajkert et al., submitted 2019).

Study 1 and Study 2 focus on behavioural strategies during a hippocampus-dependent memory integration task. This task is a modified version of the associative inference paradigm (Preston, Shrager, Dudukovic, & Gabrieli, 2004; Zeithamova, Dominick, & Preston, 2012; Zeithamova & Preston, 2010). It assesses an essential hippocampal function that allows combining information from different episodes to guide decisions in new situations. In particular, it allows to investigate how new experiences may lead to the reactivation of previously stored, overlapping memories. Successful completion of this task requires binding information across overlapping experiences.

Behavioural and imaging studies suggest that the forming of inferential memories ('memory integration') may occur both during encoding ('integrative encoding', Zeithamova, Schlichting, et al., 2012) and during retrieving ('recombination at retrieval', Zeithamova, Schlichting, et al., 2012). We investigated which of the two strategies is predominantly used during memory integration: integrative encoding or recombination at retrieval.

During the experiments, participants were presented a set of overlapping object-face pairs (AB) and face-object pairs (BC) as well as non-overlapping face-object pairs (DE). After learning (encoding phase), participants completed a test (retrieval phase). They were tested on the recall of directly related associations (AB-, BC- and DE-trials, also called 'direct trials'). The participants were also tested on indirectly related associations (AC-trials, also called 'indirect trials') that were connected through the shared association with an overlapping

face (B). The experiment comprised four cycles, each of which included an encoding phase and a retrieval phase. By analysing the accuracy and the reaction time in these conditions, we aimed to investigate the behavioural strategies that compensate for hippocampal immaturity and hippocampal dysfunction.

In Study 3, we analysed retrospectively longitudinal data from patients operated on the MTL due to epilepsy. All patients underwent neuropsychological assessment as part of a standard pre- and postoperative evaluation procedure. Verbal memory and visuospatial episodic memory were assessed using a German adaptation of the Rey Auditory Verbal Learning Test (Helmstaedter, Lendt, & Lux, 2000) and the Rey-Osterrieth Complex Figure Test (Shin, Park, Park, Seol, & Kwon, 2006), respectively.

2.1. Study 1: Behavioural Strategies in the Developing Brain

Despite the crucial role of learning and remembering across the lifespan, only a few researchers have investigated the influence of age-related changes on memory integration. For example, Schlichting and colleagues (2017) reported that children (6–11 years) and adolescents (12–16 years) showed a performance difference between indirect trials and direct trials. This difference, however, was not observed among young adults (18–30 years).

The purpose of Study 1 was to describe in more detail the developmental changes in inferential memory performance. To do so, we compared children during middle childhood (9–10 years, n = 25), adolescents (12–13 years, n = 23), and young adults (19–25 years, n = 20) with respect to their ability to form inferential memories. We hypothesised that children show poorer memory performance than other age groups, especially with respect to indirect trials.

2.2. Study 2: Behavioural Strategies in the Lesioned Mature Brain

So far, little is known about the effects of hippocampal damage on memory integration. Previous studies found that hippocampal activity increases during tasks that require making inferences from past knowledge compared to tasks that require directly learned associations

(Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Preston et al., 2004). However, it remained unclear if and, if so, how an acquired hippocampal dysfunction influences the memory integration.

The aim of Study 2 was, thus, to test whether hippocampal lesions impair performance in the memory integration task. We recruited subjects (n = 5) who suffered from MTL damage in adulthood (four postsurgical lesions following resection of a benign brain tumour, one postencephalitic lesion), as well as healthy control participants (n = 17) selected to match age and years of education of all patients. We hypothesised that acquired hippocampal lesions decrease memory performance in indirect trials, while direct trials remain unimpaired.

2.3. Study 3: Structural Changes in the Lesioned Mature Brain

Recent findings suggest that an increased recruitment of the contralateral hippocampus and extratemporal regions after a hippocampal resection may be an important part of the compensation mechanisms for hippocampal dysfunction (Bettus et al., 2009; Bonelli et al., 2010; Finke et al., 2013; Sidhu et al., 2013). In healthy humans, hippocampal plasticity may occur on a timescale ranging from hours to years (Draganski et al., 2006; Erickson et al., 2011; Sagi et al., 2012; Tavor, Hofstetter, & Assaf, 2013; Thomas et al., 2016; Woollett & Maguire, 2011). However, the temporal properties of contralateral hippocampal plasticity as well as connected areas after focal damage are still subject of research.

In Study 3, we therefore investigated whether unilateral resection of the MTL, including the hippocampus, induces measurable volumetric changes in the contralateral hippocampus and related brain areas. All patients underwent a unilateral resection of the left (n = 19) and right (n = 12) MTL, including the hippocampus. We studied patients before surgery and 3 months after surgery using voxel-based morphometry (VBM) and neuropsychological assessment. We investigated possible volumetric changes of the contralateral hippocampus and the significance of these structural changes.

3. Manuscripts

3.1. Manuscript 1: Behavioural Strategies in the Developing Brain

Integrating across memory episodes: Developmental trends

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3.2. Manuscript 2: Behavioural Strategies in the Lesioned Mature Brain

Memory integration in humans with hippocampal lesions

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3.3. Manuscript 3: Structural Changes in the Lesioned Mature Brain

Early volumetric changes of hippocampus and medial prefrontal cortex following medial temporal lobe resection

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4. Summary of the Results

This chapter presents a brief summary of the findings of each study. For a detailed description of the analyses conducted, please see the manuscripts in chapter 3 above.

4.1. Study 1: Behavioural Strategies in the Developing Brain

To assess behavioural strategies during brain development, we compared the performance of three participant groups of different ages in an associative memory task (see chapter 2). For statistical comparisons, we used two trial types: indirect trials and direct trials. We included only the indirect trials (AC) for which both corresponding direct trials (AB, BC) were correctly remembered. We used only the non-overlapping pairs (DE) as direct trials.

4.1.1. Accuracy

For the statistical evaluation of the data, we conducted a mixed analysis of variance (ANOVA) on accuracy measures with the following factors: cycle x trial type x age group. For a detailed description of this analysis see the section ‘Accuracy’ in the paper reprint (page 20 of this thesis). Neither the main effect for cycle nor any interaction involving cycle was significant, so we merged all data across cycles for further analyses.

We found a significant effect of the trial type: the accuracy in direct trials (DE) was significantly higher than in indirect trials (AC). There was also a significant difference in the respective performances of the age groups. A post hoc test revealed that young adults outperformed teenagers who for their part outperformed children.

4.1.2. Reaction Time

To evaluate the reaction time, we used a mixed ANOVA with the following factors: cycle x trial type x age group. For a detailed description of this analysis see the section ‘Reaction Time’ in the paper reprint (page 20 of this thesis).

We found a significant main effect of cycle and an interaction between cycle and trial type. The reaction time dropped across cycles and this decline was greater in the indirect trials

(AC) than in the direct trials. The trial type effect, the age group effect, and an interaction between the two also reached the significance level. For further exploration, we calculated the difference in reaction time between the indirect and direct trials. This revealed that children were particularly slower than teenagers and young adults in making judgements on indirect trials (AC) compared to direct trials (DE).

4.1.3. Correlation Analyses

Based on the results described above, we hypothesised that participants who formed integrated representations show a higher correlation between direct and indirect trials. To investigate this hypothesis, we used the path models implemented in Mplus (Muthén & Muthén, 1998-2010) to calculate a partial correlation between the accuracy in direct (AB, BC) and indirect (AC) trials. For a detailed description of these analyses see the section 'Correlation between accuracy on direct (AB, BC) and inference (AC) trials' in the paper reprint (page 21 of this thesis).

The analysis revealed that young adults showed a higher correlation between the accuracy in direct and in indirect trials compared to children. The AC-AB/BC correlations of teenagers and young adults as well as the correlations of children and teenagers did not significantly differ from each other.

4.1.4. Conclusions

Children showed significantly larger differences in reaction times between indirect and direct trials than teenagers and young adults. The longer reaction times for indirect trials support the idea that children may recombine the overlapping pairs during the test. Thus, it is very likely that children rely more on making inferences during retrieval rather than during encoding.

Young adults, on the other hand, showed the lowest differences between reaction times for indirect and direct trials. Thus, young adults may be more likely to form integrated representations of overlapping pairs at different memory processing stages. Furthermore, the results

of the correlation analyses revealed that young adults relied closely on direct associations for making inferential decisions, whereas children were less consistent in forming integrated representations.

Taken together, our data indicate that an age-related shift in the integrative memory performance takes place between middle childhood and young adulthood. Children are less consistent when forming integrated representations, and make inferential decisions during the retrieval phase. On the other hand, young adults present more consistent behavioural strategies for forming integrated representations, both during the encoding and/or the retrieval phase.

4.2. Study 2: Behavioural Strategies in the Lesioned Mature Brain

We used indirect and direct trials for statistical analyses. As no significant difference was observed between the AB-, BC-, and DE-trials, we pooled these trials and applied them as direct trials for further analyses.

4.2.1. Accuracy

The performance of the patients and healthy controls was analysed separately for the direct (AB, BC, and DE) and for the indirect (AC) trials. While we did not find a significant difference between groups in the direct trials, the performance in the indirect trials was significantly worse in the patient group compared to the control group. For a detailed description of these analyses see the section ‘Accuracy’ in the paper reprint (page 31 of this thesis).

The analysis of the performance across cycles revealed that the group difference in indirect trials changed over the course of the experiment. While there was no statistically significant difference between patients and controls in the indirect trials in cycles 1 and 2, patients showed a significantly decreased performance in cycles 3 and 4. By contrast, the performance in the direct trials did not differ between patients and controls across cycles.

4.2.2. Reaction Time

We analysed reaction times of the two main trial types across cycles. For a detailed description of these analyses see the section 'Reaction Times' in the paper reprint (page 32 of this thesis). No significant differences in the reaction times between patients and controls in the indirect (AC) and direct trials (AB, BC, DE) were observed. Reaction times decreased in the indirect trials for both groups without significant differences between groups. The reaction time for the direct trials across cycles remained constant and no significant changes were observed.

4.2.3. Correlation Analyses

For further exploration of the data, we conducted correlation analyses between the individual performance in the indirect trials (AC) and in the direct trials (AB, BC, DE). The number of individuals in the patient group was too small for these analyses, so we conducted the analyses exclusively for the control group. For a detailed description of these analyses see the section 'Correlation Analyses' in the paper reprint (page 32 of this thesis). In cycle 1, AC-performance correlated significantly with the performance in all of the direct trial types, whereas in cycle 4 AC-performance correlated significantly with the performance in the BC-trials only.

4.2.4. Conclusions

At the beginning of the experiment, patients performed on indirect trials at a level similar to that of the control group. This suggests that patients did not show impairments initially on an inferential memory task. However, despite increasing familiarity with the task, the performance of the patients on the indirect trials decreased during the experiment.

On the other hand, the controls improved their accuracy in the indirect trials. Interestingly, a further analysis revealed a growing reliance on BC-trials for indirect decisions among the task. This observed behavioural pattern of the control group may be interpreted as an increased tendency to form integrated representations during or following the encoding phase. Assuming that the underlying integration mechanism in patients was the same as in

the control group, the decreasing memory performance on indirect trials during the experiment may point to a preserved retrieval-based strategy and an impaired integrative encoding in patients.

4.3. Study 3: Structural Changes in the Lesioned Mature Brain

In this retrospective study, we analysed pre- and postoperative neuropsychological and structural neuroimaging data of patients who had undergone unilateral resection of the MTL for the treatment of epilepsy. Both groups of patients, i.e. with either left-sided or right-sided surgery, showed a similar extent of resection. The lesions affected the anterior hippocampus, amygdala, entorhinal cortex, and some parts of the perirhinal cortex in all patients. Additional damage to the parahippocampal and inferotemporal cortex was found in some patients.

4.3.1. Neuropsychological Assessment

Both patient groups did not significantly differ in their demographic and disease-related variables. Longitudinal group differences in memory performance between both patient groups were assessed using mixed ANOVA with the following factors: resection side x time point. For a detailed description of these analyses see the section 'Neuropsychological assessment' in the manuscript reprint (page 45 of this thesis). The ANOVAs were conducted separately for both verbal and visuospatial memory. On the verbal memory test, the group with a left-sided pathology showed a significantly decreased performance compared to the patients with a right-sided pathology. Conversely, on the non-verbal memory test, patients with a right-sided pathology performed significantly worse than patients with a left-sided pathology.

4.3.2. Longitudinal Grey Matter Changes in the Hippocampus and the DMN

To assess hippocampal volume changes, we applied a VBM analysis that was modified to evaluate longitudinal structural changes (Douaud et al., 2009). For a detailed description of these analyses see the section 'Longitudinal grey matter changes in the hippocampus and the DMN' in the paper reprint (page 45 of this thesis).

After left-sided resections, a region in the right hippocampus homologous to the resected area showed a significant increase in grey matter volume. In addition, an exploratory analysis

including the brain regions belonging to the DMN revealed a grey matter volume increase in the left medial prefrontal cortex in patients with left-sided resection. In patients with right-sided resections, we neither observed a significant volume change nor did we find a correlation between the observed volume changes and the memory performance.

4.3.3. Conclusions

The longitudinal study revealed a significant increase of the right hippocampal volume and a volume increase in the DMN after the left MTL resection. Postsurgical plasticity occurred 3 months after MTL resection and, thus, surprisingly early. These results demonstrate that the resection of an already dysfunctional hippocampus may trigger significant postsurgical plasticity processes. Furthermore, these structural reorganisation processes extend to include distant but functionally connected brain regions.

Further research is needed to assess the function of the structural reorganisation for the memory. A better understanding of these processes and their functional relevance at the individual level is crucial for presurgical investigations. Individualised diagnostic markers would help to predict the postoperative outcome and to assess the rehabilitative potential.

5. Discussion

Studies 1-3 revealed that developing and lesioned brains adapt structurally and behaviourally to hippocampal dysfunction on multiple levels. Both mechanisms may facilitate successful adaptations: structural plasticity, which involves hippocampal and extrahippocampal changes, and a behavioural compensation, which is context-dependent and may support flexible behavioural strategies. In the following chapter, the most relevant results of Studies 1-3 and their implications for adaptive processes will be discussed.

5.1. Study 1: Behavioural Strategies in the Developing Brain – Decision Making in Children

We applied an associative memory task to compare developmental changes in the performance of children, teenagers, and young adults. In terms of accuracy, young adults performed better than teenagers in both trial types, who in turn performed better than children. Contrary to our expectation, children did not perform worse on indirect trials than on direct trials. However, children reacted significantly slower in indirect trials compared to other groups.

Although a recent study (Schlichting et al., 2017) found for children and adolescents a significantly lower memory performance in the indirect trials compared to the direct trials, in Study 1 we did not observe similar differences in accuracy between the groups. In our Study, the repeated inference tests as well as previous knowledge about overlapping trials probably prepared the subjects for reoccurring inference trials. These modifications in the task structure seem to be the most plausible explanations for the discrepancies between both studies in the inferential memory performance (cf. Schlichting & Preston, 2015; Zeithamova, Dominick, et al., 2012).

The absence of the expected shift in the memory performance among different age groups may also suggest that the inferential memory develops earlier during childhood than expected. A recent review (Keresztes, Ngo, Lindenberger, Werkle-Bergner, & Newcombe,

2018) supports this suggestion by claiming that the developing memory system relies more on generalisation and detecting regularities than on encoding and remembering particular information. Based on the assumption that generalisation is supported by pattern completion, it is convincing that these processes also support memory inference: For example, generalisation may occur by filling in new representations relying on previously stored knowledge (Yassa & Stark, 2011).

Although the accuracy on indirect and direct trials did not differ significantly in the children group, children showed the greatest delay in reaction time between indirect and direct trials. A recent study concerning reaction time and hippocampal activity pattern during memory integration reported that fast inferences may be facilitated by integration at encoding (Schlichting, Zeithamova, & Preston, 2014). This study linked short reaction times with a similar hippocampal activity pattern during encoding of BC-trials and during retrieval of AC-trials. According to these findings, the increased reaction times during indirect trials in the children group in our Study 3 may indicate that children are more likely to mainly rely on a retrieval-based strategy. Pursuant to this interpretation, children would first retrieve the direct associations and then make the inferential judgement.

Taken together, our findings point to a developmental shift in building inferential memory. Children seem to rely more on recombination at retrieval, whereas young adults form integrated representations at different stages of memory processing. Furthermore, supportive conditions like familiarity with the task and task structure may play a crucial role in integrating partially overlapping information, especially in a developing brain.

5.2. Study 2: Behavioural Strategies in the Lesioned Mature Brain – Decision Making in Patients with Hippocampal Dysfunction

In Study 2, we compared the inferential memory performance of control participants and patients with MTL damage. In the beginning of the experiment, both groups presented a similar accuracy level on both trial types. By the end of the experiment, the accuracy of the patients, however, dropped across cycles – but only for the indirect trials. The decreased performance

may not simply be explained by hippocampal damage, but likely results from the dysfunction of an additional integration mechanism.

Contrary to the performance of the patient group, the controls improved their accuracy during the experiment. They also showed an increasing correlation between BC-pairs and AC-pairs, which allows to assume that the anticipation of repeated AC-decisions might have influenced controls to form integrated ABC-representations when encoding the BC-pairs. This may indicate a shift in memory integration from relying on recombination at retrieval to encoding-based inference across cycles.

Assuming that patients relied on the same integration mechanism as controls, the decreasing memory performance on indirect trials during the experiment may point to a preserved retrieval-based strategy and an impaired integrative encoding in patients. It seems that the patients – similarly to children (Shing et al., 2019) – show an intact retrieval-based mechanism during forming inferential representations.

Recent findings in healthy controls underpin the central role of the hippocampus within networks for memory integration during retrieval (Heckers et al., 2004; Preston et al., 2004) but also during encoding (Shohamy & Wagner, 2008; Wimmer & Shohamy, 2012; Zeithamova, Dominick, et al., 2012). The encoding-based integration in visual inferential tasks seems to particularly depend on the posterior ventromedial prefrontal cortex and the right anterior hippocampus (Schlichting & Preston, 2015) – and the right hippocampus is the very brain region that was affected in all patients participating in this study.

Previously to Study 2, there have been no lesion studies on associative inference in human patients. Our research provides additional support for previous studies reporting that the contribution of the hippocampus and prefrontal areas to memory integration is not constant, but rather is modulated by contextual factors such as the task structure (Schlichting, Mumford, & Preston, 2015; Zeithamova, Dominick, et al., 2012). The inferential decisions may be sufficiently supported by networks outside the damaged MTL. This implies that memory integra-

tion relies on the flexible interaction of hippocampus-dependent and hippocampus-independent mechanisms of memory integration.

In summary, these findings provide a link between the imaging studies of memory integration/inferential reasoning in healthy controls and the behavioural studies in neuropsychiatric patients by showing that damage to the hippocampus is sufficient to create a memory integration deficit and to leave the associative memory functions unimpaired. However, the observed deficits in inferential memory may be sufficiently compensated by structures outside the damaged MTL. Future studies, thus, should further explore conditions that influence reliance on integrated representations.

5.3. Study 3: Structural Changes in the Lesioned Mature Brain – Early Plasticity Processes

Study 3 revealed structural plasticity 3 months after the MTL resection and underline the relevance of early postoperative plasticity, even in patients with a long-standing unilateral hippocampal dysfunction.

Hippocampal plasticity was previously observed in healthy subjects (Draganski et al., 2006; Erickson et al., 2011; Woollett & Maguire, 2011) but also in patients with neurological and neuropsychiatric disorders (Mufson et al., 2015; Pajonk et al., 2010; Rosen et al., 2011; ten Brinke et al., 2015). Recent studies reported that the contralesional hippocampus as well as the ipsilateral hippocampus remnant can compensate unilateral hippocampal damage at a functional level (Bonelli et al., 2013; Sidhu et al., 2016; Stretton et al., 2014). These functional changes were observed as early as 3 months postoperatively, with further reorganisation at 12 months after the surgery (Sidhu et al., 2016; Stretton et al., 2014). In Study 3, we demonstrated that postoperative reorganisation includes not only functional but also structural plasticity and may occur as early as 3 months postoperatively.

Our findings underlined the importance of pre- and postoperative reorganisation for patients with a hippocampal dysfunction. A previous study (Braun et al., 2008) compared patient groups with similar surgical lesions to the right MTL but different pre-operative disease

courses. This study showed that patients suffering from hippocampal sclerosis, which develops early in life, did not reveal memory deficits on a non-verbal memory task. On the contrary, reduced memory performance was shown for patients with similar right-sided temporal lobe lesions but with shorter preoperative disease duration and operated due to benign tumours. In a further imaging study, Finke and colleagues (2013) showed that both patient groups revealed strikingly distinct activation patterns. These patterns were associated with different behavioural performance: successful memory compensation in the patient group operated due to hippocampal sclerosis correlated positively with increased activation of the contralesional hippocampus and an increased functional engagement of the memory network in the neocortex. Our findings demonstrate that postoperative plasticity may be also triggered in addition to such long-standing preoperative plasticity processes and occur on a surprisingly short timescale.

Functional studies with non-operated patients suffering from MTL epilepsy observed abnormal connectivity in the ipsilateral and contralateral temporal lobe, in extratemporal regions, and in brain areas related to the DMN (Bettus et al., 2009; Frings, Schulze-Bonhage, Spreer, & Wagner, 2009; Liao et al., 2011; Voets et al., 2012). Despite a wide range of literature on the DMN and MTL epilepsy, no study explicitly addressed the question of postoperative changes in structure and function within the DMN. So, in Study 3, we addressed such structural changes. We showed that postlesional reorganisation processes not only cause a significant volume increase in contralateral homologous areas but also induce early changes in large-scale networks. Structural variations have been suggested to underlie functional connectivity alterations in patients with MTL epilepsy (Voets et al., 2012), so that the observed hippocampal volume increase may contribute to the postsurgical normalisation of functional network alterations in these patients (Sidhu et al., 2016; Stretton et al., 2014).

Study 3 revealed that postlesional processes induce significant structural changes on a short timescale. The structural reorganisation processes can extend beyond contralateral homologous areas to include functionally connected brain regions and may potentially contribute to functional network changes and to an improvement of the memory performance.

Further studies are needed to characterise these processes and establish their role for functional and behavioural compensation processes.

5.4. Conclusions

The brain adapts to hippocampal dysfunction on multiple levels. In situations that require hippocampal integrity, both structural plasticity and context-dependent behavioural compensation allow for flexible behavioural strategies. It would be worthwhile for the future to undertake studies that focus on the interaction between the behavioural and the structural mechanisms. Also, future studies that will use repeated structural neuroimaging and neuropsychological assessments may reveal critical time windows for successful reorganisation, both during the development of the brain and after hippocampal damage. This knowledge would contribute to improving teaching programmes, to taking into consideration the developing course of memory performance, and to individualising cognitive rehabilitation approaches for patients with temporal lobe resection.

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7. Erklärung

Hiermit erkläre ich, die Dissertation selbstständig und nur unter Verwendung der angegebenen Hilfen und Hilfsmittel angefertigt zu haben.
Ich habe mich anderwärts nicht um einen Doktorgrad beworben und besitze keinen Doktorgrad in dem Promotionsfach.
Ich erkläre, dass ich die Dissertation oder Teile davon nicht bereits bei einer anderen wissenschaftlichen Einrichtung eingereicht habe und dass sie dort weder angenommen noch abgelehnt wurde.
Ich erkläre die Kenntnisnahme der dem Verfahren zugrunde liegenden Promotionsordnung der Mathematisch-Naturwissenschaftliche Fakultät II der Humboldt-Universität zu Berlin vom 3. August 2006. Weiterhin erkläre ich, dass keine Zusammenarbeit mit gewerblichen Promotionsbearbeiterinnen/Promotionsberatern stattgefunden hat und dass die Grundsätze der Humboldt-Universität zu Berlin zur Sicherung guter wissenschaftlicher Praxis eingehalten wurden.
Mit der Erfassung der Daten gemäß „Satzung zur Erhebung von Daten über Abschluss- und Qualifikationsarbeiten“, Amtl. Mitteilungsblatt der HUB Nr. 63/2010 bin ich einverstanden.

Declaration

I hereby declare that I completed the doctoral thesis independently based on the stated resources and aids. I have not applied for a doctoral degree elsewhere and do not have a corresponding doctoral degree in this doctoral subject.
I have not submitted the doctoral thesis, or parts of it, to another academic institution and the thesis has not been accepted or rejected.
I declare that I have acknowledged the Doctoral Degree Regulations which underlie the procedure of the Faculty of Mathematics and Natural Sciences II (Humboldt-University), as amended on 3rd August 2006. Furthermore, I declare that no collaboration with commercial doctoral degree supervisors took place, and that the principles of Humboldt-Universität zu Berlin for ensuring good academic practice were abided by.
I agree that my data will be collected according to "Satzung zur Erhebung von Daten über Abschluss- und Qualifikationsarbeiten", Amtl. Mitteilungsblatt der HUB Nr. 63/2010.

.....

Datum / Unterschrift der Kandidatin
Date / signature of the candidate

8. Akademischer Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Berlin, den 14. Oktober 2019 .....
Anna Pajkert