Development of Declarative Memory in Preterm and Full-Term Born Children

Evidence from Neuropsychological Tests, Structural Brain Imaging, and Event-Related Potentials

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Abbreviations

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AVLT	Auditory Verbal Learning Test
BW	Birth Weight
CT	Computerized Tomography
DIPS	Diagnostisches Interview bei Psychischen Störungen
DSM	Diagnostic and Statistical Manual
EEG	Electroencephalography
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
GA	Gestational Age
HAWIK-R	Hamburg-Wechsler-Intelligenztest für Kinder
IF	Intellectual Functioning
IQ	Intelligence Quotient
ISEI	International Socio-Economic Index of Occupational Status
IVH	Intraventricular Hemorrhage
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
NICU	Neonatal Intensive Care Unit
PFC	Prefrontal Cortex
PVL	Periventricular Leukomalacia
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
ROC	Receiver Operating Characteristics
SES	Socio-Economic Status
VLMT	Verbaler Lern- und Merkfähigkeitstest
WISC	Wechsler Intelligence Scale for Children

Abstract

Several studies have reported deficits in recognition and recall in children who were born prematurely. Moreover, prematurity is often associated with marked volume reductions in the hippocampus, which is an important brain structure for episodic memory. Still an important question is whether deficits in behavioral performance are due to differences in memory functions in preterm children as compared to full-term children. In the present thesis, neuropsychological tests, structural magnetic resonance imaging (MRI), and event-related potentials (ERPs) were used to shed light on the role of the hippocampus in declarative long-term memory in preterm and full-term children. Four studies were performed to examine developmental differences in declarative memory between these populations.

In Study 1, neuropsychological tests were used to explore semantic and episodic memory. Additionally, a recognition memory experiment with a speeded (fostering familiarity-based retrieval) and nonspeeded (supporting hippocampus-dependent recollection) response condition was conducted to examine episodic memory retrieval processes. To obtain volumetric data of the hippocampus, structural MRI was applied. Preterm children showed reduced hippocampal volumes relative to full-term children. Although the groups did not differ in episodic memory performance, preterm children showed impairments in semantic memory tasks. This suggests that semantic memory is functionally affected by prematurity. Nonetheless, only episodic memory performance was positively correlated with hippocampal volume in full-term but not in preterm children. These results suggest that preterm children recruit a neural network for episodic memory that differs from that used by full-term children.

Study 2 and Study 3 added supportive ERP evidence by showing that, although both groups showed comparable ERP correlates of familiarity in the speeded condition of the recognition experiment, the ERP correlate of recollection in the nonspeeded condition was reduced in preterm children. As in Study 1, recognition memory performance was found to be unimpaired in preterm children. Furthermore, in the preterm group, the magnitude of the ERP correlate of recollection was negatively correlated with the magnitude of the ERP correlate of familiarity, suggesting that within the brains of preterm children reduced recollective processing may be compensated by enhanced familiarity-based remembering. Thus, these results provide tentative support for the assumption that in the preterm brain other brain structures compensate for reduced hippocampal volumes to reach a performance similar to those of full-term children.

Study 4 investigated whether a task-resource artefact can alternatively explain the reduction in recollective processing in preterm children, because one might propose that recollection requires a greater amount of cognitive resources or is the more difficult process than familiarity and is therefore selectively reduced. To assess the influence of task difficulty on performance in both groups, task difficulty was manipulated first, between an item memory task (easier task) and a source memory task (more difficult task) and second, by using short lags (easier task) and long lags (more difficult task) for the repetition of items. By showing similar memory accuracy between preterm and full-term children, irrespective of the difficulty of the tasks, the present data suggest that a task-resource artefact does not seem to provide an alternative explanation for the selective reduction in recollective processing in preterm children as compared to full-term controls.

Taken together, these findings provide evidence for the presence of alterations in declarative long-term memory processing in preterm children at early school-age with uncomplicated neonatal courses compared to full-term children. Although prematurity was not found to be associated with impairments in episodic memory performance, it appears to induce functional changes in episodic retrieval processing, possibly due to hippocampal volume reductions in preterm children. These functional changes may underlie the development of alternative neural pathways for episodic memory processes which enable preterm children to reach performance similar to that seen in full-term subjects.

General Introduction

Memory is one of the most essential cognitive abilities in humans, allowing individuals to build a stable knowledge base and to remember details of one's everyday life. The critical stages of memory processing include the encoding, storage, and retrieval of information, which refer to the acquisition of new information, the maintenance of this information over an extended time period, and the access to this stored information, respectively. Different regions of the human brain are involved for meeting all these requirements. As each brain structure underlies different maturational changes during the developmental course (Huttenlocher & Dabholkar, 1997), qualitative and quantitative changes in memory performance occur over the lifespan. In consequence, a major goal of memory research is to gain a deep understanding of developmental changes in memory and of the maturation of brain systems, which underlie memory changes from infancy over childhood to adulthood.

An appropriate model to investigate the relationship between the maturation of brain systems and corresponding changes in memory performance is to use developmental populations in which specific functions are compromised, such as children born prior to term. Preterm children are prone to damage to the hippocampus, which is assumed to support memory in general and declarative long-term memory in particular. As Luciana (2003) points out, studies on preterm born children are able to add new knowledge to theories of cognitive development, because they provide neuroscientists with a unique temporal window through which the dynamics of early brain maturation can be observed. This issue is highlighted in recent investigations documenting that shortened gestation, as in preterm individuals, has long-lasting influences on neurodevelopment (Davis et al., 2011).

Notably, in a recent review of the worldwide incidence of preterm birth, Beck et al. (2010) stated that the morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological, and economic costs. Compared to children born at term, preterm children are at a greater risk for suffering from brain damage and related neurological disorders, such as neuropsychological or behavioral impairments. Therefore, researchers have focused attention on the quality of life of survivors of preterm births.

Before presenting the four studies that were conducted in the present thesis to further elucidate the development of declarative long-term memory in preterm and full-term born children at early school-age, it is necessary to describe the theoretical background in detail. For this purpose, three theoretical parts will be presented. Part 1 introduces different memory systems with a focus on recognition memory. In addition, important developmental aspects of declarative long-term memory in general and recognition memory in particular will be reviewed. By this, the investigatory framework for the following studies is provided and it is easier to follow the research on the impact of prematurity on memory processes presented in the second theoretical part. Part 2 then gives an overview of prematurity and its neurodevelopmental outcomes with a particular focus on the development of episodic memory. Part 3 describes the different methods and approaches of cognitive psychology that were used to investigate the developmental differences in declarative long-term memory between preterm and full-term children. Finally, the main objectives of the four studies conducted in the present thesis will be summarized.

1 The Declarative Memory System and its Development

Most neuroscientists assume that there are different memory systems, which serve distinct functions (e.g., Atkinson & Shiffrin, 1968; Squire & Knowlton, 1995; Tulving, 1995). On the basis of studies of patients with circumscribed memory disorders, who are impaired in some kinds of memory abilities but show completely intact performance in others (Moscovitch et al., 2005; Squire & Zola, 1996) and of studies applying neuroimaging methods (e.g., electroencephalography (EEG), functional magnetic resonance imaging (fMRI), positron emission tomography), one fundamental distinction can be drawn according to the retention time of information: short-term versus long-term memory. Short-term memory refers to the type of memory used to maintain a limited amount of information in an active state over a brief time period (Baddeley, 2000). By contrast, long-term memory reflects the memory ability of maintaining information over longer delays. Long-term memory can be further subdivided into nondeclarative and declarative memory. Nondeclarative memories are typically described as acting unconsciously or automatically, which is the case for conditioned responses, habit and skill learning, or priming. By contrast, declarative memory contents reach conscious awareness, such as when knowledge about facts or events is remembered (de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006). Subsequently, declarative memory can be divided into episodic and semantic memory. Whereas episodic memory refers to the memory for individual events that can be located in time and space, such as remembering what dress you were wearing during the wedding of your sister, semantic memory represents general knowledge of the world that is context-free and can be used across different situations, such as knowing who Christopher Columbus was (Baddeley, 2001). Thus, in contrast to semantic memories, episodic memories have a high specificity and depend on the context in which they were acquired. Figure 1 shows a taxonomy of different memory systems and subsystems.

Studies examining the neural correlates of these memory systems were able to reveal that each memory subsystem is mediated by distinct brain regions (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Squire & Zola, 1996). For instance, declarative memory is supported by the diencephalon and the medial temporal lobe (MTL) including the hippocampus, entorhinal, perirhinal, and parahippocampal cortices. By contrast, nondeclarative memory seems to depend on the striatum, the neocortex, the amygdala, and the cerebellum (Squire & Zola, 1996).

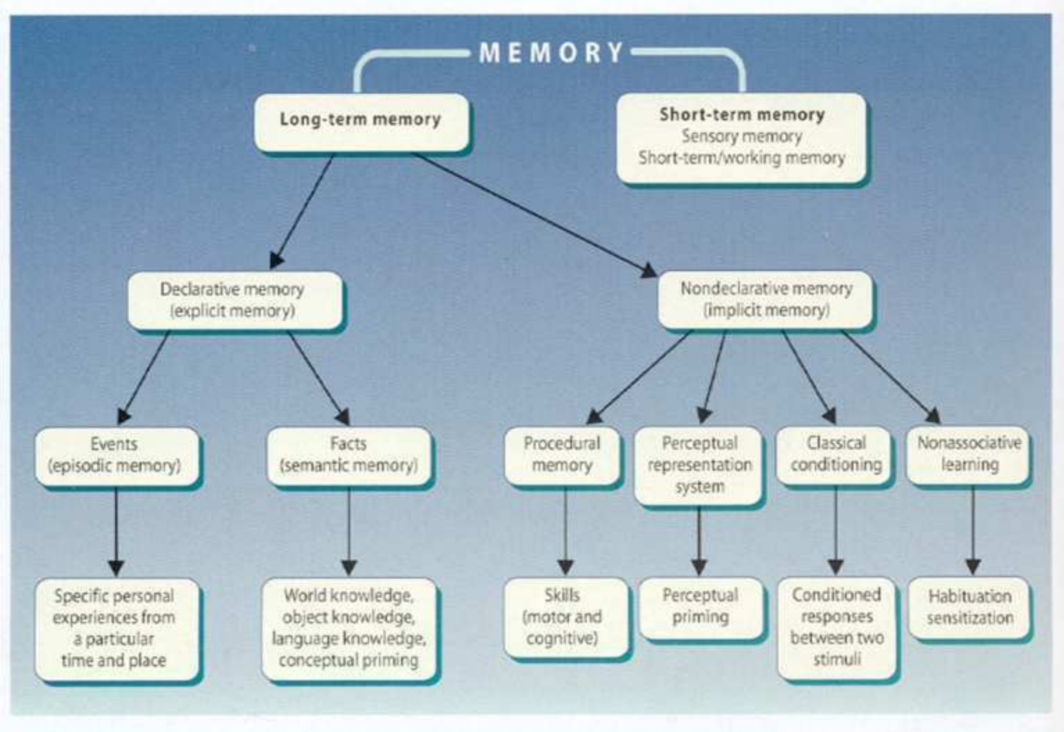


Figure 1: A taxonomy of memory systems in humans (adopted from Gazzaniga, Ivry, & Mangun, 2002).

To summarize, memory is unlikely a unitary system, but rather seems to consist of different types of memories that serve distinct cognitive requirements. Moreover, there is evidence that different brain structures and their interconnections contribute to the performance of dissociable memory systems. In the next section, declarative long-term memory will be discussed in more detail, as this type of memory is especially vulnerable to the deterioration resulting from a variety of pre- and postnatal clinical conditions (Bauer, 2010).

1.1 Development of Declarative Memory

The declarative memory system shows greater age-related changes than the nondeclarative memory system (see Cycowicz, 2000; de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006; Nelson, 1995; Richmond & Nelson, 2007, for reviews). Using a longitudinal design, Lum, Kidd, Davis, and Conti-Ramsden (2010) found a significant increase in performance in a declarative memory task (word pairs subtest from the Children’s Memory Scale) as compared to a nondeclarative memory task (i.e., procedural memory, assessed with a serial reaction time task) between the ages of 5½ and 6½ years. These results suggest that declarative and nondeclarative memory follow different developmental trajectories.

With regard to the development of declarative long-term memory, there seem to be three fundamental findings (Hayne, 2004). First, younger children learn more slowly than older children. Second, younger children’s memories decay faster over time compared to the memories of older children. Third, younger children are less flexible to exploit retrieval cues in the service of flexible remembering than older children. Similarly to these findings, focusing on the time frame between infancy and early childhood, Bauer (2010) reviewed several developmental changes in declarative memory in healthy populations. For instance, age-related changes occur with regard to the temporal extent, the robustness, and the specificity of memories, changing from temporally limited to temporally extended memories, from vulnerable to robust memories, and from memories that are less specific in the features that are encoded to memories that are more specific. Following this line of argumentation, de Haan et al. (2006) proposed that the development of declarative memory abilities appears to unfold in a sequence beginning with novelty preference and familiarity-based recognition, followed by recall, by flexible memory, and ultimately by source memory. By this, semantic memory, which is independent of the recall of contextual information, is assumed to develop at first, whereas episodic memory, which depends on the recall of the source, is supposed to emerge later during development.

On the behavioral level, recall and recognition tests are usually applied to examine the development of declarative memory. However, there are several difficulties when studying the development of declarative memory only with behavioral data. For example, most of the age improvements in declarative memory performance depend on factors such as the use of mnemonic strategies or knowledge about one's memory (e.g., metamemory), which are not fully developed until early school-age (Perner & Ruffman, 1995). By this, it can be hypothesized that children up to the age of three to six years may not differentiate between different mental states, like belief, knowledge, and (true) memory. Thus, tasks that are appropriate for older age groups are not necessarily adequate for younger age groups, which creates difficulties in comparing memory performance across different age groups. Another disadvantage may be potential motivational differences between age groups. Whereas younger children's interest and motivation fluctuate rapidly, older children, adolescents, and adults can more efficiently regulate their behavioral state. These difficulties have to be kept in mind when interpreting developmental studies. One advantageous alternative to pure behavioral studies is conducting studies that combine multiple measures (e.g., ERPs, fMRI) to try to reveal causal links between the activity and changes of specific brain regions and the development of behavior.

In recent years, an increasing number of neuroimaging studies provided evidence that declarative memory ability develops from childhood through adolescence and into young adulthood (e.g., Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; Ofen et al., 2007), largely depending on the maturation of the prefrontal cortex (PFC). In this context, in a longitudinal MRI study Gogtay et al. (2004) reported that the PFC, which is important for cognitive control processes (e.g., Raye, Johnson, Mitchell, Nolde, & D'Esposito, 2000), showed delayed maturation until late adolescence (see Paus, 2005, for a review). Given the delayed maturation of the PFC and its involvement in strategic memory retrieval, the formation of detailed memories for experiences might be attenuated in younger age groups relative to adults (Ofen et al., 2007).

To further elucidate the relationship between the maturation of brain structures and the developmental changes in declarative memory, Chiu et al.

(2006) examined age-related differences in the activation patterns of the PFC and the MTL in younger (7 to 8 years old) and older (10 to 18 years old) children during the episodic encoding of sentences (story comprehension task). They found that older children remembered significantly more sentences from the stories than the younger children. With respect to the fMRI findings, MTL activation predicted subsequent performance in remembering sentences in younger children, whereas activation in both MTL and prefrontal regions was associated with successful sentence recall in older children. These results provide evidence for the view that age-related improvements in declarative memory performance depend on the maturation of the PFC.

Additional evidence for the improvement of declarative memory performance with age comes from studies which examine item versus source aspects of episodic memory (Cycowicz, Friedman, Snodgrass, & Duff, 2001; Cycowicz, Friedman, & Duff, 2003; Czernochowski, Mecklinger, Johansson, & Brinkmann, 2005; Czernochowski, Mecklinger, & Johansson, 2009; Sprondel, Kipp, & Mecklinger, in press). Within the episodic memory domain, it is possible to distinguish between memory about the occurrence of an event (item memory) and memory for the context in which knowledge about the event was acquired (source memory). Item memory tasks require the discrimination between previously studied and new items and can be solved by using a general sense of familiarity that the item is old without constructing a vivid representation of the study episode. By contrast, source memory tasks require the retrieval of contextual details surrounding the item’s prior occurrence. Moreover, source memory relies on controlled memory processes to a greater degree (Dobbins, Foley, Schacter, & Wagner, 2002; see also Simons & Spiers, 2003, for a review).

To investigate the developmental aspects of item and source memory, Cycowicz et al. (2001) required children aged 7 to 8 years and young adults to study a list of pictures presented in either red or green color for a subsequent memory test. Following the study phase, the participants either had to decide whether or not the items had been previously presented (old-new decision in the item recognition task) or they had to retrieve the color in which the items had been presented (old-green, old-red, new source in the source memory task). The authors found that item memory and source memory performance improved with age. However, source memory performance showed greater age-related improvements compared to item memory performance. Additionally, the authors administered neuropsychological tests that are presumed to depend either on frontal lobe function or MTL functions. Using correlational analyses, Cycowicz et al. (2001) revealed a double dissociation: Item recognition performance was correlated with performance in the neuropsychological test presumed to be sensitive to MTL function, but not with performance in the test of frontal lobe function. By contrast, accuracy in source memory was correlated with the test of frontal lobe function, but not with the test presumed to assess MTL function. These findings suggest that frontal lobe structures are involved in successful source memory and support the view that age-related improvements in declarative memory performance depend on the maturation of frontal brain regions.

Further evidence that source memory, which seems to depend on the maturation of frontal brain regions, develops relatively slowly compared to item memory comes from an ERP study by Sprondel et al. (in press). These authors examined the ERP correlates of item and source memory in children (7 to 8 years old), adolescents (13 to 14 years old), and young adults (20 to 29 years old) while performing a continuous recognition memory task. With regard to item memory, Sprondel et al. found that adults showed the putative ERP correlates of familiarity and recollection, whereas ERP effects in children and adolescents suggested a strong reliance on recollection. In contrast, the ERP correlates of source memory refined with age, showing an increase in strategic recollection as well as an improvement of post-retrieval monitoring from childhood to adolescence. Moreover, the authors found that memory performance increased with age and was particularly low for source memory in children. These findings suggest that recollection is available for item memory judgments by childhood, whereas the retrieval of source information is less efficient at that time.

Taken together, behavioral and neuroimaging studies suggest that declarative long-term memory ability develops from childhood through adolescence and into young adulthood. Moreover, there is accumulating evidence that the prolonged development of specific brain structures (e.g., protracted maturation of the PFC) contributes to these age-related changes.

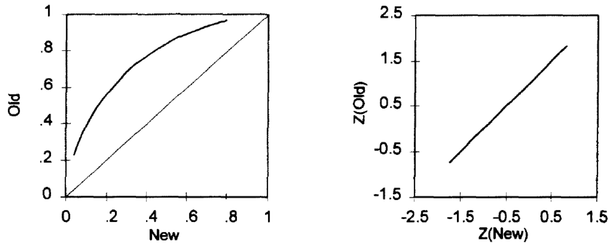
1.2 Recognition Memory

The mental ability of becoming aware that a particular information has been encountered before is referred to as recognition memory. Currently, two contrasting accounts of this form of episodic memory exist: dual-process models versus single-process models. The single-process account assumes that recognition is based on a unidimensional continuum of global memory strength (Squire, Wixted, & Clark, 2007). In contrast, according to dual-process models of recognition memory, episodic memory retrieval is subserved by two qualitatively distinct processes: familiarity and recollection (Yonelinas, 2002). Familiarity refers to a fast-acting memory process, whereby a feeling of knowing someone or something is elicited in the absence of the retrieval of contextual information. By contrast, recollection refers to the slower and more effortful retrieval of contextual information from a prior episode, including the retrieval of the spatial and temporal context. The contemporary literature reports considerable evidence in support of the dual-process account of recognition memory (Aggleton & Brown, 1999, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Mandler, 1980).

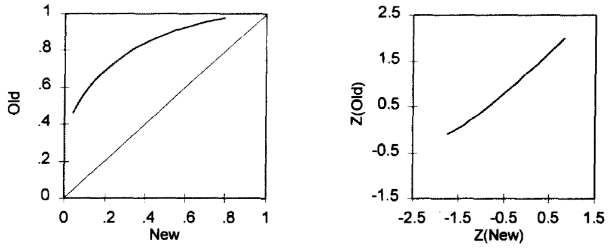
Several techniques were used to examine the relative contribution of familiarity and recollection to recognition memory including receiver-operating characteristics (ROC; Yonelinas, 1997), the process dissociation procedure (Jacoby, 1991), and the remember/know procedure (Tulving, 1985).

ROCs are functions that relate hit (i.e., items correctly recognized as old) rates to false alarm (i.e., new items incorrectly recognized as old) rates while participants make recognition judgments at different levels of confidence. The shapes of ROC curves provide information about the underlying memory subprocesses (Yonelinas, 1997; see Figure 2). If recognition judgments are based on familiarity alone, a curvilinear ROC curve that is symmetrical along the diagonal as in Figure 2a is expected by the dual-process model. By contrast, if performance relies exclusively on recollection, then the ROC should be linear and approach the point 1.1 of the coordinate system as in Figure 2d. Given that recollection is associated with high-confidence responses, increasing levels of recollection shift the lower left part of the ROC upward on the y-axis, resulting in an ROC that is asymmetrical along the diagonal. If both familiarity and recollection contribute to performance, the dual-process model predicts an ROC that is curvilinear and asymmetrical along the diagonal as in Figure 2b.

a) Familiarity



b) Familiarity and Recollection



d) Recollection

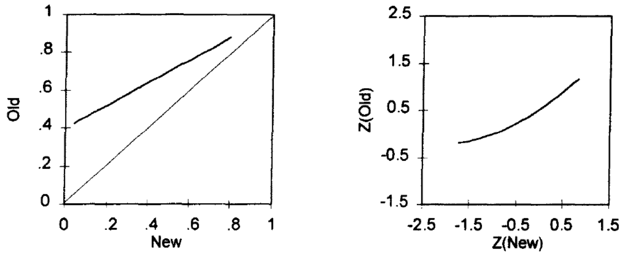


Figure 2: ROCs generated by (a) the equal-variance signal detection model (familiarity), (b) the dual-process signal detection model (familiarity and recollection), and (d) the high-threshold model (recollection). ROCs are plotted in probability space and z-space in the left and right panels, respectively (adopted from Yonelinas, 1997).

The process dissociation procedure consists of two conditions, an inclusion and exclusion condition. Initially, participants are instructed to memorize items in two different contexts (e.g., words presented auditorily and in written form). Subsequently, recognition tests with an inclusion and an exclusion condition follow. In the inclusion condition, participants have to respond “old” to all items presented previously regardless of the context in which they were presented. By contrast, in the exclusion condition, participants have to respond “old” only to items which were presented in one of the two study contexts (e.g., words presented in written form). Accordingly, correct responses in the exclusion condition should be based solely on recollection, whereas correct responses in the inclusion condition should be based on both familiarity and recollection.

In the remember/know (R/K) procedure, participants have to evaluate their memory states during a recognition memory test and are asked whether they recollect qualitative details about the item from the study phase (R-response), they merely have a feeling of familiarity with the item (K-response), or they have not encountered the item previously (New). R-responses are believed to reflect recollection, whereas K-responses are assumed to represent familiarity-based memory processes (Tulving, 1985).

With regard to the neuronal networks underlying familiarity and recollection, recent functional neuroimaging studies have not yielded completely unequivocal evidence. However, although currently controversially discussed (see Bird & Burgess, 2008; Eichenbaum et al., 2007, for reviews), there is substantial evidence that in adults, familiarity and recollection are supported by different subregions of the medial temporal lobes (Aggleton & Brown, 2005; Bowles et al., 2007; Yonelinas et al., 2002). The hippocampal formation is assumed to be critical for recollection, whereas the anterior part of the parahippocampal region (comprising entorhinal, perirhinal, and parahippocampal cortices) centered around the perirhinal cortex subserves familiarity-based memory. Furthermore, there is some evidence that the posterior two-thirds of the hippocampus are more involved in episodic memory retrieval, especially in recollection, than its anterior part (Daselaar, Fleck, & Cabeza, 2006; Ludowig et al., 2008).

Further evidence for the neuroanatomical dissociation of familiarity and recollection is provided by neuropsychological case studies, revealing that brain lesions of the anterior temporal lobe including perirhinal cortex but sparing the hippocampus appear to disrupt familiarity while leaving recollection intact (Bowles et al., 2007). In contrast, selective recollection impairments are associated with restricted hippocampal damage (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Yonelinas et al., 2002).

Based on the assumption that familiarity and recollection are distinct cognitive processes, several studies have demonstrated that they are also distinguishable on the basis of qualitatively distinct ERP components (see Figure 3; Friedman & Johnson, 2000; Mecklinger, 2000). The putative ERP correlate of familiarity is the mid-frontal old/new effect, that is, more positive going waveforms for previously studied compared to unstudied items that are most pronounced between 300 and 500 msec at frontal electrode sides. By contrast, recollection is associated with a somewhat later occurring ERP effect, that is, more positive going waveforms for studied than unstudied items between 400 and 600 msec at parietal recording sites. This ERP difference is termed the parietal old/new effect.

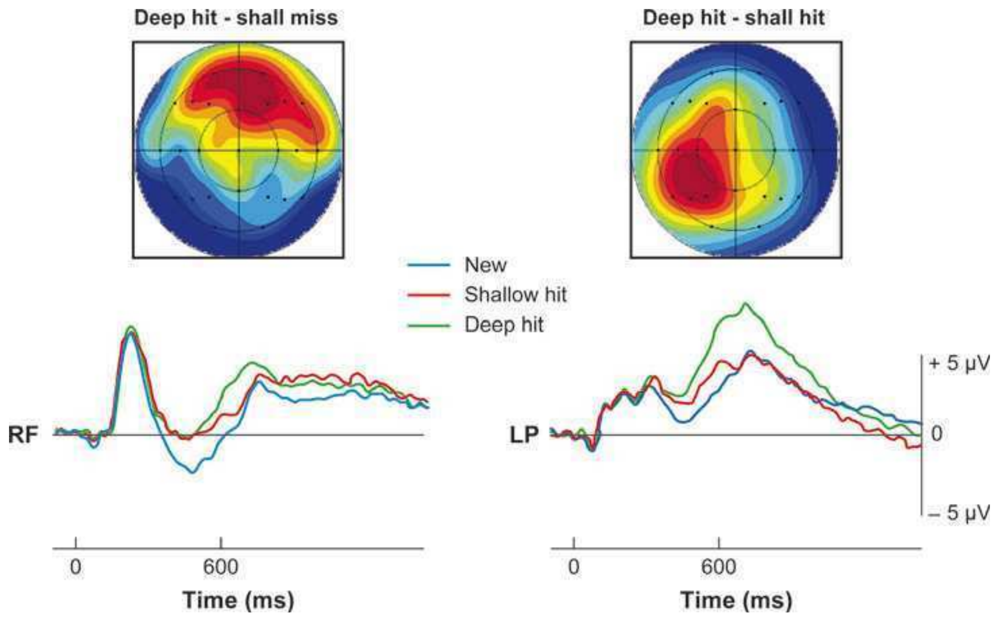


Figure 3: ERPs from Rugg et al. (2002) illustrating a mid-frontal ERP modulation (left panel) associated with familiarity and a parietally distributed (right panel) related to recollection. In this study, the familiarity effect was evident for deeply and shallowly encoding items, whereas the recollection effect was most pronounced for the deeply encoding items (adopted from Eichenbaum et al., 2007).

An increasing number of findings indicate that these two old/new modulations can be experimentally dissociated and by this provide reliable measures of recollection and familiarity (see Mecklinger & Jäger, 2009; Rugg & Curran, 2007, for reviews). For example, the parietal old/new effect is reduced for words encoded under divided attention (Curran, 2004) and under shallow processing (Rugg et al., 1998; see Figure 3) conditions, whereas the mid-frontal old/new effect was not affected by these manipulations. Conversely, using the remember/know procedure, Woodruff, Hayama, and Rugg (2006) found that the mid-frontal old/new effect varies monotonically with familiarity strength as indexed by response confidence for items associated with K-responses, whereas the parietal old/new effect was insensitive to confidence but enhanced for recollected items. The mid-frontal old/new effect has furthermore been found larger for rare than for common names and has by this been dissociated from conceptual priming which was sensitive to name celebrity but not to name frequency (Stenberg, Hellman, Johansson, & Rosén, 2008).

Taken together, behavioral, neuroimaging, neuropsychological, and electrophysiological studies suggest that familiarity and recollection are dissociable processes. The hippocampus is assumed to play a specific role in recollection, while the anterior part of the parahippocampal region centered around the perirhinal cortex contribute to familiarity-based recognition.

1.3 Development of Recognition Memory

As already discussed above, declarative long-term memory can be characterized as a continuous process by which the ability to retain and retrieve information improves from infancy over childhood to adulthood. Despite the large number of studies that examined the developmental trajectories of declarative memory in general (Chiu et al., 2006; Cycowicz, Friedman, & Snodgrass, 2001; Cycowicz et al., 2001; Czernochowski et al., 2009; Sprondel et al., in press), so far only little is known about the development of the two processes underlying recognition memory (i.e., familiarity and recollection). There is some evidence for the view that recollection shows more developmental changes than familiarity (Anooshian, 1999; Billingsley, Smith, & McAndrews, 2002; Ghetti & Angelini, 2008; Ofen et al., 2007). For example, Billingsley et al. (2002) studied groups of 8-10, 11-13, 14-16, and 17-19 year-olds with the R/K procedure and demonstrated an age-related increase in R-responses but not in K-responses between early school-age and adulthood. Similarly, using a picture recognition memory task, Ofen et al. (2007) reported an increase of recognition memory accuracy for recognition that was accompanied by recollection of details from the original experience between the ages of eight and 24, whereas familiarity-based recognition did not change with age. However, the R/K procedure has been criticized for its reliance on subjective reports of familiarity and recollection, and with respect to developmental and clinical studies, for the presumably large interindividual variability in interpreting the difference between remembering and knowing (Strack & Förster, 1995).

In an effort to overcome these limitations, Ghetti and Angelini (2008) recently applied ROC curves to examine the development of familiarity and recollection in children and adolescents between six and 18 years of age. The authors found an age-related improvement for recollection from childhood to adolescence after a semantic but not after a perceptual encoding task. In contrast, familiarity increased only from age six to eight regardless of the encoding condition. These data suggest that familiarity is stable at around eight years, whereas recollection shows a relatively prolonged maturational course.

Taken together, these findings from behavioral investigations suggest that age differences in recognition memory primarily reflect age-related improvements in recollection from childhood through adolescence to adulthood. In contrast, familiarity shows early developmental changes and only small age-related changes after the age of eight years. However, there are some methodological limitations in these studies that need to be discussed. As already mentioned, studies employing the R/K procedure require participants to elaborate or to introspect their memory states, and this form of metamemory may be affected by age (Holland Joyner & Kurtz-Costes, 1997; Roebers, 2002; Roebers & Howie, 2003). For example, in the aforementioned studies by Billingsley et al. (2002) and Ofen et al. (2007), it was not directly tested whether all age groups follow the R/K instruction in the same way and how these subjective reports are related to objective measures of familiarity and recollection. Thus, any developmental changes in familiarity and recollection may potentially reflect age-related changes in the ability to follow instructions and/or to assess memory states. A second concern relates to the estimates of familiarity and recollection derived from ROC studies. First, as confidence ratings required in ROC studies also depend on the ability to distinguish between different memory states, again, age-related changes are possible. Second, only very few ROC studies that examined different age groups tested whether the model assumptions hold to the same extent across all age groups (c.f. Ghetti & Angelini, 2008). By this, age comparisons of ROC curves and derived familiarity and recollection estimates can produce misleading results.

ERPs provide an alternative methodological approach for the study of familiarity and recollection from developmental perspectives because they do not depend on subjective reports of memory states as the aforementioned approaches. Whereas the parietal old/new effect, the putative ERP correlate of recollection, can be reliably recorded at early school-age, so far, data concerning developmental changes in the mid-frontal old/new effect, the putative ERP correlate of familiarity, reveal inconsistent pattern of results (Czernochowski et al., 2005, 2009; Friedman, de Chastelaine, Nessler, & Malcolm, 2010; Hepworth, Rovet, & Taylor, 2001; Marshall, Drummey, Fox, & Newcombe, 2002; van Strien, Glimmerveen, Martens, & de Bruin, 2009). For example, Czernochowski et al. (2005) investigated the relative contributions of familiarity and recollection to recognition memory in 6-8 and 10-12 year-old children as well as in 20-29 year-old adults using a recognition memory exclusion task (Jacoby, 1991). In this task, line drawings of objects were used as retrieval cues for previously studied photos and spoken words. A parietal old/new effect was present in all age groups, irrespective of target category, albeit at a slightly longer latency and with larger amplitude in the two children groups as compared with young adults. Similarly, using words and faces as test stimuli, Hepworth et al. (2001) demonstrated a parietal old/new effect for eleven to 14-year-old children. These findings suggest that recollection is available for recognition judgments at early school-age.

However, the ERP correlate of familiarity is less reliably observed in younger age groups. In the aforementioned study by Czernochowski et al. (2005), no mid-frontal old/new effect was obtained for neither group of children. Similarly, using a repeated study-test recognition memory paradigm, Friedman et al. (2010) found no mid-frontal old/new effect in nine to ten year-old children. By contrast, using a continuous recognition memory task in which old/new decisions were required for continuously presented pictures of everyday objects, Czernochowski et al. (2009) even found an old/new effect at frontal recording sites in the opposite direction for ten to twelve-year-old children, that is, the ERPs were more positive going for new than for old items.

On the one hand, these differences between studies may result from different task characteristics. Specifically, in contrast to the recognition memory exclusion task used by Czernochowski et al. (2005) and the repeated study-test paradigm used by Friedman et al. (2010), there were no explicit encoding instructions in the continuous recognition paradigm (Czernochowski et al., 2009). In fact, in this latter memory task, encoding and retrieval demands were interleaved within a trial.

On the other hand, the absence of a mid-frontal old/new effect in the former studies can be attributed to a specific retrieval and decision strategy employed by the children in the recognition memory exclusion task and the repeated study-test paradigm. In both studies, all children groups showed a very conservative response criterion and only responded “old” when they were highly certain about this. This decision strategy may have attenuated any contribution of familiarity to recognition judgments for previously studied items (Azimian-Faridani & Wilding, 2006). Another reason for not finding a correlate for familiarity in children could be that these studies may have lacked an adequate operational definition of familiarity. Besides this, the old/new difference in the opposite direction found in the study by Czernochowski et al. (2009) may result from a component overlap with the Nc, a fronto-centrally focused negative component frequently reported in infant and children ERP studies. The Nc has been interpreted as presumably reflecting the allocation of attention to novel and unexpected events (de Haan, Johnson, & Halit, 2003). A similar attentional mechanism may also account for the results of Hepworth et al. (2001), who found an old/new difference in the opposite direction in eleven- to 14-year-olds at frontal recording sites as well. A recent study by van Strien et al. (2009) suggests a less matured semantic memory system in younger children groups. Examining the development of verbal recognition memory with an extended continuous word recognition paradigm, they found a midlatency old/new effect (labeled the N400 old/new effect) to be smaller over parietal regions for 8- to 9- as compared with 11- to 12-year-old children.

In summary, although a large number of studies examined the developmental trajectories of recognition memory, there is less consistent evidence with regard to the development of familiarity and recollection. While behavioral data suggest that familiarity-based recognition is in place relatively early in infancy and childhood, the putative ERP correlate of familiarity is not reliably observed in younger age groups. By contrast, the putative ERP correlate of recollection can be reliably recorded at early school-age, assuming that recollection is available for recognition judgments at that age. In the present thesis, the different temporal dynamics of familiarity and recollection are used to test recognition memory in school-aged children and adults (see Study 2).

Up to here, the different types of memory and the brain structures involved in each memory system were described. In addition, a dual-process model of recognition memory was presented and the findings that support the view that familiarity and recollection are two qualitatively distinct processes of episodic memory retrieval were described. Finally, the age-related changes in declarative memory in general and in recognition memory in particular were summarized.

2 Neurodevelopmental Outcomes After Preterm Birth

In the following, a population will be presented that provides researchers with the opportunity to examine the dynamics of early brain maturation on later memory performance. Infants born during the third trimester of pregnancy (i.e., < 37 weeks of gestation), when neural migration is in progress, are at an increased risk for brain injury and poor cognitive outcomes relative to infants born later in gestation. Thus, this population can help to understand the extent to which the developing brain is able to recover from early brain injury.

2.1 Prematurity

In humans, pregnancy normally lasts 40 gestational weeks (nine months). According to gestational length, a delivery before 37 weeks of gestation is defined as a preterm birth (World Health Organization [WHO], 1992), and these preterm births are further classified as moderately, very, or extremely preterm, occurring at 32-36, 28-31, and ≤ 27 weeks of gestation, respectively. Some studies (Taylor, Minich, Klein, & Hack, 2004) define preterm births on the basis of the birth weight (BW), including low, very low, and extremely low BW (< 2500 g, < 1500 g, and < 1000 g, respectively). However, the classification solely on BW criteria has the limitation that growth-restricted infants with more advanced gestational ages (GA) are misclassified (Johansson & Cnattigius, 2010). Hence, both measures of prematurity (i.e., GA and BW) are usually used for classification.

Contrary to the general belief, preterm birth is a common pregnancy complication. Beck et al. (2010) reported that 9.6% of all births that occurred in 2005 worldwide were preterm. Moreover, the incidence of prematurity has increased in the last years, at least in the United States of America (Hamilton et al., 2007; see Figure 4). Several factors are discussed which possibly contribute to this upward trend including increasing rates of multiple births, greater use of assisted reproduction techniques, increases in the proportion of birth among women over 34 years of age, and changes in clinical practices, such as greater use of elective Caesarean section (Beck et al., 2010). Furthermore, the conditions in the neonatal intensive care units have improved (e.g., highly qualified staffing, refined medical support), resulting in the survival of even extremely immature infants.

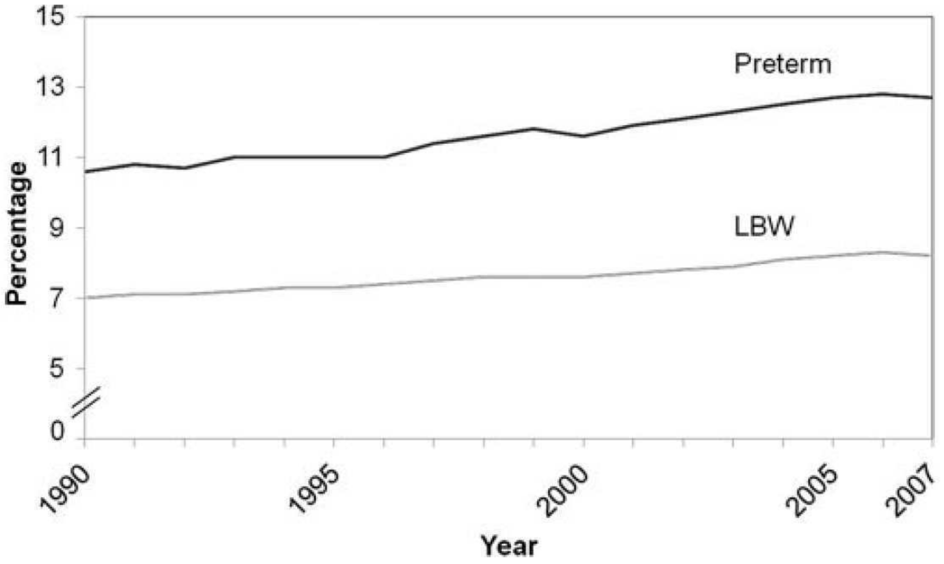


Figure 4: Percent preterm and percent low BW (LBW): United States, 1990-2006 (final) and 2007 (preliminary). LBW is <2500 g and preterm birth is <37 completed weeks of gestation (adopted from Heron et al., 2010).

There is a large number of risk factors for preterm deliveries (Johansson & Cnattigius, 2010) including genetic factors (e.g., polymorphism of genes), infections (e.g., bacterial vaginosis), socioeconomic status (e.g., low education of parents), multiple pregnancies (e.g., birth of twins), maternal characteristics (e.g., low and high maternal age), smoking and substance abuse (e.g., narcotics and alcohol) as well as air pollution (e.g., ozone).

Several studies have demonstrated that children born preterm have higher rates for neurological, behavioral, and neuropsychological problems compared to children born at term, and the risk gets higher the more immature the children are at the time of the delivery (Fanaroff et al., 2007; Foulder-Hughes & Cooke, 2003; Taylor et al., 2000). However, immaturity is not the only risk factor for later impairments (Luciana, 2003). In fact, there is a host of factors and the interaction among them that influences the neurodevelopmental outcomes of preterm birth.

Figure 5 summarizes the factors that determine the nature of cognitive development in preterm children.

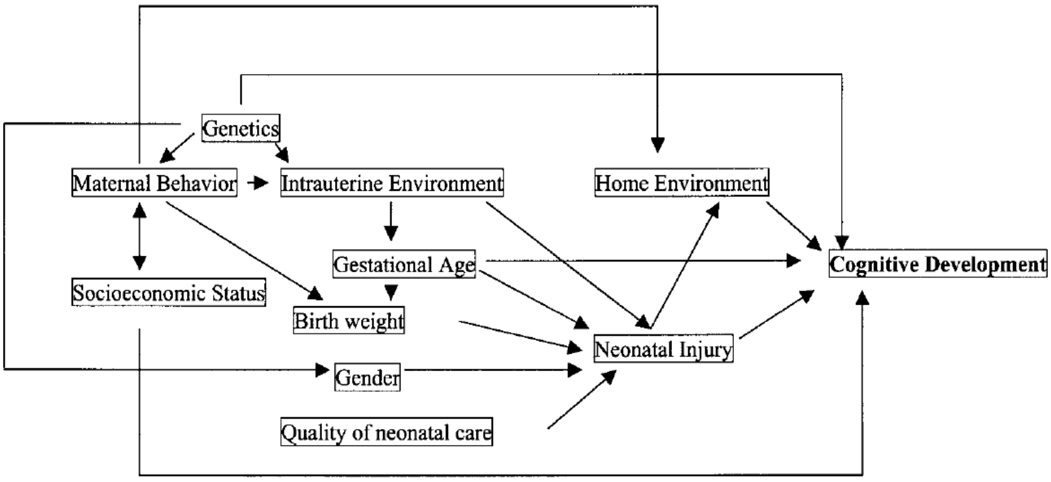


Figure 5: The source of influence on cognitive development in the preterm infant. The child's cognitive status in adulthood will be determined by genetic, sociodemographic, and neonatal risk factors, as well as interactions among these variables (adopted from Luciana, 2003).

2.2 Neuroimaging Findings in Preterm Children

It has been reported that shortened gestation has persisting influences on the structure and function of the nervous system (Davis et al., 2011). ERP and MRI studies have demonstrated functional and structural changes in the brains of preterm individuals immediately after birth as well as later brain growth failure. However, while volume measurements of the whole brain and specific areas of the brain have frequently been used to investigate structural changes in the preterm brain (see Cooke, 2010, for a review), ERPs have so far been underutilized in the evaluation of functional changes (see de Regnier, 2008, for a review). Moreover, most ERP studies with preterm populations have focused on the newborn infant, whereas only very few studies have been performed in preterm individuals at a later stage of life. For example, de Regnier, Georgieff, & Nelson (1997) compared ERPs using a test of shape recognition (one familiar stimulus and one novel stimulus) at four months of age in preterm and full-term infants. In contrast to the full-term group, preterm infants did not show the expected negativity in response to the novel stimulus. Similarly, using an auditory recognition memory experiment in which the maternal voice (familiar stimulus) was presented alternately with the stranger's voice (novel stimulus), Therien, Worwa, Mattia, and de Regnier (2004) found no significant differences between the ERPs from the maternal and stranger's voice in preterm newborns (born 24 to 32 weeks gestation; tested 39 to 42 weeks gestation). In contrast, full-term newborns (born 39 to 42 weeks gestation; tested 1 to 3 days of age) showed a negative slow wave to the stranger's voice. The authors concluded that preterm infants recruit a neural network for recognition memory that differs from the one used by full-term infants.

As already mentioned, there is an extensive literature documenting structural changes in the brains of preterm children (see Cooke, 2010, for a review). For example, Peterson et al. (2000) showed regional brain volume reductions in eight-year-old preterm children compared to term controls (i.e., smaller volumes in the amygdala, basal ganglia, cerebellum, corpus callosum, and hippocampus). Furthermore, Abernethy, Palaniappan, and Cooke (2002) showed that preterm adolescence had smaller volume measurements for the caudate nucleus, a structure which is involved in goal-directed action (Grahn, Parkinson, & Owen, 2008) as well as in memory (Packard & White, 1991), compared to full-term adolescence. In addition to regional specific brain changes, reductions in overall cortical tissue were found in preterm individuals, including abnormalities in cerebral white and gray matter (Inder, Anderson, Spencer, Wells, & Volpe, 2003; Kesler et al., 2004). There is also evidence that the size of the lateral ventricles is disproportionately enlarged in preterm children and adolescents (Kesler et al., 2004; Peterson et al., 2000; Stewart et al., 1999). Notably, a few studies have demonstrated a significant positive relationship between regional brain volumes and GA at birth, suggesting that the degree of prematurity is important for brain development (Davis et al., 2011; Peterson et al., 2000).

Apart from quantitative differences related to abnormal growth and development of the brain, a high prevalence of qualitative differences has been described in preterm individuals. For example, Abernethy, Klafkowski, Foulder-Hughes, and Cooke (2003) reported the presence of different lesions, including periventricular leukomalacia (PVL) and porencephaly in seven-year-old preterm children. The reasons assumed for the presence of quantitative and qualitative brain changes in preterm individuals are the disturbance of the cortical development and brain injury (see Luciana, 2003; Ment, Hirtz, & Hüppi, 2009; Volpe, 2009, for reviews).

The brain is most rapidly growing during fetal life (12-40 gestational weeks) and early neonatal life (de Graaf-Peters & Hadders-Algra, 2006). Therefore, any brain tissue that is maturing in these time windows is highly vulnerable to insults. In general, the development of the human central nervous system occurs in a certain sequence of events (de Graaf-Peters & Hadders-Algra, 2006; Richmond & Nelson, 2007). Initially, the processes of neuronal proliferation and migration take place, which have largely concluded by 22-24 weeks of gestation, followed by the development of dendritic and axonal ramifications. Between 24-40 weeks of gestation, a substantial proportion of synapses is created, which connect the axon of one neuron to the dendrite of another neuron. This process of synaptogenesis reaches its maximum in the first year of life and is followed by a gradual reduction during childhood and early adulthood (i.e., synaptic pruning). In addition, after the period of cellular proliferation, the effect of myelination (i.e., the thickening of the myelin sheath surrounding axons) reaches its maximum (in the third trimester of gestation) and is almost completed by the end of the second year of life.

To summarize, the basic stages in the cell development in the brain occur in the prenatal period. During these crucial periods of human brain development, mainly in the late second and third trimester of gestation, premature delivery occurs, and this disturbance may lead to changes in the brain development of preterm individuals (see Ment et al., 2009, for a review of the empirical findings regarding changes in brain development).

Following preterm delivery, the babies undergo prolonged intensive care in the neonatal intensive care units (NICU) with exposure to numerous noxious stimuli (e.g., bright light, constant noise, several analgesics) and these environments have additional adverse effects on the developing central nervous system (Als et al., 2004). In addition, it has been highlighted that nutritional deprivation in the neonatal period is associated with impaired brain development.

Among the affected brain structures, the hippocampus has been reported to often show marked volume reduction in preterm children (Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000). With regard to the development of the hippocampus, Utsunomiya, Takano, Okazaki, and Mitsudome (1999) reported two growth spurts. The first sharp increase in hippocampal volume occurs in the second half of pregnancy; a second still larger increase appears postnataly until the age of two years. Thereafter, hippocampal volume continues to increase slowly. By this, it is understandable that preterm delivery affects hippocampal volumes. However, the full adverse effects of prematurity on hippocampal development and their relationship with memory performance might not be apparent until childhood, as a large hippocampal growth spurt occurs between birth and two years of age.

As mentioned above, a second reason for quantitative and qualitative brain changes in preterm individuals is brain injury. In this respect two serious complications are discussed: hypoxia and ischemia (Luciana, 2003). While hypoxia is the reduction in oxygen supply despite adequate perfusion of the tissue by blood, ischemia refers to restriction in blood supply which leads to a low oxygen state. Both are related to intraventricular hemorrhage (IVH) and PVL. IVH is a bleeding inside or around the lateral cerebral ventricles. The initiation of IVH may be caused by fluctuations in cerebral perfusion and cerebral venous pressure (Volpe, 2001). In contrast, PVL is related to necrosis of the white matter surrounding the lateral ventricles (Luciana, 2003). Notably, glial cells in the periventricular region differentiate into specialized subtypes, such as the oligodendrocyte, during the third trimester of pregnancy. As this is the time period when preterm births are most likely to occur, this can account for the disruption of myelination that depends on the formation of oligodendrocytes. Importantly, there are many brain structures which are vulnerable to such complications (e.g., caudate nucleus, corpus callosum, hippocampus, thalamus).

In addition to episodes of hypoxia and ischemia as peri- and postnatal brain injuries, immunological responses of the mother to intrauterine infections are discussed as causes for the elevated vulnerability of the brain in preterm individuals (Luciana, 2003). Notably, with regard to specific damages of the hippocampus, recent studies have demonstrated that, besides hypoxic-ischemic insults, increases in glutamate release, dysregulation of enzymatic activity, (intrauterine) nutrient deficiencies, hypoglycemia, or prolonged exposure to glucocorticoids can cause increases in hippocampal cell loss (Cheatham, Sesma, Bauer, & Georgieff, 2010).

In sum, a considerable amount of data has demonstrated that prematurity is associated with a high prevalence of brain damage and neurodevelopmental sequelae. However, some brain structures are more vulnerable to prematurity than others (e.g., hippocampus). Hence, functions attributed to more vulnerable structures that reach functional maturity early in life (i.e., hippocampus) will be impaired in childhood.

2.3 Cognitive Outcomes of Preterm Children

Cognitive impairments are the most common disabilities identified among preterm children, adolescents, and adults, including deficits in intellectual functioning and memory (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Luu et al., 2009; see Aylward, 2005, for a review). For example, Luu et al. (2009) examined 375 preterm children and 111 full-term control children at 12 years of age. The preterm group obtained significantly lower full-scale as well as verbal and performance intelligence quotient (IQ) scores relative to controls, even after the exclusion of 38 preterm children with severe brain injury (i.e., grade 3 to 4 IVH, PVL, or grade 2 and above ventriculomegaly). However, although many of the reported IQ differences between preterm and full-term individuals are statistically significant, the mean group IQ of preterm individuals falls in the borderline to average range (Aylward, 2002). Because IQ scores are only composite scores of various subtests, they may mask more subtle differences. Therefore, it is important to have a closer look at the subtests of IQ tests, and to explicitly examine distinct cognitive functions.

Although there are several studies which examined memory and learning in preterm individuals (e.g., Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2004; Briscoe, Gathercole, & Marlow, 2001; Isaacs et al., 2000; Narberhaus et al., 2007), the data are not entirely conclusive. While evidence suggests that working memory is impaired in children born preterm (Isaacs et al., 2000; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Sansavini et al., 2007), there are inconsistent results with regard to declarative long-term memory performance (Caldú et al., 2006; Curtis, Zhuang, Townsend, Hu, & Nelson, 2006; Giménez et al., 2004, 2005; Isaacs et al., 2000; Narberhaus et al., 2007, 2009; Rushe et al., 2001). Using standardized neuropsychological tests, Caldú et al. (2006) found impairments in declarative long-term memory in 13-year-old preterm adolescents compared to a full-term control group. Specifically, preterm adolescents obtained significantly lower scores in measures of verbal learning (i.e., Rey Auditory Verbal Learning Test), on the global score of the Rivermead Behavioural Memory Test (RBMT), a measure of everyday episodic memory, and in semantic verbal fluency tests. However, these authors pointed out that the preterm sample included several participants with neurological complications, such as hemorrhage or perinatal hypoxia, which makes it difficult to examine the pure effects of prematurity. Using similar standardized neuropsychological tests, Rushe et al. (2001) found no group differences in different measures of long-term memory (i.e., Logical Memory subtest and delayed recall scores of the RBMT, delayed recall of the Rey-Osterrieth Complex Figure) in 14- to 15-year-old preterm adolescents. However, the preterm group was impaired relative to controls on the verbal fluency test. The authors interpreted these impairments as deficits in language production, which had also been documented in previous studies (Vohr, García Coll, & Oh, 1988). In a similar vein, Narberhaus et al. (2007) found no group differences after controlling for intelligence between preterm and full-term born adolescents (14 years), neither in the performance in the RBMT nor the Rey Auditory Verbal Learning Test (RAVLT). Again, these authors emphasized the heterogeneous preterm sample, which comprised participants with a wide range of perinatal complications (e.g., IVH, respiratory problems) that were not analyzed separately. Critically, this issue, the variability in the inclusion and exclusion of preterm individuals with various complications, holds also for most of the other studies examining preterm individuals. Therefore, the comparison of different studies with heterogeneous preterm samples should be treated with caution.

2.4 Development of Episodic Memory in Preterm Children

Impairments of episodic memory have frequently been reported in preterm children (Caldú et al., 2006; Giménez et al., 2004, 2005; Isaacs et al., 2000). Since the hippocampus is critical for episodic memory, a few studies investigated the relationship between hippocampal volume and episodic memory performance in preterm individuals (Curtis et al., 2006; Giménez et al., 2004, 2005; Isaacs et al., 2000; Narberhaus et al., 2009). So far, however, the few studies which have investigated this relationship revealed inconsistent results. For example, Isaacs et al. (2000) found bilaterally reduced hippocampal volumes as well as reduced scores in the RBMT in adolescents born preterm. Additionally, a regression analysis indicated that hippocampal volume was a predictor of performance in the RBMT. This suggests a positive relationship between hippocampal volume and episodic memory performance in preterm adolescents. Similarly, using voxel-based morphometry, Giménez et al. (2004) found bilateral reductions of hippocampal volume in preterm relative to full-term adolescents. The reduction was more pronounced for the left as compared to the right hippocampus. In addition, in preterm adolescents, positive correlations between left hippocampal gray matter reductions and verbal memory (i.e., learning scores and percentage of memory loss of the RAVLT) were found, that is, the greater the volume loss, the lower the performances. Figure 6 shows the positive correlation between the left hippocampal gray matter value and the percentage of memory loss in the RAVLT. The authors concluded that left hippocampal volume loss may be responsible for memory impairments in preterm individuals.

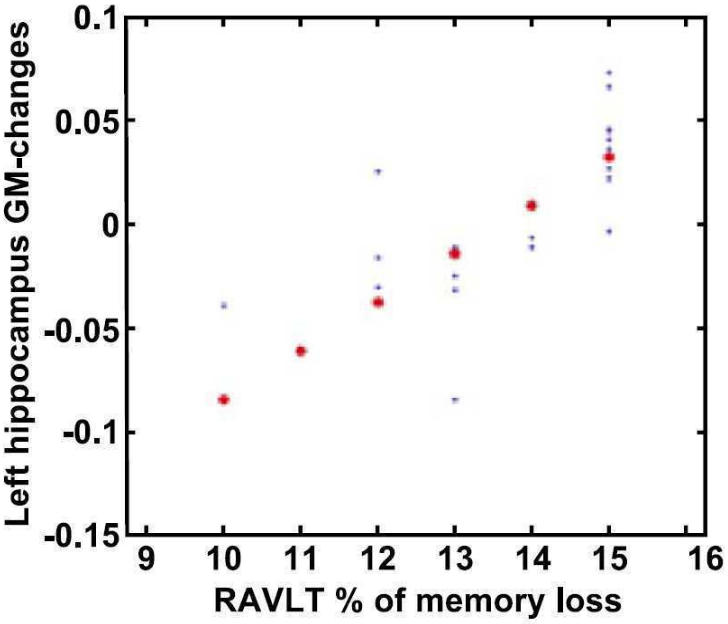


Figure 6: Correlation between gray matter volume in the left hippocampus and percent of memory loss in the Rey Auditory Verbal Learning Test (RAVLT) of the premature group (red points: data adjusted to the theoretical model; blue points: real data (adopted from Giménez et al., 2004).

To further elucidate the relationship between the hippocampus and episodic memory performance, Giménez et al. (2005) used structural MRI and applied an episodic face-name recognition task with functional MRI. At first, they replicated their results from the former study, showing bilateral hippocampal volume reduction in preterm adolescents with a left predominance of the reduction. Furthermore, they found increased activation in the right hippocampus during the encoding phase of the recognition experiment only in preterm adolescents but not in controls. In addition, this activation was positively correlated with recognition performance. The increased activation in the more preserved right hippocampus in the premature group was taken as evidence for a compensatory mechanism for the impaired left hippocampus. These findings suggest that compensatory processes may support task performance in preterm individuals.

There is also evidence from fMRI studies which indicates that other brain structures compensate for structural damages in specific brain regions in preterm individuals to reach performances similar to those of full-term participants (Curtis et al., 2006; Lawrence et al., 2009; Narberhaus et al., 2009; see also Ment &

Constable, 2007, for a review of empirical findings supporting this proposal). For instance, Narberhaus et al. (2009) did not find any group difference in episodic memory performance in a visual paired associates task between preterm and full-term adults. However, the preterm adults were found to activate different neural networks than controls during both encoding and recognition of picture pairs. In addition, in the premature group, the absolute amount of gray matter in the hippocampus was reduced bilaterally. These results suggest a functional compensation within the brains of preterm adults.

This suggestion may be compatible with the findings by Curtis et al. (2006). Their results again indicated a lack of behavioral differences in an episodic delayed match to sample perceptuomotor task between preterm and full-term adolescents. However, preterm subjects showed greater activation during encoding in the right and left caudate nucleus compared to controls. The authors argued that the reasons for different activation levels in caudate nucleus between groups may lie in altered connections in the neuronal network underlying episodic memory functioning.

Notably, as already mentioned, most of the preterm subjects in the aforementioned studies suffered perinatal complications (e.g., IVH, hypoxia), so the inconsistent results of the relationship between hippocampal volume and episodic memory performance could be explained by varying degrees of hypoxic-ischemic or metabolic insults to the hippocampus (Thompson et al., 2008). Moreover, recent behavioral data revealed that the ability to recall information from memory can be enhanced by experiences in the extrauterine environment when risk factors in an infant’s history are at a minimum (e.g., lower grade IVH, short duration of mechanical ventilation), even though experiences in the extrauterine world are no substitute for the expected intrauterine environment (see Cheatham et al., 2010, for a review). Therefore, to investigate the pure impact of prematurity, in the present thesis (see Study 1) episodic memory performance and hippocampal volumes were examined in a sample of preterm children with uncomplicated neonatal courses (e.g., no IVH or hypoxic-ischemic injury).

Taken together, studies examining declarative long-term memory in preterm children show inconsistent patterns of impairments. Whereas some studies found impairments, particularly in episodic memory performance, which was related to reduced hippocampal volumes (Giménez et al., 2004, 2005; Isaacs et al., 2000), other studies found no group differences between preterm and full-term individuals in episodic memory performance (Curtis et al., 2006; Narberhaus et al., 2007, 2009; Rushe et al., 2001). Most importantly, however, only very few studies have systematically compared both subsystems of declarative long-term memory (i.e., semantic and episodic memory) in preterm individuals (Isaacs et al., 2000), and this makes it in an even more complex manner difficult to evaluate the extent and the nature of deficits in this memory system.

3 Neuroscientific Methods

For a comprehensive understanding of declarative memory functioning in preterm and full-term individuals, it is important to use a converging method approach, which applies both neuropsychological tests and neuroimaging techniques. Although a between group comparison can be of high quality even if only one method is used, the combination of different techniques makes the findings more robust, as any method per se has unique strength and limitations. The integration of several techniques not only enables the identification of strengths and weaknesses within individuals, but also the monitoring of functionally relevant brain processes and the exploration of the developmental trajectories of different declarative memory processes in preterm children compared to full-term born controls. By this, the understanding of the brain–behavior relations during cognitive development in both populations will improve. In the following, the theoretical background of the three methods (i.e., neuropsychological tests, ERPs, and MRI) used in the present studies is described in more detail.

3.1 Neuropsychological Tests

Neuropsychological assessment (e.g., standardized tests of intelligence or memory) is one method of examining the human brain by studying its behavioral effects. It allows a systematic measurement of the performance of a person in a relatively short period of time (de Koning, 2009). Moreover, it is assumed that neuropsychological tests can provide reliable measures of the integrity of specific brain structures (Lezak, 1995). In general, neuropsychological testing reduces the subjectivity in traditional neurological examinations by conducting assessments that lead to quantifiable standardized scores. These standardized scores increase the reliability of the assessment and allow for a more precise and sensitive baseline for comparisons across time.

However, there are some particular requirements arising with the application of neuropsychological tests. For example, some cognitive functions are indissolubly connected and this makes the exact interpretation of only one test result difficult. Hence, for the understanding of the relationship between different cognitive functions, a comprehensive neuropsychological assessment is necessary (Lezak, 1995). Another important aspect involves confounding variables, such as motivation, stress, fatigue, and cultural background. As these variables can distort the test results, it is particularly important to use valid and reliable tests with adequate norms. Moreover, it is necessary to use additional methods to gain a deeper and comprehensive understanding of cognitive processing and the functioning of the brain.

A detailed description of the neuropsychological tests used in the present thesis can be found in the method part of Study 1.

3.2 Electroencephalography (EEG)

Electrophysiological techniques such as the EEG are frequently used to study the development of brain functions in children. The EEG is typically recorded through electrodes placed on different points on the surface of the human scalp and reflects the electrical activity of the brain. The electrodes are usually applied according to the 10-20 system that defines the electrode position in terms of the relative distances along the nasion-inion axis (Jasper, 1958). The non-invasive EEG provides a method to directly examine brain processes and to draw inferences about regional brain activity. The EEG represents a pattern of variation in voltage over time, whereby the amplitude of the normal EEG can vary between approximately -100 and +100 µV (Coles & Rugg, 1995). The frequency ranges to 40 Hz or more.

If a stimulus is presented to a participant while recording the EEG, an epoch of the EEG that is time-locked to the presentation of this stimulus can be defined. The voltage changes that are specifically related to the brain’s response to the stimulus are referred to as ERPs. As these voltage changes are often rather small compared to the background EEG (low signal-to-noise ratio), the EEG signal is averaged over many presentations of the stimulus. By this, most of the random EEG activity is cancelled out while the activity which is related to the information processing is preserved. Finally, the resulting ERP waveform can be described in terms of positive and negative peaks, so called “components”. These components are sensitive towards experimental manipulations and vary in amplitude, polarity, latency, and topography. By this, they can be used as markers for cognitive processes.

In the method part of Study 2, a detailed description of the electrophysiological recording used in the present EEG experiment is given.

With regard to the origin of the ERP it is assumed that scalp-recorded ERP waveforms reflect the sum of simultaneous post-synaptic activity of several thousand neurons. In particular, ERPs recorded from the scalp represent net electrical fields associated with the activity of populations of neurons (Coles & Rugg, 1995; Davidson, Jackson, & Larson, 2000). However, only activity of those neurons that summate their individual electrical fields to produce a dipolar field (a field with positive and negative charges between which current flows) can be recorded with the EEG. Because these neurons share the same parallel orientation, these configurations are called “open fields”. In contrast, neurons that are organized in a random manner generate electrical fields that are oriented in different directions and therefore do not produce any detectable field outside them.

One important advantage of ERPs is that they can provide information about the nature of stimulus processing in the absence of overt behavioral responses. While ERPs are characterized by an excellent temporal resolution in the millisecond range to monitor functionally relevant brain processes, the spatial resolution is relatively poor. This is due to the highly resistive properties of the skull, which acts like a low-pass filter and disperses the electrical activity over broad areas of the scalp. Hence, scalp-recorded ERPs do not allow direct inferences about the location of the neuronal generators of any particular ERP component (Coles & Rugg, 1995).

Several studies have demonstrated that the basic shape of ERP waveforms change systematically as a function of age (Coch, Skendzel, Grossi, & Neville, 2005; Holcomb, Coffey, & Neville, 1992). In general, ERP components are larger and show longer latencies in younger children than adults. The amplitudes and latencies decrease as children progress from age five to sixteen. There are several causes for these developmental changes. Whereas changes in ERP amplitudes likely reflect differences in synaptic density, head size, and skull thickness, decreasing ERP latencies are most likely due to changes in myelination as well as increasing proficiency in processing different types of information (de Haan, 2008; Mills & Sheehan, 2007). In this context, longer ERP latencies in children are often accompanied by longer reaction times in behavioral paradigms in younger age groups. Thus, age differences in ERP components could result from the interaction of anatomical or physiological changes and maturational changes in the brain (Casey, Giedd, & Thomas, 2000; Cycowicz, 2000).

3.3 Structural Magnetic Resonance Imaging

Structural MRI is an imaging technique used to create images of the brain's soft tissue by measuring the permanent characteristics (e.g., shape and size) of brain structures. With this neuroimaging method, the brain is displayed in tomographic slices, which enables the investigation of changes in the brain. This non-invasive technique is one of the most powerful diagnostic tools in radiology clinics as well as in research. The signal from which MR images are derived arises from the hydrogen atoms (H) of water (H_2O), especially from the nucleus of the hydrogen atom. This nucleus contains a positively charged and spinning single proton and a single electron. It is the proton, which is of relevance for MRI. Importantly, most human tissue is water-based, whereby the amount of water in each type of tissue varies. Hence, different types of tissue behave in slightly different ways when stimulated in the MRI machine, and this can be used to construct a three dimensional image of the layout of these tissues (Ward, 2006).

To acquire MRI scans, a sequence of events is necessary (see Weishaupt, Köchli, & Marincek, 2006, for detailed description of the MRI methodology). Initially, the person is placed within the scanner of the MRI machine and a strong magnetic field inside the scanner is applied across the brain. This constantly applied external magnetic field is measured in units called tesla (T). Typical scanners have field strengths between 1.5 T and 3 T. While hydrogen protons in

H_2O have only weak and randomly oriented magnetic fields on their own, the strong external magnetic field will align them in the direction of this external magnetic field like compass needles, allowing the phenomenon of nuclear magnetic resonance to occur. After the alignment of the protons, a brief radiofrequency pulse is applied. As the protons absorb the energy of this pulse, the orientation of the aligned protons is knocked by 90° as compared to their original orientation. Immediately after excitation, the radiofrequency pulse is removed, whereby the absorbed energy dissipates and the tipped hydrogen protons are pulled back into their original alignment. This synchronized rebound or relaxation results in a loss of energy, and produces signals that are picked up by detectors surrounding the head. Thereafter, the scanner serially repeats the processes within different slices of the brain. By systematically measuring the signals throughout the three-dimensional volume of the head, the MRI system can then construct the actual image, reflecting the distribution of protons in the tissue. Thereby, a specialized computer program translates the physical characteristics of a volume element or “voxel” of tissue into a two dimensional image. Figure 7 shows the sequence of events for acquiring an MRI scan.

The speed of relaxation of the protons depends on the local tissue type. For example, gray matter, white matter, or spinal fluid, each relax at different rates. In general, three relaxation times are used: T1, T2, and T2*. T1, or longitudinal relaxation time, is the time by which nuclear protons (“spins”) return to thermal equilibrium (initial state) after irradiation by a radiofrequency pulse. Commonly, these T1-weighted images are used for structural images of the brain (see Figure 8, centre). T2, or transverse relaxation time, refers to the lifetime or decay of spin echo signal. When in the misaligned state, at 90° to the magnetic field, the MR signal also decays because of local interactions with nearby molecules, and this is termed the T2 component. T2* forms the basis of the image created in functional MRI experiments. Thereby, deoxyhaemoglobin produces distortions in the T2 component.

The MRI protocol used in the present thesis can be found in the method part of Study 1.

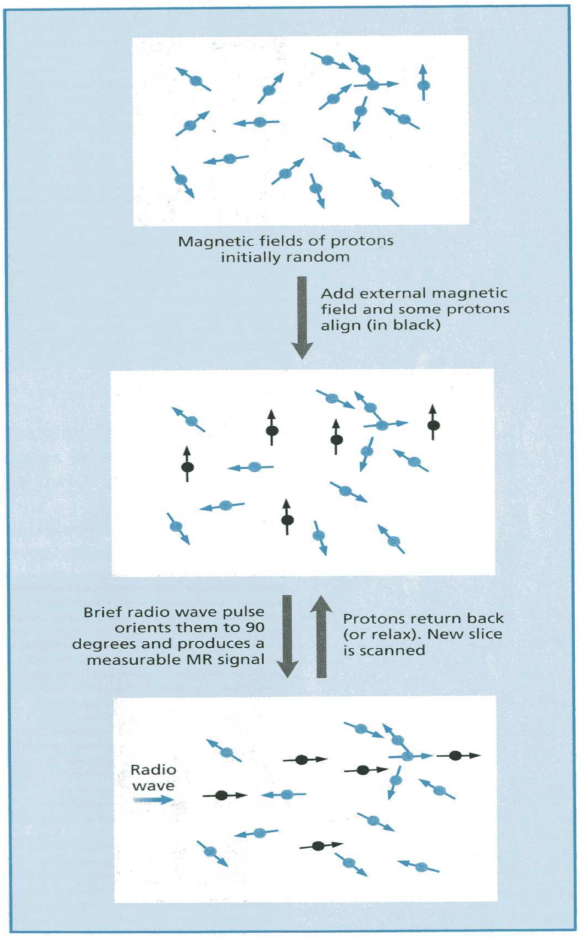


Figure 7: The sequence of events in the acquisition of an MRI scan (adopted from Ward, 2006).

Although collecting MRI images is relatively time-consuming, this technique offers several advantages when compared to other structural imaging methods. As can be seen in Figure 8, MRI provides a much clearer image of the brain than computerized tomography (CT). Unlike CT, MRI does not involve ionizing radiation. In addition, with MRI it is easy to see the individual sulci and gyri of the cerebral cortex and to resolve structures that are smaller than 1 mm, allowing views of small, subcortical structures. By this, MRI can define alterations in cerebral development, including both global and regional reductions in cerebral growth. Moreover, the understanding of alterations in the sequence of normal cerebral development can also provide a greater understanding of the impact of prematurity on brain development and on brain functions.

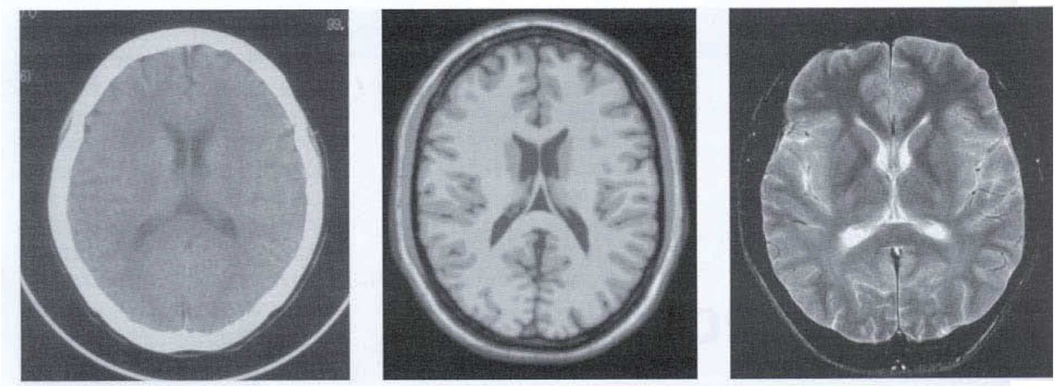


Figure 8: An example of computerized tomography (CT; left), T1-weighted MRI (centre) and T2-weighted MRI (right) scans of the brain (adopted from Ward, 2006).

In summary, for the examination of declarative long-term memory performance, its functionally relevant brain processes and underlying brain structures, standardized neuropsychological tests, ERPs, and structural MRI can be used, respectively. By the mutual application of these different scientific methods, a comprehensive understanding of the developmental trajectories of declarative long-term memory processes in preterm and full-term born children can be provided.

4 Aims of the Present Studies

So far, the theoretical framework and empirical background relevant for the examination of declarative long-term memory in preterm and full-term born children have been presented. In the following, the four experiments conducted to examine the developmental trajectories of declarative long-term memory and its underlying processes in both populations will be discussed.

The global aim of the present thesis was to examine the effects of prematurity on the development of declarative long-term memory. More specifically, functional and structural brain changes with respect to declarative long-term memory functions were investigated in preterm children of early school-age as compared to a full-term born control group. To this end, different scientific methods were used: neuropsychological tests, ERPs, and structural MRI. It is important to mention that the present thesis is not able to investigate all aspects of the declarative memory system. Thus, besides investigating the development of declarative memory in general (Study 1), a particular focus is laid on episodic memory and its specific retrieval processes, namely familiarity and recollection (Study 1, 2, 3, and 4).

Study 1 investigated the two subsystems of declarative long-term memory (episodic and semantic memory) in 7- to 11-year-old preterm children with uncomplicated neonatal courses and in age-matched full-term control children. In addition, the question about the potential relationship between these subsystems and hippocampal volume in both groups has been addressed. By this means, Study 1 enabled linking the estimates of episodic and semantic memory to their putative neuronal basis. More specifically, standardized neuropsychological tests were used to explore semantic and episodic memory performance. A recognition memory experiment was conducted to investigate specific episodic memory retrieval processes. To obtain volumetric data of the hippocampus, structural MRI was applied. By correlating hippocampal volumes with episodic and semantic memory measures in both groups, it was analyzed whether or not the same relationship exists between hippocampal volumes and episodic and semantic memory performance in preterm and full-term children.

Study 2 and Study 3 aimed at examining the development of episodic memory retrieval processes (i.e., familiarity and recollection) in preterm children with uncomplicated neonatal courses and in full-term children by means of ERPs. More precisely, Study 2 investigated whether a mid-frontal old/new effect, the putative ERP correlate of familiarity, can be recorded in full-term children at early school-age under experimental conditions that encourage familiarity-based remembering and attenuate recollection. To this end, Study 2 compared the ERP correlates of familiarity and recollection in school-aged full-term children to those of young adults. By this, Study 2 aimed at establishing a template for the investigation of the ERP correlates of familiarity and recollection in preterm children. Study 3 investigated then whether or not preterm children show the same developmental trajectories of the ERP correlates of familiarity and recollection as full-term children. This investigation allowed testing potential differences in the neural processing in both groups. More specifically, Study 3 tested the hypothesis that prematurity, which has been found to be associated with marked reductions of hippocampal volumes, selectively affects recollective processing as indexed by a reduction of the late parietal ERP old/new effect. Furthermore, as recent studies suggest an association between brain development and the GA at birth, an additional aim of Study 3 was to elucidate whether the degree of prematurity (i.e., GA) is associated with the extent of modulation in the neural systems underlying retrieval processing in preterm children.

Finally, Study 4 addressed the question whether a task-resource artefact can alternatively explain a selective reduction in recollective processing in preterm children compared to full-term children. The term task-resource artefact is used when two tasks (e.g., Task A and Task B) share the same neural/cognitive resource but one task (e.g., Task B) uses it more. If brain damage depletes this resource then Task B may be selectively impaired (Ward, 2006). On the basis of a task-resource artefact, one might propose that recollection requires a greater amount of cognitive resources or is the more difficult process than familiarity. Therefore, Study 4 examined whether preterm children are selectively impaired in tasks that are more difficult or require a higher amount of cognitive resources compared to full-term children. By this, Study 4 contributed to a well-founded knowledge of the relationship between prematurity and reduced recollective processing.

5 Study 1

Hippocampal Volume Mediates Episodic Memory Performance in Full-Term But Not Preterm Children

5.1 Background and Research Question

In the light of the above mentioned findings that the hippocampus, which is a key structure in episodic memory, is often markedly reduced in its volume in preterm compared to full-term children, the main goal of Study 1 was to elucidate the relationship between hippocampal volume and episodic memory performance in preterm children with uncomplicated neonatal courses compared to full-term control children. For this purpose, first, structural changes in the hippocampi of the two children groups were assessed by means of MR measures. Second, episodic memory was explored in both groups. Whereas standardized neuropsychological tests were used to assess general episodic memory performance, a recognition memory experiment with a speeded (fostering familiarity) and a nonspeeded (supporting hippocampus-dependent contextual recollection) response condition was conducted to examine the specific episodic memory retrieval subprocesses (Mecklinger, Brunnemann, & Kipp, 2011).

Since episodic memory is only one of the two subsystems of declarative long-term memory (episodic vs. semantic memory; Tulving, 1972), it was of additional interest to investigate whether the two subsystems, episodic and semantic memory, are equally affected by prematurity. This is particularly important because so far only few studies have systematically compared both subsystems of declarative long-term memory in preterm individuals (Isaacs et al., 2000). Furthermore, there is still a debate whether the hippocampus is important for semantic memory as well (e.g., Manns, Hopkins, & Squire, 2003; Tulving & Markowitsch, 1998). While some theories posit that the hippocampus is involved in episodic but not semantic memory retrieval, other theories assume that both semantic and episodic memory retrieval engage the hippocampus (see Ryan, Hoscheidt, & Nadel, 2008, for a review). Hence, semantic memory was explored with additional neuropsychological tests and in both groups the relationship between hippocampal volume and semantic memory performance was investigated.

To elucidate whether any deficits in declarative long-term memory were independent of reduced intelligence and working memory performance, intellectual functioning (IF) and working memory were assessed with additional neuropsychological tests. This issue is particularly important because previous studies have demonstrated reduced IF (Luu et al., 2009) as well as reduced working memory performance (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009) in preterm children.

Finally, to elucidate the relationship between hippocampal volume and episodic memory performance in preterm and full-term children, hippocampal volumes were correlated with episodic memory measures in both groups. On the basis of studies that showed that the entire hippocampus is involved in episodic memory (Vargha-Khadem et al., 1997; but see also Tulving & Markowitsch, 1998), general episodic memory performances in the neuropsychological tests were correlated with the total hippocampal volume. Moreover, as the posterior two-thirds of the hippocampus are more involved in recollection-based memory retrieval (Daselaar et al., 2006; Ludowig et al., 2008), performances in the recognition memory experiment were correlated with the posterior two-thirds of hippocampal volume.

To summarize, Study 1 aimed to disentangle the subsystems of declarative long-term memory (episodic and semantic memory) that are affected or spared by the changes of brain functions as found in preterm children. In addition, the study addressed the question about the relationship between hippocampal volume and episodic and semantic memory performance in preterm children with uncomplicated neonatal courses and full-term children.

5.2 Hypotheses

On the basis of the aforementioned results in preterm individuals (Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000), it was hypothesized that hippocampal volumes are reduced in preterm children with uncomplicated neonatal courses compared to full-term children. Moreover, due to potential compensatory mechanisms within the brains of preterm individuals, semantic and episodic memory performance should only be marginally impaired in preterm children with uncomplicated neonatal courses.

If the entire hippocampus supports episodic memory and the posterior two-thirds of the hippocampus subserve recollection-based memory retrieval, for full-term children, (1) positive correlations between the total hippocampal volume and general episodic memory performances in the neuropsychological tests and (2) positive correlations between the posterior two-thirds of hippocampal volume and performance in the nonspeeded response condition of the recognition memory experiment were expected. For the preterm group, reduced correlations between hippocampal volumes and episodic memory performances were expected, possibly reflecting that within the brains of preterm children other brain structures functionally compensate for reduced functioning of the hippocampus. However, on the basis of the mixed pattern of results regarding the hippocampal involvement in semantic memory retrieval, no specific predictions were made regarding the relationship between hippocampal volume and semantic memory performance in preterm and full-term children.

5.3 Methods

Participants

Twenty-six children born preterm were recruited from archives of the Department of Pediatrics and Neonatology at the university hospital in Homburg. Inclusion criteria for this study were: (a) no intracranial hemorrhage, (b) no major surgeries during the first year of life, and (c) no craniofacial malformations, no cerebral palsy, or other neurological diseases. The MR images of four preterm children could not be analyzed due to movement artifacts and technical failures. These children were excluded from further analyses. The mean GA of the remaining 22 preterm children was 30.5 weeks (range: 26-34) and the mean BW was 1359 g (range: 880-1920). The corrected age (corrected to 40 weeks gestation) and gender distribution was: seven to ten years old (mean age: 8.66, range: 7;05-10;11; 14 female). Two subjects were left-handed. The socio-economic status (SES) was determined according to the International Socio-Economic Index of occupational status (ISEI) developed by Ganzeboom, de Graaf, Treiman, and de Leeuw (1992). The range of this Index is between 10 (e.g., Cook's Helper) and 90 (e.g., Judges). The mean value for the preterm group was 53.77 (range: 31-84). All children had respiratory disease, with 20 of the 22 children requiring intubation within the first 30 minutes after birth. According to parent reports on the Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter (Kinder-DIPS; Unnewehr, Schneider, & Margraf, 1998), seven of the 22 preterm children obtained a psychiatric diagnosis (see Table 1). The psychiatric disorders were classified according to DSM-IV (American Psychiatric Association [APA], 1994). All children attended mainstream schools at the time of the present assessment.

The control group consisted of 24 age-matched children born full-term, all of whom had had a normal neonatal course. The MR images of five control children could not be analyzed due to movement artifacts and technical failures. The mean GA of the remaining 19 controls was 40.2 weeks (range: 38-43) and the mean BW was 3435 g (range: 2000-4400). The corrected age and gender distribution was: seven to eleven years old (mean age: 9.06, range: 7;06-11;01; 8 female). All subjects were right-handed. The mean value of the SES was 64.68 (range: 37-88) and thus significantly higher than in the preterm group, $t(39) = 2.31$, $p < .05$. To control for confounding influences of this factor on memory differences between preterm and full-term children (Herrmann & Guadagno, 1997), additional covariance analyses (ANCOVAs) with SES as a covariate were carried out in the case of group differences in any of the measured variables. The control children were recruited from schools in Saarbrücken and in the immediate vicinity. One of the 19 full-term born children obtained a psychiatric diagnosis according to the Kinder-DIPS (see Table 1).

The socio-demographic characteristics of the two groups are shown in Table 1. All participants were native German speakers and reported themselves to be in good health. The children received € 8.00/hour for participation.

Additionally, the parents of all children received € 12.00 for travelling expenses. The study was approved by the Ethics Committee of the Saarland Medical Association (ID No. 151/07) and all children and parents gave written informed consent.

*Table 1: Socio-demographic characteristics for the preterm and full-term group. All values except for Apgar scores, days on ventilator, postnatal steroids, and diagnoses about psychiatric disorders are means (SE; range). NA = not available. *After controlling for gender.*

Variable	Control Group (N = 19)	Preterm Group (N = 22)	Statistics
Neonatal characteristics			
Gestation at birth (weeks)	40.21 (0.30; 38.0-43.0)	30.50 (0.45; 26.0-34.0)	$t(39) = 17.48$, $p < .001$
Birth weight (g)	3434.74 (127.32; 2000-4400)	1358.64 (64.16; 880-1920)	$t(39) = 15.17$, $p < .001$
1-Minute Apgar score, median	10; (range, 8-10)	7; (range, 1-9)	$t(39) = 6.30$, $p < .001$
5-Minute Apgar score, median	10; (range, 9-10)	8; (range, 1-10)	$t(39) = 5.25$, $p < .001$
Days on ventilator, median	NA	4; (range, 1-12)	
Postnatal steroids (Solu-Decortin)	NA	7	
Females/males	8/11	14/8	$\chi^2(1) = 1.90$, $p = .17$
SES	64.68 (3.01; 37-88)	53.77 (3.54; 31-84)	$t(39) = 2.31$, $p < .05$
Anthropometric data at assessment			
Corrected age in years	9.06 (0.23; 7.06-11.01)	8.66 (0.18; 7.05-10.11)	$t(39) = 1.38$, $p = .17$
Height (cm)*	144.34 (1.97; 131.0-160.0)	135.34 (1.71; 126.0-158.0)	$F = 12.86$, $p < .001$
Weight (kg)*	36.29 (1.56; 27.0-55.5)	30.68 (1.41; 23.0-46.0)	$F = 7.49$, $p < .01$
Occipito-frontal head circumference*	54.16 (0.40; 50.0-57.0)	52.77 (0.34; 50.0-56.0)	$F = 4.83$, $p < .05$
Attention deficit hyperactivity disorder	0	2	
Separation anxiety disorder	0	1	
Specific phobia	0	2	
Enuresis	1	1	
Oppositional Defiant Disorder	0	1	

Procedure

There were three sessions: MRI scan, neuropsychological tests, and recognition memory experiment.

Magnetic Resonance Imaging

Scanning took place within a 1.5-Tesla Siemens Sonata scanner. No sedation was administered. A 3D MP-RAGE sequence was obtained with a repetition time of 1900 ms; echo time, 3.93 ms; inversion time, 1100 ms; flip angle, 15°; matrix size, 256 x 256; field of view, 256 mm; partition thickness, 1 mm; 176 sagittal partitions.

Qualitative Image Analysis. To explore qualitative changes within the brains of all participants, images were analyzed by two experienced pediatric neuroradiologists (P. P., W. R.) who were blind to the group membership of the children. They determined the presence of focal, central, or generalized atrophy and abnormalities in the whole brain.

Quantitative Image Analysis. Following the exploitation of Kipp, Mecklinger, Becker, Reith, and Gortner (2010), volumetric analysis comprised the measurement of hippocampal volumes and cerebral volume, using MRIcron software. First, cerebral volume was outlined manually in the coronal view. For this measurement, every tenth slice was traced. By summing up the cross-sectional areas and then multiplying this with the slice distance (i.e., 10 mm), the final volume was estimated. Second, the hippocampus was manually segmented in the coronal and sagittal view, always tracing right hippocampal volume first. The determination of the posterior limit of the hippocampus began two contiguous slices before the slice with the maximal visible length of the fornix. To exactly determine the anterior boundary, the alvear covering of the hippocampus was used, which was included in the measurements. Thereby, the demarcation of the hippocampus from the amygdala was facilitated. The medial and inferior border was marked by the contrast between gray and white matter. While uncus and subiculum were included in the measurements (Cook, Fish, Shorvon, Straughan, & Stevens, 1992), fimbria and choroid plexus were excluded. Tracing of the hippocampus of all subjects was conducted by one operator alone, blind to the group membership of the children. To assess variation in the measurement of volumes by this operator, six randomly chosen hippocampi were measured a second time. Intra-observer reliability was high, with a correlation value of .97. To correct the measured hippocampal volume for cerebral volume, the covariance method as described by Jack et al. (1989) was used:

$$cHc = mHc - g(mCV - meanCV)$$

where cHc = corrected hippocampal volume, mHc = measured hippocampal volume, g = gradient of regression line between hippocampal volume & cerebral volume of all the children of one group, mCV = measured cerebral volume, and meanCV = mean cerebral volume of all the children of one group.

To explore different subregions of the hippocampus, a quantitatively objective method (see Greicius et al., 2003) was used. The total slice number of each hippocampus was divided into thirds along the anterior-posterior axis (anterior, middle, posterior part); with the larger number of slices assigned to the anterior division when the total slice number was an odd number. As recollection-based memory retrieval is subserved mainly by the posterior two-thirds of the hippocampus (Daselaar et al., 2006; Greicius et al., 2003), the middle and posterior part of each hippocampus were summed (for left and right hippocampus, respectively).

Memory Assessment

The neuropsychological tests lasted one and a half hour and were carried out in the laboratory of the Experimental Neuropsychology Unit at Saarland University.

Intelligence. To establish whether any deficits in memory were independent of reduced intelligence, IF was assessed using the Raven’s Coloured Progressive Matrices Test (Raven, Raven, & Court, 2002).

Working Memory. To test working memory performance, a subtest of the Hamburg-Wechsler-Intelligenztest für Kinder (HAWIK-R; Tewes, 1997) was used – German version of the Wechsler Intelligence Scale for Children (WISC): forward and backward digit span test.

Semantic Memory. The semantic memory performance was measured by using three further subtests of the HAWIK-R: general knowledge, general comprehension, and vocabulary.

Episodic Memory. The episodic memory performance was measured in two modalities. *1)* To measure verbal episodic memory, the German version of the Auditory Verbal Learning Test (AVLT) – the Verbaler Lern- und Merkfähigkeitstest (VLMT; Helmstaedter, Lendt, & Lux, 2001) was administered. *2)* To measure visual episodic memory, the Rey-Osterrieth Complex Figure was administered (Osterrieth, 1944).

Retrieval Processes of Recognition Memory. The two memory retrieval processes, familiarity and recollection, were measured with a recognition memory experiment consisting of two study-test cycles, one with a speeded and one with a nonspeeded response condition (see Mecklinger et al., 2011). In both study phases, the subjects viewed 60 pictures that were presented consecutively. They were instructed to make an indoor/outdoor judgment and to memorize the pictures. Each picture was presented for 1000 msec, preceded by a fixation cross (400 msec). There was a retention interval of one minute between the study and the test phase. During this retention interval, the subjects had to perform a simple arithmetic task. In each of the two test phases, the subjects viewed a total of 120 pictures (50% old) and were instructed to make old/new recognition decisions by pressing a corresponding key. In the test trial, each picture was presented for 1050 msec, preceded by a fixation cross (500 msec). In the speeded condition, subjects were instructed to give their old–new responses during picture presentation (i.e., maximal response time = 1050 msec). If no response was given during presentation of the picture, subjects were informed about the time-out by a brief sound, and the trial was discarded from analysis. If a response was given in time, a feedback stimulus (smiley or frown face) was presented for 500 msec indicating whether a correct or incorrect response had been given. In the nonspeeded condition, subjects were given unlimited time to respond. Immediately after the response, the feedback stimulus was presented.

Data Analyses

Data were analyzed using SPSS version 17.0. For the comparisons of cerebral, absolute and corrected (see covariance method described under *quantitative image analysis*) hippocampal volumes between preterm and full-term children, *t*-tests were used. To control for generalized scaling effects within the brain, ANCOVAs with gender as covariate were calculated (cf. Nosarti et al., 2002; Peterson et al., 2000). Repeated-measures ANCOVAs (controlling for gender) were used to explore hemispheric differences in left and right corrected hippocampal volumes as well as in the posterior two-thirds of corrected hippocampal volumes between the two groups.

To investigate group differences in neuropsychological variables, *t*-tests and ANCOVAs (controlling for SES and/or IF) were used. To determine the relative power of SES and IF in predicting performances, multiple regressions were conducted in case of an influence of the covariates on any of the measured variables.

To investigate group differences in memory accuracy and response times (RT) in the recognition memory experiment, repeated-measures analyses of variance (ANOVAs) were used. Memory accuracy was analyzed by means of the discrimination index (Pr), that is, hit rates minus false alarm rates (Snodgrass & Corwin, 1988), for both response conditions. In the speeded test block, all trials with time-out responses or in which no response was given were discarded from analysis. Furthermore, in both response conditions, trials with RTs faster than 200 msec were discarded. RTs were measured separately for hits and correct rejections, for both response conditions.

Within the preterm and full-term group, the relationships of mean (left and right) corrected hippocampal volume with episodic memory variables of the neuropsychological tests and relationships of mean (left and right) corrected hippocampal volume of the posterior two-thirds with the discrimination index Pr of the recognition experiment were examined by means of partial correlations (controlling for gender). Additionally, the relationship between mean corrected hippocampal volume and semantic memory variables was explored. Two-tailed tests and significance levels of $p < .05$ were used for all analyses.

5.4 Results

Qualitative Image Analysis. Of the 22 preterm children, only one child demonstrated focal frontal atrophy. The other 21 preterm children as well as the 19 full-term children were judged to have brain scans that were entirely normal on visual inspection by the pediatric neuroradiologists.

Quantitative Image Analysis. Cerebral and hippocampal volumes of 22 preterm and 19 full-term control children were analyzed. Table 2 presents the results of the volumetric measurements. Cerebral volume differed significantly between both groups, $t(39) = 2.63$, $p < .02$; showing a 7.9% decrease in the preterm group compared with the group of full-term children. This difference persisted after controlling for gender in an ANCOVA, $F(1, 38) = 4.68$, $p < .04$.

Preterm children also differed significantly from full-term controls in left and right absolute hippocampal volumes (left: $t(39) = 3.38$, $p < .01$; right: $t(39) = 3.45$, $p < .01$); preterm children showing a 12.0% reduction of left absolute hippocampal volume and a 12.9% reduction of right absolute hippocampal volume compared to full-term controls. As in cerebral volume, these differences persisted after controlling for gender (left: $F(1, 38) = 10.04$, $p < .01$; right: $F(1, 38) = 9.60$, $p < .01$). As the group comparisons of absolute and corrected hippocampal volumes revealed the same results (see Table 2), only outcomes of corrected hippocampal volumes will be reported below.

An ANCOVA with the factors Hemisphere (left vs. right), Group, and Gender as covariate performed for corrected hippocampal volumes yielded main effects of Group, $F(1, 38) = 22.59$, $p < .001$, and Hemisphere (right > left: $F(1, 38) = 5.06$, $p = .03$). The interaction of Hemisphere and Group was not significant ($F < 1$, $p = .71$). These results indicated that preterm children had smaller corrected hippocampal volumes compared to controls, and that both groups had larger right versus left hippocampal volumes.

In a next step, the posterior two-thirds of corrected hippocampal volumes were compared between preterm and full-term children. An ANCOVA with the factors Hemisphere (left vs. right), Group, and Gender as covariate performed for the posterior two-thirds of corrected hippocampal volumes yielded main effects of Group, $F(1, 38) = 19.99$, $p < .001$, and Hemisphere (right > left: $F(1, 38) = 6.46$, $p < .02$). The interaction of Hemisphere and Group was not significant ($F < 1$, $p = .92$). These results showed that preterm children had smaller corrected hippocampal volumes of the posterior two-thirds relative to controls, and that both groups had larger right versus left hippocampal volumes of the posterior two-thirds.

*Table 2: Volumetric measurements in the preterm and full-term control group. All values are means (SE; range). *Hippocampal volumes corrected for cerebral volumes (Jack et al., 1989).*

Volume (cm^3)	Control Group (N = 19)	Preterm Group (N = 22)	ANCOVA: gender as covariate
Cerebral Volume	1283.39 (27.43; 1026.7-1479.2)	1181.54 (27.12; 952.4-1442.2)	$F = 4.68$, $p < .04$
Left Hippocampus	2.83 (0.08; 2.32-3.42)	2.49 (0.07; 1.87-3.19)	$F = 10.04$, $p < .01$
Left Hippocampus*	2.83 (0.06; 2.10-3.43)	2.49 (0.06; 2.07-3.12)	$F = 18.91$, $p < .001$
Left posterior + middle*	1.75 (0.04; 1.29-2.03)	1.51 (0.05; 1.16-2.02)	$F = 16.13$, $p < .001$
Right Hippocampus	3.02 (0.10; 2.16-3.70)	2.63 (0.06; 2.00-3.06)	$F = 9.60$, $p < .01$
Right Hippocampus*	3.02 (0.09; 2.29-3.57)	2.63 (0.05; 2.22-2.98)	$F = 16.56$, $p < .001$
Right posterior + middle*	1.92 (0.06; 1.54-2.48)	1.67 (0.03; 1.43-2.04)	$F = 11.80$, $p = .01$
Left/Right Hippocampus*	2.93 (0.07; 2.20-3.42)	2.56 (0.05; 2.21-2.97)	$F = 22.59$, $p < .001$
(Left/Right) posterior + middle*	1.83 (0.05; 1.52-2.20)	1.59 (0.03; 1.41-1.91)	$F = 19.99$, $p < .001$

Table 3 shows the volumetric measurements in the preterm and control group, separately for boys and girls. Boys had larger cerebral volumes than girls, in both the preterm, $t(20) = 2.55$, $p < .02$, and full-term group, $t(17) = 3.57$, $p < .01$. Concerning hippocampal volumes, no significant differences were found between full-term born boys and girls. In preterm children, girls had larger left corrected hippocampal volumes, $t(20) = -2.12$, $p < .05$, as well as larger left corrected hippocampal volumes of the posterior two-thirds, $t(20) = -2.11$, $p < .05$, than boys. Concerning right corrected hippocampal volumes, no significant differences were found between preterm girls and boys.

Taken together, cerebral, absolute and corrected hippocampal volumes were reduced in preterm children relative to full-term controls, suggesting that adverse effects of prematurity on hippocampal and cerebral volumes were apparent in preterm children at early school-age with uncomplicated neonatal courses.

*Table 3: Volumetric measurements in the preterm and full-term control group, by gender. All values are means (SE; range). *After controlling for cerebral volume.* $^{+}p < .05$.

Volume (cm^3)	Control Group (N = 19)		Preterm Group (N = 22)	
	Males (N = 11)	Females (N = 8)	Males (N = 8)	Females (N = 14)
Cerebral Volume	1348.36 (24.37; 1222.4-1479.2)	1194.05 (38.18; 1026.7-1342.2)$^{+}$	1262.86 (43.55; 1088.1-1442.2)	1135.07 (28.75; 952.4-1270.9)$^{+}$
Left Hippocampus*	2.81 (0.09; 2.11-3.20)	2.86 (0.10; 2.48-3.43)	2.34 (0.07; 2.07-2.64)	2.57 (0.07; 2.14-3.12)$^{+}$
Left posterior + middle*	1.76 (0.05; 1.48-2.03)	1.74 (0.08; 1.29-2.00)	1.40 (0.06; 1.16-1.73)	1.58 (0.06; 1.18-2.02)$^{+}$
Right Hippocampus*	3.02 (0.12; 2.29-3.51)	3.04 (0.13; 2.59-3.57)	2.58 (0.08; 2.22-2.84)	2.66 (0.06; 2.28-2.98)
Right posterior + middle*	1.93 (0.08; 1.56-2.27)	1.91 (0.11; 1.54-2.45)	1.66 (0.05; 1.51-1.90)	1.67 (0.05; 1.43-2.04)

Memory Assessment. Table 4 summarizes the results for preterm and full-term children in the neuropsychological tests and recognition memory experiment. IF (Coloured Progressive Matrices) differed between the preterm and full-term group even after controlling for SES, $F(1, 38) = 6.20$, $p < .02$. By contrast, comparison of working memory performance showed no significant difference between groups (p value = .35). Regarding semantic memory, preterm children showed lower performance in all three subtests of the HAWIK-R compared to full-term children (General Knowledge: $t(39) = 4.15$, $p < .001$; General Comprehension: $t(39) = 3.66$, $p < .01$; Vocabulary: $t(39) = 2.07$, $p < .05$). However, in contrast to the subtests general knowledge and general comprehension in the subtest vocabulary the group difference disappeared when taking SES and IF as covariates into account (p value = .69). Multiple regressions with vocabulary as the criterion variable and SES or IF as independent variables revealed that IF accounted for 19.4% ($F(1, 39) = 9.41$, $p < .01$) and SES for 17.1% ($F(1, 39) = 8.05$, $p < .01$) of the variance in vocabulary. Regarding episodic memory, no group differences were obtained for verbal memory (immediate recall, learning gains, delayed recall, recognition, loss after delay) or visual memory (immediate and delayed recall). The copy performance of the Rey-Osterrieth Complex Figure differed significantly between groups, $t(39) = 2.54$, $p < .02$, but this difference disappeared when SES and IF were used as covariates (p value = .25).

In the recognition memory experiment, one preterm child reached insufficient memory accuracy (memory performance did not exceed chance performance) and was excluded from further analyses. For the remaining 21 preterm and 19 full-term born children, an ANOVA with the factors Response Condition (speeded vs. nonspeeded) and Group for the memory accuracy (Pr) yielded only a main effect of Response Condition, $F(1, 38) = 64.01$, $p < .001$. This result indicated that both groups responded more accurately in the nonspeeded than in the speeded response condition. For mean response times, an ANOVA with the factors Response Condition (speeded vs. nonspeeded), Item Type (Hits, Correct Rejections), and Group revealed reliable main effects of Response Condition, $F(1, 38) = 102.50$, $p < .001$, and Item Type, $F(1, 38) = 4.46$, $p < .05$. The interaction of Response Condition and Item Type did not reach statistical significance, $F(1, 38) = 3.83$, $p = .058$. These results indicated that both groups took more time for responding in the nonspeeded than in the speeded condition, and also took more time for responding for Correct Rejections than for Hits.

Table 4: Neuropsychological and recognition task results for each group. Standard errors of the means are given in parentheses. All scores except for HAWIK-R, Rey-Osterrieth Complex Figure immediate and delayed recall scores as well as memory accuracy and RTs in the recognition task are raw scores. In case of group differences in the initial t-test, an ANCOVA with SES and/or intellectual functioning (IF) as covariates was carried out.

Cognitive Ability	Control Group (N = 19)	Preterm Group (N = 22)	*p* values (*t*-tests)	*p* values of the ANCOVA: SES[1]and/or IF[2] as covariates
Intellectual Functioning				
Coloured Progressive Matrices	32.58 (0.50)	29.27 (0.95)	< .01	.02[1]
Working Memory				
Digit Span (HAWIK-R)[a]	11.26 (0.67)	10.45 (0.54)	.35	-
Semantic Memory (HAWIK-R)				
General Knowledge	14.47 (0.56)	11.18 (0.55)	< .001	<.02[1,2]
General Comprehension	13.00 (0.47)	10.18 (0.59)	< .01	< .05[1,2]
Vocabulary	14.37 (0.59)	12.27 (0.79)	< .05	.69[1,2]
Episodic Memory				
Verbal Memory (VLMT)[b]				
- immediate recall	7.53 (0.34)	7.05 (0.36)	.34	-
- learning gains	54.37 (2.15)	49.50 (2.37)	.14	-
- delayed recall	11.95 (0.44)	11.00 (0.46)	.15	-
- recognition	14.47 (0.16)	14.55 (0.17)	.76	-
- loss after delay	1.21 (0.29)	0.50 (0.37)	.15	-
Visual Memory (Rey-Osterrieth Complex Figure)				
- copy	29.58 (1.18)	25.57 (1.06)	< .02	.25[1,2]
- immediate recall[c]	64.30 (3.59)	63.09 (2.79)	.79	-
- delayed recall[c]	61.92 (3.75)	57.34 (3.01)	.34	-

Memory Retrieval Processes				
Recognition Memory Task (speeded)				
- memory accuracy (Pr)	0.47 (0.04)	0.45 (0.04)	.70	-
- RT Hits	734 (15)	734 (11)	> .99	-
- RT Correct Rejections	737 (11)	744 (12)	.66	-
Recognition Memory Task (nonspeeded)				
- memory accuracy (Pr)	0.73 (0.03)	0.66 (0.04)	.22	-
- RT Hits	1282 (97)	1221 (74)	.61	-
- RT Correct Rejections	1310 (61)	1322 (89)	.91	-

[a] HAWIK-R (Tewes, 1997) is the German version of the WISC. Scores are standardized scores based on chronological age norms (Mean = 10, SD = 3).

[b] VLMT (Helmstaedter et al., 2001) is the German version of the Auditory Verbal Learning Test (AVLT).

[c] Immediate and delayed recall performance is the percent immediate/delayed recall score which is the immediate or delayed raw score divided by the copy raw score multiplied with 100 (Lezak, 1995).

Relations between Volumetric Data and Memory Variables. On the basis of recent studies which revealed a relationship between the hippocampus and episodic memory processes (Giménez et al., 2004, 2005; Isaacs et al., 2000), the mean of left and right corrected hippocampal volumes were correlated with memory variables for each children group separately. Because both, left and right, corrected hippocampal volumes were reduced in preterm children, a mean of left and right corrected hippocampal volume was calculated for each subject (see Table 2).

For full-term controls, partial correlations controlling for gender showed that the smaller the mean corrected hippocampal volume, the worse the delayed recall performance of the Rey-Osterrieth Complex Figure, r = .47, $p < .05$. In contrast, the statistically significant correlation between mean corrected hippocampal volume and learning gains of the VLMT (r = .55, $p < .02$) diminished after removing one potential outlier that differed more than three standard deviations from the group mean in his score of learning gains of the VLMT (r = .17, $p > .51$). The investigation of the mean posterior two-thirds of corrected hippocampal volume in relation to the discrimination index Pr revealed only a positive correlation between the posterior two-thirds of corrected hippocampal volume and memory accuracy in the nonspeeded response condition (r = .57, $p < .02$). No statistically significant correlations were detected between volumetric measurements and other episodic memory variables. There were also no significant correlations between the mean corrected hippocampal volume and semantic memory variables.

For preterm children, no significant correlations were found in either of the analyses.

5.5 Discussion

The goal of Study 1 was to systematically examine the hippocampal volume and its relationship with episodic and semantic memory performance in preterm children with uncomplicated neonatal courses relative to a full-term born control group. For this purpose, structural changes in the hippocampal volumes of preterm and full-term children were assessed by means of structural MRI. To examine episodic and semantic memory performance, standardized neuropsychological tests were used. Additionally, a recognition memory experiment was conducted to elucidate whether specific episodic memory retrieval processes were affected by prematurity. Finally, to elucidate the relationship between hippocampal volume and episodic and semantic memory performance in preterm and full-term children, hippocampal volume was correlated with episodic and semantic memory measures in both groups. It was expected that preterm children show reduced hippocampal volumes relative to an age-matched full-term control group, whereas episodic and semantic memory performance should only be marginally impaired. Additionally, reduced correlations between hippocampal volume and episodic memory performances were predicted for preterm children compared to the full-term control group. With regard to the relationships between hippocampal volume and semantic memory performances in preterm and full-term children, no specific predictions were made.

Consistent with the hypothesis, preterm children showed reduced hippocampal volumes relative to the full-term control group. While no group differences were found in episodic memory performance, preterm children showed lower performance in semantic memory tasks relative to controls. Furthermore, in full-term children, hippocampal volume was positively correlated with delayed recall performance of the Rey-Osterrieth Complex Figure and with memory accuracy in the nonspeeded condition of the recognition memory experiment. For preterm children, no such relationships were obtained.

The volumetric results will be discussed first, followed by the discussion of semantic and episodic memory outcomes and the relationships between hippocampal volume and memory variables.

Volumetric Outcomes

Consistent with other quantitative MRI studies (Giménez et al., 2004; Nosarti et al., 2002; Peterson et al., 2000), cerebral and absolute hippocampal volumes were reduced in preterm relative to full-term children. As reduced hippocampal volumes persisted after correcting for cerebral volume, it can be concluded that these reduced sizes are disproportionately greater than it would be predicted on the basis of the smaller brains of the preterm children. Reductions in cerebral volume and corrected hippocampal volumes were not related to measures of prematurity (i.e., GA, BW, 5-Minute Apgar Score). By this, the reasons for the disproportionate hippocampal volume loss in preterm children still remain unclear. One explanation is that perinatal variables (e.g., postnatal steroids) negatively affect the growth of the hippocampi. Notably, Thompson et al. (2008) have reported a negative impact of several perinatal variables (e.g., postnatal steroids, indomethacin treatment) on hippocampal volumes in preterm infants. However, given the small number of preterm children to whom postnatal steroids were administered in the present sample (to seven of the 22 preterm children) and the fact that the sample contained only children with uncomplicated neonatal courses, it is refrained from drawing firm conclusions on the relationship between hippocampal volumes and perinatal events. Further empirical data are required to elucidate such a relation.

Currently, only tentative hypotheses about alternative explanations for the disproportionate hippocampal volume loss in preterm children can be made. Given that the hippocampus is also vulnerable to stress (McEwen, 1999), one possibility is that stressful neonatal environmental conditions (e.g., bright light, constant noise) in the intensive care units have an impact on the development of the hippocampus (Als et al., 2004; Perlman, 2001). Critically, preterm babies are exposed to these conditions to a higher extent than full-term babies. Thus, it is conceivable that early stressful experiences have influenced the hippocampal volume loss in the present preterm group. With hindsight however it is difficult to measure the impact of early exposure to potentially harmful interventions in children. Overall, the volumetric data reported here converge with previous observations, showing a disproportionate vulnerability of hippocampal volume in the developing brains of preterm children.

Regarding gender differences in cerebral volume, the present results support the findings of previous studies (Nosarti et al., 2002; Sgouros, Goldin, Hockley, Wake, & Natarajan, 1999), showing larger cerebral volume in boys than girls in both groups. However, regarding the role of gender differences in hippocampal volumes no consistency in previous research is found. Whilst some studies have reported gender differences in hippocampal volumes in full-term (boys had larger left and right hippocampal volumes), but not in preterm individuals (Nosarti et al., 2002), others did not find a gender difference in neither group (Thompson et al., 2009). The present data even demonstrated a different pattern, showing a gender difference only in preterm children (boys had smaller left corrected hippocampal volumes). The reasons for diverging patterns in gender differences in hippocampal volumes of preterm and full-term children are still unclear. However, some of the available evidence suggest that environmental stress early in life affects boys more severely than girls, which has been attributed to evolutionary mechanisms that maximize reproductive survival (for details, see Elsmén, Steen, & Hellström-Westas, 2004). It is thus conceivable that preterm boys were born earlier and also have lower BWs than girls, which result in a longer stay in the stressful intensive care units. However, this view was not confirmed by the present study. Notably, Thompson et al. (2009) suggest that gender differences depend on the stage of development and on hormonal influences. Therefore, to elucidate the pattern of gender differences, it could be revealing to measure hormonal influences on hippocampal development in a longitudinal study.

Memory Outcomes

The assessment of IF and working memory made it possible to establish whether the semantic memory deficits in preterm children demonstrated here were independent of reduced intelligence and working memory performance. The data analysis revealed that, whilst IF was reduced in preterm relative to full-term children, working memory performance did not differ between groups ensuring that declarative long-term memory was not confounded by the ability to retain information over a short time period. However, to control for the influence of IF on semantic memory performance, additional covariance analyses with IF as a covariate were carried out. These analyses showed that in contrast to the two other subtests of the HAWIK-R (i.e., general knowledge, general comprehension), the group difference in vocabulary was rather due to differences in IF and SES and not related to prematurity. This result is supported by previous studies with full-term children that showed that vocabulary is influenced by IF (Ullstadius, Gustafsson, & Carlstedt, 2002) and SES (see Hoff, 2006, for a review).

The finding that using neuropsychological tests group differences in semantic memory were ascertained is consistent with previous studies in preterm and full-term children (Luu et al., 2009). This deficit may have been caused by differences in the neural processing of semantic material between preterm and full-term children (see Ment & Constable, 2007, for a review). For example, using fMRI, Peterson et al. (2002) reported that preterm children activated brain regions during a semantic task that resembled those activated in a phonological task in full-term controls. The greater this resemblance, the lower were the verbal comprehension IQ scores and the poorer the language comprehension during the scanning task of the preterm children. These results suggest that deficits in semantic memory may be due to changes in the neural networks underlying language processing.

Nevertheless, the question remains, why reduced hippocampal volumes in combination with semantic memory deficits were found in preterm children. Although due to the concurrence of both results one can assume a relationship between hippocampal volume and semantic memory, this was not validated by the correlation analyses. So far, there is still debate whether the hippocampus is equally important for semantic and episodic memory (e.g., Manns et al., 2003; Tulving & Markowitsch, 1998; see also Ryan et al., 2008, for a review). Given that in the present study volumetric changes were determined only in the hippocampus, volume reductions in other brain regions which are important for semantic memory, such as the anterior temporal cortex, cannot be ruled out (Rogers et al., 2006).

Examination of general episodic memory performances and memory accuracy in the picture recognition memory experiment revealed no group differences. Thus, these results indicate that neither general episodic memory nor specific retrieval processes (i.e., familiarity and recollection) were influenced by prematurity.

In the light of the finding that hippocampal volumes were reduced in preterm children, the question arises, why no group differences in episodic memory performance were found. On the one hand, this absence of impairments in episodic memory in preterm children contradicts studies showing a loss of episodic memory in subjects with bilateral damage of the hippocampus (Giménez et al., 2005; Isaacs et al., 2000; see also Vargha-Khadem, Gadian, & Mishkin, 2001). In this way, the current finding of no behavioral impairments on episodic memory tasks despite reduced hippocampal volumes suggests a dissociation between hippocampal volume and memory performance in preterm children. This conclusion may be further substantiated by the fact that in the present study hippocampal volume was positively correlated with delayed recall performance of the Rey-Osterrieth Complex Figure and with recognition accuracy in the nonspeeded response condition in full-term but not in preterm children. This finding could be related to those earlier studies which did also not find behavioral differences between preterm and full-term participants but showed that the neural network underlying episodic memory is modified in preterm individuals (Curtis et al., 2006; Narberhaus et al., 2009). For example, in the study by Narberhaus et al. (2009), preterm adults did not differ from full-term controls in episodic memory performance in a visual paired associates task, but the preterm adults were found to activate different neural networks than controls during both encoding and recognition of picture pairs. As such, a tentative explanation for why hippocampal volume has been found to be unrelated to episodic memory function in preterm children in the present study may be that preterm children recruit a neural network for episodic memory that differs from the one used by full-term children.

On the basis of the relationship between hippocampal volume and episodic memory found in full-term controls only, one could argue that outliers within the full-term group have caused the diverging results in both groups. However, this possibility can be ruled out as the correlations remained statistically significant even after controlling for outliers. To further examine the statistical power in the present correlations, it was calculated how large the preterm sample should be in order to find small effects with a power of .80 for the correlation of hippocampal volume with delayed recall performance of the Rey-Osterrieth Complex Figure ($r = -.12$, $p = .61$) and with recognition accuracy in the nonspeeded response condition ($r = -.13$, $p = .60$). For this purpose, the program G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) was used in which .05 as α and the measured correlation coefficients were entered. This analysis revealed that the required preterm sample size amounts to $N = 428$ and $N = 364$ to reject the null hypothesis of zero correlation, for both correlations respectively. Thus, due to the relatively small preterm sample size in the present study, the conclusions drawn here are only preliminary and must await reassessment in a follow-up study with a larger sample size.

Taken together, Study 1 provides evidence for changes in declarative long-term memory in preterm children. As there were no group differences in episodic memory performance, the impairments in semantic memory in preterm children can be taken to reflect selective difficulties that are not fully explainable by IF and SES. An important endeavor for future research is to explore the brain mechanisms which underlie this selective impairment in semantic memory. Furthermore, because hippocampal volume seems to mediate episodic memory performance in full-term but not preterm children, it could be suggested that preterm children at that age recruit a neural network for episodic memory that differs from the one used by full-term children.

6 Study 2

Two Processes for Recognition Memory in Children of Early School Age: An Event-Related Potential Study[1]

6.1 Background and Research Question

Study 1 led to the tentative suggestion that preterm children recruit a neural network for episodic memory that differs from the one used by full-term born children. In order to provide a template for understanding the neurobehavioral basis of prematurity, the aim of Study 2 was to delineate the normative processes that underlie episodic memory retrieval in full-term children at early school-age. Specifically, Study 2 examined the ERP correlates of familiarity and recollection and their development in school-aged full-term children (Mecklinger et al., 2011[2]). By this, Study 2 established a model for the investigation of the two subprocesses of recognition memory in preterm children.

ERPs provide an excellent temporal resolution to monitor functionally relevant brain processes. As mentioned above, however, previous studies failed to verify the ERP correlate of familiarity in children. Therefore, in this study it was explored whether a mid-frontal old/new effect, the putative ERP correlate of familiarity, can be recorded from full-term children at early school-age under experimental conditions that encourage familiarity-based remembering and attenuate recollection. To this end, the ERP patterns of the full-term children were compared with those of young adults to examine age-related differences in the ERP correlates of familiarity and recollection. Furthermore, it was explored whether both ERP correlates show similar developmental differences. By this, the present study searched for converging evidence regarding measures of the two subprocesses of recognition memory and their developmental trajectories.

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[1] The data reported in this study are also reported in the following article: Mecklinger, A., Brunnemann, N., & Kipp, K. H. (2011). Two processes for recognition memory in children of early school-age: An event-related potential study. *Journal of Cognitive Neuroscience, 23*(2), 435-446.

In the present operational definitions of familiarity and recollection, the focus was on the temporal dynamics of both processes. On the basis of previous studies that showed that familiarity is available earlier than recollection (Hintzman & Caulton, 1997; Hintzman & Curran, 1994), recognition memory in full-term children and adults was tested with a response deadline procedure, in which recognition decisions were required very quickly. A number of studies have shown that under speeded response conditions (i.e., when participants have to give a recognition memory decision within 800 msec) recollection is diminished and tends to be at chance level while familiarity-based memory is still above chance (Boldini, Russo, & Avons, 2004; Hintzman & Caulton, 1997). As familiarity is fostered under speeded response conditions, it was expected that the ERP correlate of familiarity will be present and the correlate of recollection to be diminished when speeded recognition judgments have to be given.

Thus, Study 2 was conducted in anticipation of Study 3, because the former aimed to demonstrate that the putative ERP correlate of familiarity can be recorded from full-term children under conditions where children are forced to make old/new decisions quickly, and, in turn, recollection is hindered. Study 3 then used the response deadline procedure to disentangle the episodic memory subprocesses that are affected and spared by the changes in brain function that accompany prematurity.

6.2 Hypotheses

Following this line of thought, it was expected that if recognition memory performance depends more on familiarity than on recollection in a speeded response condition, performance for adults should be lower than that in a nonspeeded condition. Regarding the neural correlates elicited in the speeded condition, a mid-frontal old/new effect but no parietal effect should be apparent. Given the availability of familiarity at early school-age, as suggested by the findings of Ghetti and Angelini (2008), it was predicted that full-term children show the same performance and ERP pattern as the adult control group under a speeded response condition.

For the nonspeeded condition, the following predictions were made: In full-term children and adults, recognition memory performance should be higher than in the speeded condition because recognition depends on both recollection and familiarity. With regard to the neural correlates, an early frontal and late parietal old/new effect were predicted for adults. For full-term children, a parietal old/new effect was predicted. However, on the basis of the mixed pattern of results concerning the ERP correlate of familiarity in standard item recognition tasks, no specific predictions were made regarding the frontal old/new effect for full-term children in this condition.

6.3 Methods

Participants

Twenty-six full-term born children and 26 young adults participated in the study. Five adults and eight full-term children had to be excluded from further analyses due to a too low number of artifact-free ERP trials that resulted of a combination of low performance levels and excessive movement artifacts. One adult was excluded because of technical problems during recording. The age and gender distributions within each group were as follows: 8- to 10-year-old full-term children (mean age = 9.12 ± 0.90; 9 girls; one left-handed) and 19- to 27-year-old young adults (mean age = 22.05 ± 2.52; 10 women; all right-handed). All participants were native German speakers and reported themselves to be in good health. The children were recruited from schools in Saarbrücken and in the immediate vicinity. Young adults were undergraduate students at Saarland University, who either received course credit or were paid for their participation (€ 8.00/hr). Informed consent was obtained from all adult participants and parents of all children. In addition, the children signed assent forms.

Stimuli

The experimental stimuli were selected from a colored version of the Snodgrass and Vanderwart line drawings (Rossion & Pourtois, 2004). In total, 240 colored line drawings of common objects and animals were selected that were divided into two blocks of 120 items each. Of the 120 pictures in a block, 60 were randomly assigned to the study phase, whereas the remaining 60 were assigned as new items to the test phase. The order of pictures within a block was randomized separately for each participant. The assignment of pictures to old/new status and experimental block was balanced across subjects. For the practice lists, additional 30 pictures from a database from Becker, Kipp, and Mecklinger (2009) were used.

Procedure

Participants were seated in a comfortable chair throughout the experiment. The stimuli were presented in central vision on a computer monitor. The whole session lasted approximately 2 1/2 hr, including setting up the EEG cap. The experiment consisted of two study-test cycles, one for the speeded and one for the nonspeeded condition. As it was assumed that it would be more difficult to change from nonspeeded to speeded response requirements than vice versa and to control for interindividual variability in changing the response procedure, the study-test cycle for the speeded condition was always performed first.

Each cycle included a study phase, a retention interval, and a test phase. In both cycles, participants responded by using two buttons, one for each hand, with response hands counterbalanced across participants. Participants were given a practice block with 10 study and 20 test trials (speeded test block) or 5 study and 10 test trials (nonspeeded test block) before each study-test cycle. Generally, the subjects performed the practice blocks once, but occasionally the practice block preceding the first study-test cycle had to be repeated to ensure that the subjects understood the task instructions. In both study phases, the subjects viewed 60 pictures that were presented consecutively and were instructed to memorize the picture and to make an indoor/outdoor judgment by pressing a corresponding key. Each picture was presented for 1000 msec, preceded by a fixation cross (400 msec). After a fixed intertrial interval of 1400 msec, the next fixation cross appeared. Relative to two age-matched norm samples, the range of percent correct indoor/outdoor judgments was 0.48 to 0.90 for adults and 0.34 to 0.85 for full-term children. By this, task performance in the study phases was highly similar for both groups.[2]

There was a retention interval of one minute between the study and the test phase. During this retention interval, the subjects had to perform an easy arithmetic task. The children had to count backward in steps of two from a given number between 18 and 20. The adults had to count backward in steps of seven from a number between 400 and 600.

In each of the two test phases, the subjects viewed a total of 120 pictures (50% old) and were instructed to make old/new recognition decisions. A test trial began with a fixation cross (500 msec), followed by the critical picture presented for either 750 msec (adults) or 1050 msec (children). In the speeded condition, subjects were instructed to give their old–new responses during picture presentation (maximal response time = 750 and 1050 msec for adults and children, respectively). Different response deadlines were used for children and adults to account for the generally slower processing speed of children (Picton & Taylor, 2007). In fact, a pilot study revealed that under nonspeeded conditions, recognition judgments for the stimulus materials used in this study took about 300 msec longer for children than for adults. If the response was given after the presentation of the picture, subjects were informed about their time-out response by means of a brief sound, and the trial was discarded from analysis. If a response was given in time, a feedback stimulus (smiley or frown face) was presented indicating whether the correct or incorrect response had been given. In the nonspeeded condition, subjects were given unlimited time to respond. Immediately after the response, the feedback stimulus was presented. The intertrial interval was 2000 msec in both test blocks. Subjects were given a break every 15 trials in both test blocks. To ensure that the children had understood the

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[2] To examine whether performance in the indoor/outdoor judgment task was comparable across groups, an additional analysis was performed, in which the range of correct judgments relative to an age-matched norm sample (n = 10) was calculated only for those objects with high across-rater agreement in the norm samples of both age groups (e.g., traffic light, cake). For these items with high interrater agreement, the percentage of correct judgments were 0.79% and 0.86% for children and adults, respectively, and by this, well above chance and not significantly different from each other. In this analysis, the ranges of the percentage of correct judgments were 0.49–0.97% for adults and 0.58–0.93% for children. This means that for those items that can unambiguously be classified as indoor or outdoor in the respective group, there is no across-group difference in the percent correct judgments. By this, it could be concluded that both groups encoded the stimuli in a highly similar way.

procedure, they were asked to explain the instruction to the experimenter in their own words before each block and were corrected if necessary.

EEG Recording

EEG was recorded continuously with a sampling rate of 250 Hz with 27 Ag/AgCl electrodes from the following sites (adapted from the standard 10-20 system): FP1, FP2, F7, F3, FZ, F4, F8, FC5, FC3, FCZ, FC4, FC6, T7, C3, CZ, C4, T8, CP3, CPZ, CP4, P7, P3, PZ, P4, P8, O1, and O2. The left mastoid served as an on-line reference, and all EEG electrodes were rereferenced off-line to the algebraic mean of both mastoids. The vertical EOG was recorded bipolar from additional electrodes placed on the supraorbital and infraorbital ridges of the right eye. Horizontal EOG was recorded bipolar from electrodes placed on the outer canthi of the two eyes. Electrode impedance was kept below 5 kΩ. EEG and EOG were recorded continuously and were A–D converted with 16-bit resolution at a sampling rate of 250 Hz. Off-line data processing involved low-pass filtering at 30 Hz and high-pass filtering at 0.2 Hz. Before averaging, each recording epoch was manually scanned for artifacts. Trials containing eye movement artifacts were corrected off-line using a modified version of the Gratton, Coles, and Donchin (1983) regression procedure. Trials were epoched and baseline corrected off-line with a 200-msec prestimulus period. The duration of the poststimulus period was 900 msec for the speeded and 1200 msec for the nonspeeded condition.

For each group, ERPs were averaged to correctly recognized old (Hits) and new items (Correct Rejections; CRs) for both response conditions. For adults, the mean trial numbers (range) in the speeded test block were 38 (24-52) for Hits and 38 (23-55) for CRs. The corresponding numbers for the nonspeeded test block were 43 (34-51) and 43 (33-53), respectively. For the children, the mean trial numbers (range) in the speeded test block were 27 (17-40) for Hits and 27 (17-45) for CRs. In the nonspeeded test block, the corresponding numbers were 28 (18-37) and 28 (20-42), respectively. Post hoc *t*-tests for independent samples indicate that children contributed fewer trials than young adults, but the mean number of trials for each condition was large enough to provide a sufficiently high signal-to-noise ratio for the analysis of the ERP effects of interest in both age groups.

Data Analyses

SPSS 17.0 statistical package was used for all analyses. Memory accuracy was analyzed by means of the discrimination index (Pr), that is, hit rates minus false alarm rates (Snodgrass & Corwin, 1988). In the speeded test block, all trials with time-out responses or in which no response was given were discarded from analysis. Also, in both response conditions, trials with response times faster than 200 msec were discarded. Response bias (Br) was calculated according to Snodgrass and Corwin (1988) as Br = false alarms / (1-Pr).

For statistical analysis of the ERP data, nine electrodes over left, midline, and right frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal regions (P3, Pz, P4) were used. These recording sites were selected as they cover scalp regions on the anterior–posterior and the laterality dimension at which old/new effects can be reliable recorded. To quantify the mid-frontal and parietal old/new effects, mean amplitude measures were calculated in early (300-450 msec for children and 250-400 msec for adults) and late (600-750 msec for children and 500-650 msec for adults) time windows in both response conditions. The selection of these time windows was based on visual inspection of the waveforms. They were adapted to capture the effects of interest where it was largest in each age group.

ANOVAs with the factors Item Type (Hits, CRs), Anterior–Posterior (frontal, central, parietal), Laterality (left, midline, right), Response Condition (speeded vs. nonspeeded), and Group (full-term children, adults) were conducted separately for each time window. Interactions involving the Group, the Response Condition, or the Item Type factor were then followed-up in separate group- and response-condition-specific ANOVAs. Whenever appropriate, the Greenhouse–Geisser correction for nonsphericity (Greenhouse & Geisser, 1959) was used. Corrected p values are reported along with uncorrected degrees of freedom. Treatment magnitudes (η_p^2) (Tabachnick & Fidell, 2007) were calculated to allow an assessment of effect sizes across electrode sites. For reasons of clarity, only effects involving the factors Item Type, Group, or Response Condition are reported.

6.4 Results

Behavioral Data

Memory accuracy, response bias, and response times for both groups and response conditions are illustrated in Table 5. Memory performance was high in both groups (performance did exceed chance performance) and the mean number of time-out responses in the speeded condition was highly similar across groups (0.45, range = 0-3, and 1.1, range = 0-3, for adults and full-term children, respectively). The mean number of trials with response times faster than 200 msec in the speeded condition was also highly similar across groups (0.00, range = 0, and 0.22, range = 0-2, for adults and full-term children, respectively). An ANOVA with the factors Group and Response Condition performed for the discrimination index Pr revealed main effects of Group, $F(1, 36) = 14.40$, $p < .010$, and Response Condition, $F(1, 36) = 72.19$, $p < .001$, indicating that memory accuracy was higher for adults than for children and also for the nonspeeded than the speeded response condition. For response bias, the two-way ANOVA did not reveal significant results (F values < 1), indicating that both groups used a similar response criterion that also was not modulated by the response conditions.

For mean response times, an ANOVA with the factors Group, Item Type (Hits, CRs), and Response Condition revealed reliable effects of Group, $F(1, 36) = 29.86$, $p < .001$, and Response Condition, $F(1, 36) = 96.49$, $p < .001$. As expected, adults responded faster than children and both groups took more time for responding in the nonspeeded than in the speeded condition.

Taken together, in showing higher memory accuracy for adults than for children, the present results are consistent with prior reports of age differences in item recognition memory tasks (Czernochowski et al., 2005; Ghetti and Angelini, 2008; Naus & Ornstein, 1977). They also show that the response condition manipulation was successful and comparable across groups, that is, both groups responded slower and more accurate in the nonspeeded than that in the speeded response condition.

Table 5: Mean reaction times (RTs) in milliseconds for correctly recognized old and new pictures, proportions of Hits and Correct Rejections (CRs), discrimination index (Pr), and response bias (Br) for each group in the speeded and nonspeeded condition. The standard errors of the means are given in parentheses.

	Children (N = 18)	*Adults (N = 20)*
RT Speeded		
Hits	740 (14)	568 (7)
CRs	747 (10)	565 (5)
RT Nonspeeded		
Hits	1276 (104)	905 (42)
CRs	1265 (72)	971 (49)
Proportion Hits		
Speeded	0.71 (0.03)	0.79 (0.02)
Nonspeeded	0.82 (0.03)	0.92 (0.01)
Proportion CRs		
Speeded	0.78 (0.03)	0.84 (0.02)
Nonspeeded	0.87 (0.02)	0.92 (0.01)
Performance Estimate (Pr)		
Speeded	0.49 (0.04)	0.63 (0.03)
Nonspeeded	0.68 (0.04)	0.84 (0.02)
Bias Estimate (Br)		
Speeded	0.44 (0.03)	0.44 (0.03)
Nonspeeded	0.39 (0.04)	0.45 (0.05)

ERP Data

The grand mean ERP waveforms, separately for each group and response condition at three midline electrodes, are displayed in Figure 9. Figure 10 shows the scalp topographies of the mean amplitude measures for early and late ERP effects in each group and response condition.

In the speeded condition, both groups showed an early old/new effect between 250 and 450 msec with a mid-frontal distribution for adults and a left frontal scalp distribution for children.[3] This effect reached its maximum slightly earlier in adults than in children. In the late time windows (500-650 and 600-750 msec for adults and children, respectively), no parietal old/new effect was obtained for adults, albeit for children a late effect, characterized by a larger positivity for old than new pictures seemed to emerge at parietal recording sites. In the nonspeeded condition, adults showed a topographically widespread early old/new effect, followed by a late old/new effect with a centro-parietal maximum. Conversely, for children, only a parietal old/new effect was obtained that started at around 400 msec but reached its maximum at around 700 msec at parietal recording sites. These observations were confirmed by a series of statistical analyses.[4]

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[3] It appears that there were also earlier old/new differences at around 100 msec present in both age groups in the speeded condition. However, these effects were not reliable in neither group when old/new differences were analyzed with mean amplitude measures between 100 and 250 msec.

[4] An additional statistical analysis was performed using the same time windows for the quantification of the early (300 to 450 msec) and late (500 to 650 msec) effects in both groups. These time windows were comparable with other developmental ERP studies (Cycowicz et al., 2003; Czernochowski et al., 2005). All effects and the pairwise comparisons from the initial analysis were replicated. The only difference between both analyses was that the Item Type × Anterior/Posterior × Laterality interaction for the late time interval for the children group in the speeded condition reached significance ($p < .010$), as did the Item Type effect at Cz ($p < .050$) in the follow-up analysis. An additional topographic profile analysis on rescaled old/new differences revealed that this weak late effect (500–650 msec) in the speeded condition differed in topography from the early (300 to 450 msec) effect in the speeded condition ($p < .020$) and from the late effect in the nonspeeded condition ($p < .010$).

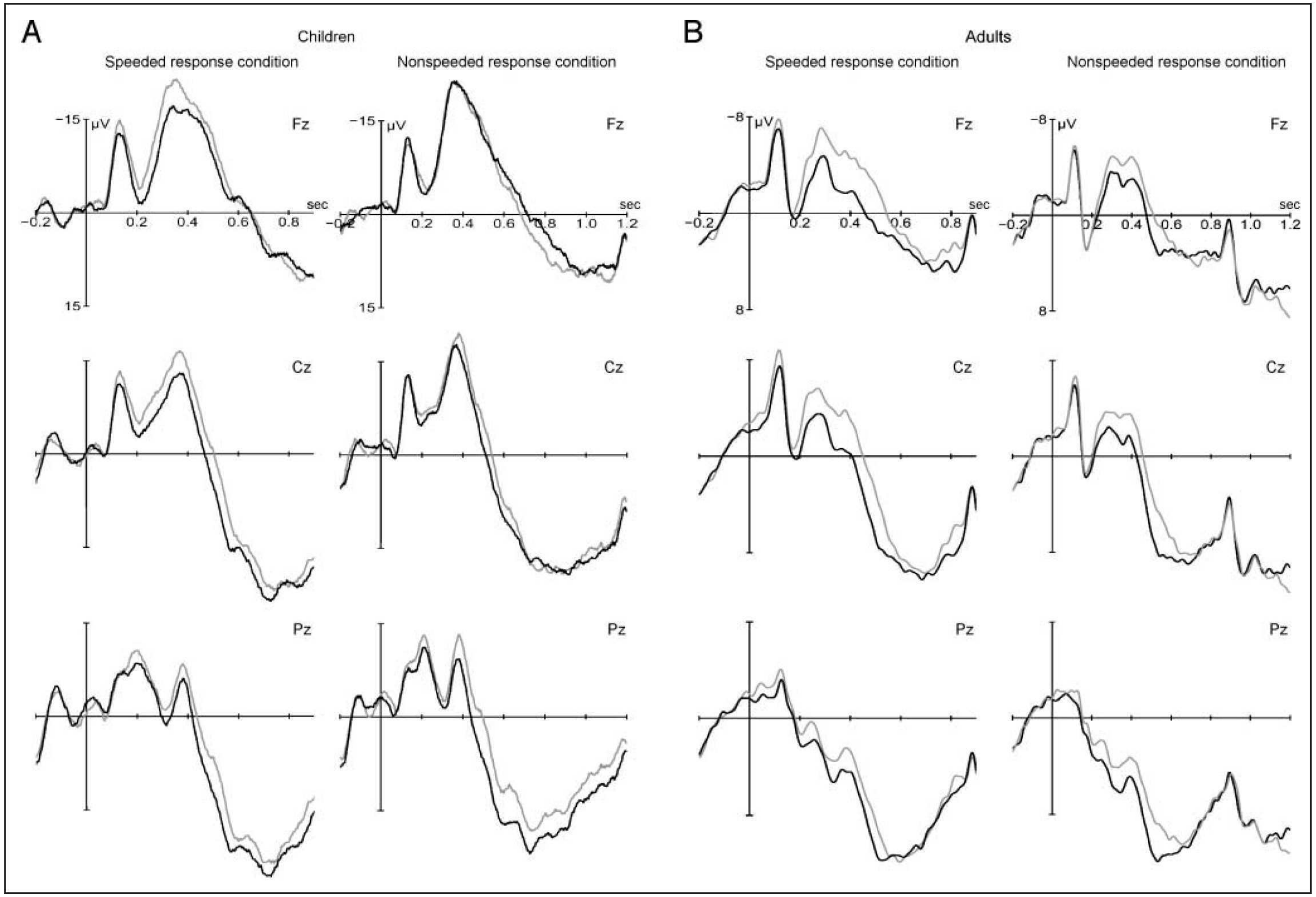

Figure 9: Grand mean ERPs elicited during the item memory task in the speeded and nonspeeded response condition for children (A) and adults (B). Correct Rejections of new items are depicted in gray lines and Hits are depicted in black lines. Note the different amplitude scaling in both groups (adopted from Mecklinger et al., 2011).

Early Time Window (Children, 300-450 msec; Adults, 250-400 msec)

For the early time window, the ANOVA with the factors Group, Item Type, Anterior/Posterior, Laterality, and Response Condition revealed main effects of Item Type, $F(1, 36) = 33.39$, $p < .001$, and Group, $F(1, 36) = 83.62$, $p < .001$. In addition, interactions among Response Condition and Group, $F(1, 36) = 9.03$, $p < .010$, among Item Type, Anterior/Posterior, and Response Condition, $F(2, 72) = 5.74$, $p < .020$, and among Response Condition, Group, Anterior/Posterior, and Laterality, $F(4, 144) = 3.19$, $p < .020$, were obtained. These interactions indicate that the early old/new (Item Type) effect differed as a function of group in both the response conditions and the recording sites. They were followed-up in response condition and group-specific analyses.

In the speeded condition, for adults, an ANOVA with the factors Item Type, Anterior/Posterior, and Laterality revealed an effect of Item Type, $F(1, 19) = 17.19$, $p < .010$, and an interaction of Item Type and Anterior/Posterior, $F(2, 38) = 7.10$, $p < .020$. The interaction reflects the fact that the early old/new effect, although significant at frontal, central, and parietal electrodes, was larger at frontal ($\eta_p^2 = .471$) and central ($\eta_p^2 = .464$) than at parietal electrodes ($\eta_p^2 = .328$). For children, there also was an effect of Item Type, $F(1, 17) = 8.87$, $p < .010$, that was embedded in a marginally significant Item Type × Laterality interaction, $F(2, 34) = 3.69$, $p = .061$. Follow-up analyses revealed that the old/new effect was stronger at midline electrodes ($\eta_p^2 = .410$) compared with left-sided ($\eta_p^2 = .339$) and right-sided electrodes ($\eta_p^2 = .110$).

In the nonspeeded condition, for adults, the three-way ANOVA revealed an effect of Item Type, $F(1, 19) = 8.44$, $p < .010$, and a three-way interaction between Item Type, Anterior/Posterior, and Laterality, $F(4, 76) = 3.79$, $p < .030$. The interaction reflects the fact that the early old/new effect, although significant at all nine electrodes, was largest at F4 ($\eta_p^2 = 0.313$) and Pz ($\eta_p^2 = 0.343$). For children, there was neither an effect of item type nor any interactions involving this factor (p values $> .150$).

To summarize, consistent with the prediction, the ERP effects in the early time window in the speeded condition were highly similar for children and adults, in that both groups showed an early frontally focused old/new effect, the ERP correlate of familiarity. In the nonspeeded condition, the ERP pattern in the early time interval differed as a function of group. For adults, a broadly distributed, albeit right-frontally focused early old/new effect, indexing familiarity, was obtained. Conversely, for children, no early ERP differences between old and new items were found. This latter result is consistent with other studies that did not find mid-frontal old/new effects for children in standard item recognition memory tasks (Hepworth et al., 2001; Shamdeen et al., 2008).

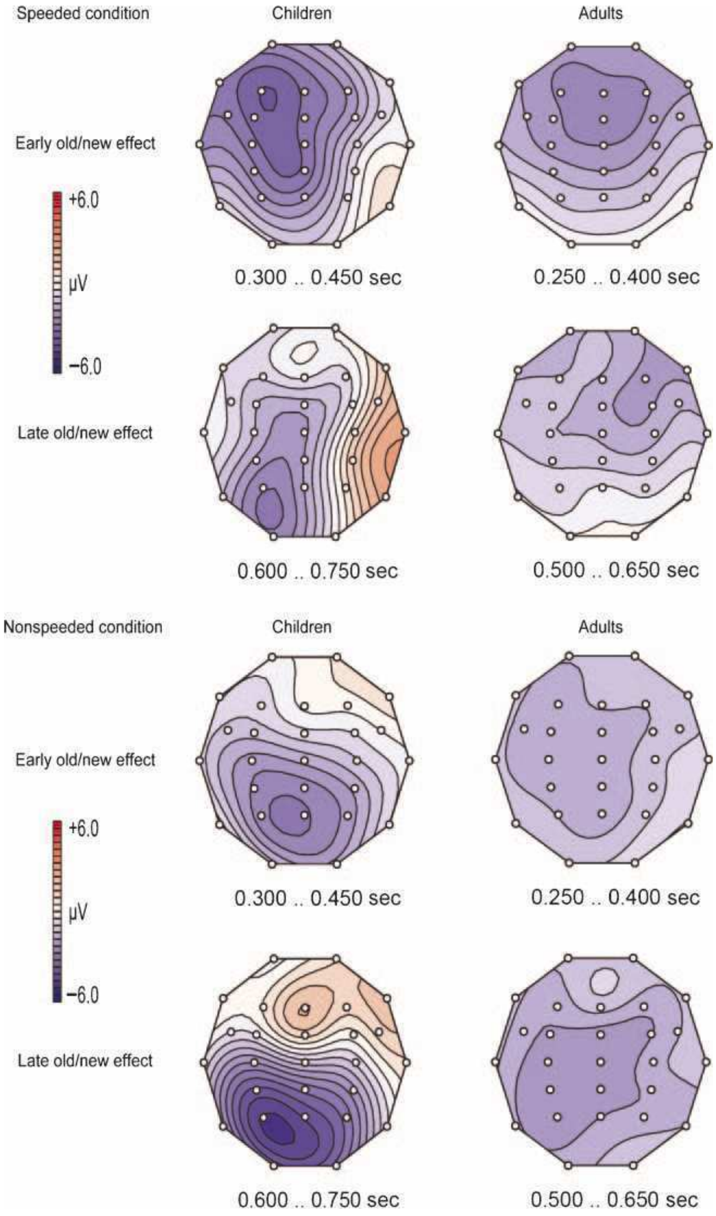

Figure 10: Scalp topographies of the early and late old/new effects (new minus old) for children and adults in the speeded and nonspeeded condition (adopted from Mecklinger et al., 2011).

Late Time Window (Children, 600-750 msec; Adults, 500-650 msec)

In the late time window, the initial five-way ANOVA revealed main effects of Item Type, $F(1, 36) = 12.03$, $p < .010$, and Response Condition, $F(1, 36) = 27.80$, $p < .001$, that were embedded in interactions among Response Condition and Group, $F(1, 36) = 17.11$, $p < .001$, Item Type, Anterior/Posterior, and Group, $F(2, 72) = 3.89$, $p < .030$, and Item Type, Anterior/Posterior, Response Condition, and Group, $F(2, 72) = 3.56$, $p < .040$. These interactions suggest that for the late time window, the item type (old/new) effects were modulated by response condition, group, and recording sites, and follow-up analyses were performed to further elucidate these interactions.

Consistent with the prediction that recollection does not contribute to recognition memory when the response deadline is shortened, in the speeded condition for adults there was neither an effect of Item Type nor any interaction involving the Item Type factor (p values > .06). For children, there was a marginal significant interaction of Item Type, Anterior/Posterior, and Laterality, $F(4, 68) = 2.92$, $p = .062$. Follow-up analyses revealed that the old versus new differences did not reach the significance at any electrode site (p values > .17).

In the nonspeeded condition, for adults, there was a main effect of Item Type, $F(1, 19) = 13.86$, $p < .010$. Effect size analyses performed for frontal, central, and parietal recording sites revealed that the old/new effect was stronger at parietal ($\eta_p^2 = .484$) than at central ($\eta_p^2 = .399$) and frontal ($\eta_p^2 = .296$) recording sites. For children, an Item Type × Anterior/Posterior interaction, $F(2, 34) = 8.89$, $p < .010$, was found. Further analyses revealed an old/new effect at parietal, $F(1, 17) = 12.89$, $p < .010$, $\eta_p^2 = .431$, but not at central ($p = .243$) or frontal sites ($p = .428$).

To summarize, as predicted, no ERP correlate of recollection was found for adults when recognition decisions were given with a response deadline. For children, a marginally significant triple interaction was found, but the differences between old and new responses did not reach significance at neither recording site in the late time interval. Also, consistent with the predictions, without response deadline both groups showed a parietally accentuated old/new effect, the correlate of recollective processing.

Topographic profile analyses. For adults in the nonspeeded condition early and late old/new effects, the putative correlates of familiarity and recollection were obtained. A topographic profile analysis was performed to assess if different neurocognitive systems support the putative ERP correlates of familiarity and recollection. If the scalp distributions of both effects differ after the data have been rescaled to remove overall amplitude differences across conditions, it can be inferred that qualitatively different neural systems and by this different cognitive processes (McCarthy & Wood, 1985; Wilding, 2006) are engaged in the early and late time windows. The rescaled new minus old difference waveforms in the early and late time window were analyzed using the whole electrode montage of 27 electrodes. The ANOVA with factors Time Window (250-400 vs. 500-650 msec) and Electrode (27) revealed a marginally significant Electrodes×Time Window interaction, $F(26, 494) = 1.43$, $p < .079$. This result tentatively verifies the distinct topographies of both effects and supports the view that differential cognitive processes underlie the putative ERP correlates of familiarity and recollection.

6.5 Discussion

Study 2 was designed to delineate the normative processes that underlie episodic memory retrieval in full-term children at early school-age to provide a template for the investigation of the ERP correlates of familiarity and recollection in preterm children. It was investigated whether a mid-frontal old/new effect, the putative ERP correlate of familiarity, can be recorded from full-term born children at early school-age and from an adult control group under a speeded response condition that encourages familiarity-based remembering and diminishes recollective processing. Furthermore, it was explored whether the ERP correlates of familiarity and recollection show similar developmental changes. In order to do so, eight- to ten-year-old full-term children and adults performed a picture recognition memory task in a speeded and a nonspeeded response condition. Group-specific response deadlines were used to account for the generally slower processing speed of school-age children (de Ribaupierre, 2002). Although recognition memory accuracy was lower in full-term children as compared with the adult group, irrespective of response condition, the ERPs showed similar old/new effects for children and for adults. In the speeded response condition, both groups showed an early frontal old/new effect, the putative ERP correlate of familiarity. No parietal old/new effect, the putative ERP correlate of recollection, was obtained in the speeded condition in either group. In the nonspeeded condition, both groups showed the parietal old/new effect, and a frontal effect was additionally observed for adults.

In the behavioral data, it was found that response times were faster and memory accuracy lower in the speeded compared to the nonspeeded response condition for both groups. Consistent with other item recognition memory studies, memory performance was higher for adults than for children (Cycowicz, Friedman, & Snodgrass, 2001; Cycowicz et al., 2001; Czernochowski et al., 2005). Notably, as apparent from Table 5, memory accuracy (Pr) in the speeded condition relative to the nonspeeded condition was lowered to 72% and 75% in the children and adult group, respectively, suggesting that the effects of the response deadline manipulation were highly comparable across groups on the behavioral level. Additionally, since there were no differential effects of response conditions on setting the decision criterion (response bias), there seem to be no differential decision strategies in both response conditions. Participants in both groups seemed rather to base their recognition judgments in the speeded condition on familiarity and attenuated recollection-based remembering. This view is supported by a recent study with a patient with a circumscribed lesion to the left anterior temporal lobe (Bowles et al., 2007). In accordance with the view that anterior temporal lobe structures are critically involved in familiarity processing, this patient showed a consistent pattern of impaired familiarity and preserved recollection across a variety of tasks. Most notably, as one would expect if a speeded response condition fosters familiarity-based remembering, this patient was strongly affected in making recognition judgments under a short response deadline but showed normal performance with a slower deadline.

The analyses of the ERP results in the early time window revealed that both, children and adults, showed an early old/new effect in the speeded response condition. On the basis of its high resemblance with the mid-frontal old/new effect reported in other studies (Jäger, Mecklinger, & Kipp, 2006; Opitz & Cornell, 2006; Rugg & Curran, 2007), this effect was taken as the ERP correlate of familiarity. As the mid-frontal old/new effect was found with a generally agreed on and empirically well-supported operational definition of familiarity, this provides further evidence for the functional significance of this effect and converging evidence for the dual-process view of recognition memory. Therefore, the observation that the mid-frontal old/new effect was found in 8- to 10-year-old full-term children and was highly similar in its temporal and topographic characteristics to the corresponding effect in adults suggests that familiarity is available for recognition judgments at early school-age under specific circumstances. Furthermore, this is consistent with other studies using the remember/know procedure (Billingsley et al., 2002) or ROC analyses (Ghetti and Angelini, 2008), which showed that there is only small age-related change in familiarity after the age of eight years, and that familiarity is immune to development after that age.

Nevertheless, it remains to be discussed, why a familiarity correlate was found for children in the present study but not in former ERP studies. A variety of previous children studies did not explicitly address the question of whether ERP old/new effects were independently sensitive to familiarity and recollection (Hepworth et al., 2001; Marshall et al., 2002) or may have used operational definitions that did not capitalize on the different temporal dynamics of familiarity and recollection. By this, these studies were not sensitive enough to dissociate familiarity and recollection as for example the variant of the process dissociation procedure employed by Czernochowski et al. (2005) or the source memory task used by Cycowicz et al. (2003). In a similar vein, van Strien et al. (2009) used highly familiar words that were shown six times in a continuous recognition task so that because of a combination of high presentation rate and high lexical frequency of the words, familiarity may not have been diagnostic for the children's recognition judgments (Stenberg et al., 2008).

To test the idea that recollection plays a negligible role when speeded recognition judgments have to be given (Boldini et al., 2004; Boldini, Russo, Punia, & Avons, 2007), a late time window was examined. For adults, no parietal old/new effect was obtained, suggesting that the influence of recollection was minimized by the speeded response deadline. For children, there also was no difference between old and new items in the late time interval. However, an old/new difference with a maximum at Cz emerged, when the same time interval (500-650 msec) as for the adults was used for the quantification of the children's late effect.[5] This suggests that this effect is subtle, restricted to a small time interval, and not reliable when the time window was adapted to adequately capture the late effects in the children ERPs (i.e., 600-750 msec). Notably, the scalp topography of this late effect between 500 and 650 msec was different from the early effect in the speeded condition and the late parietal effect in the nonspeeded condition, indicating that it reflects neither delayed familiarity processing nor recollective processing. Other studies have identified ERP differences between old and new items at posterior sites in this time range with implicit memory (Groh-Bordin, Zimmer, & Mecklinger, 2005; Nessler, Mecklinger, & Penney, 2005; Rugg et al., 1998). However, given the transient and subtle character of this effect and the observation that it was statistically not reliable when group-specific time windows were used for its quantifications, as yet no firm conclusions on the functional significance of this effect can be drawn. Further empirical data are required to disentangle the processing mechanisms reflected in these late and subtle old/new differences in children.

Although the early ERP signatures were highly similar for both groups in the speeded condition, group differences emerged in the nonspeeded condition. The adult group showed a mid-frontal old/new effect followed by a widely distributed but parietally focused late old/new effect, an ERP pattern that is frequently found in standard item recognition memory task with young adults (see Friedman & Johnson, 2000, for a review; see also Johansson, Mecklinger, & Treese, 2004). As in addition the topographic profile analysis provides tentative support for qualitative differences in the scalp topography of both effects, this pattern of results could be taken to reflect that both processes, familiarity and recollection, play a role when making recognition judgments with or without low temporal constraints. For full-term children, there was no mid-frontal old/new effect, replicating former studies that did not find this effect when nonsensitive operational definitions of familiarity were applied. Rather, the children group showed a clear parietally focused late old/new effect. This effect replicates a variety of earlier ERP studies, which showed that the ERP correlate of recollection can reliably be recorded starting at early school-age (Cycowicz et al., 2003; Czernochowski et al., 2005; de Chastelaine, Friedman, & Cycowicz, 2007; Friedman et al., 2010; Hepworth et al., 2001; van Strien et al., 2009) and implies that recollection is fully developed by the age of eight years.

To conclude, the present findings provide evidence that an early mid-frontal old/new effect, the putative ERP correlate of familiarity, can be recorded from full-term children under experimental conditions where the participants are forced to make old/new decisions quickly, and, in turn, recollection is hindered. This suggests that familiarity is available for recognition judgments at early school age under specific circumstances. Furthermore, it was shown that familiarity and recollection are functionally distinct in both full-term children and adults. Although recognition memory accuracy was lower in full-term children as compared with the adult group, irrespective of response condition, the differential contribution of familiarity in the speeded response condition and recollection in the nonspeeded response condition is highly similar across groups. This suggests that the episodic memory network used by full-term children at early school-age does not qualitatively differ from that used by adults, although it might still be less matured.

7 Study 3

Preterm Birth and its Impact on the Development of the Two Processes of Recognition Memory

7.1 Background and Research Question

Study 2 showed that an early mid-frontal old/new effect, the putative ERP correlate of familiarity, can be obtained in full-term children at early school-age under a speeded response condition. In addition, Study 2 found that full-term children show the late parietal old/new effect, the putative ERP correlate of recollection, in a nonspeeded response condition. Furthermore, Study 1 demonstrated that although preterm children showed reduced hippocampal volumes relative to full-term controls, episodic memory performance was not impaired. Additionally, in full-term but not in preterm children, hippocampal volume was positively correlated with episodic memory measures (i.e., delayed recall performance of the Rey-Osterrieth Complex Figure and memory accuracy in the nonspeeded response condition of the recognition experiment). As the latter findings suggest that preterm children at early school-age recruit a neural network for episodic memory that differs from the one used by full-term children, the present study focuses on the developmental trajectories of the ERP correlates of familiarity and recollection in preterm children with uncomplicated neonatal courses compared to the full-term control group of Study 2. Specifically, it was investigated whether prematurity affects the ERP correlate of recollection, whereas the ERP correlate of familiarity should be unaffected. So far, this question has not been paid attention to in other studies. Based on studies reporting reduced functioning of the hippocampus in preterm individuals (Giménez et al., 2004, 2005; Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000), it can be hypothesized that hippocampal recollective processing is reduced in preterm children compared to full-term controls. By contrast, the available evidence suggesting that familiarity-based processes are supported by extra-hippocampal brain regions allows for the possibility that familiarity processing is less or not affected by prematurity (Rose et al., 2011). Importantly, because of potential compensatory mechanisms in the brains of preterm individuals, recognition memory performance should be unimpaired (Curtis et al., 2006; Narberhaus et al., 2009; see also Study 1). To examine these hypotheses, the same procedure with a speeded and nonspeeded response condition as in Study 2 was administered to preterm children with uncomplicated neonatal courses.

As described in the general introduction of the present thesis, the GA at birth seems to be important for brain development (Davis et al., 2011). Hence, it was of additional interest whether the degree of prematurity (i.e., GA) is associated with the extent of modulation in the neural systems of preterm individuals. To elucidate the relationship between the GA at birth and the magnitude of the ERP correlates of familiarity and recollection, the GA of the preterm children was correlated with the magnitude of the putative ERP correlates of familiarity and recollection.

Taken together, Study 3 expected to reveal that hippocampal damage in preterm children selectively affects recollection-based processes but not the recognition memory performance, thus reflecting a functional compensation within the brains of preterm children.

7.2 Hypotheses

In keeping with the logic of the data interpretation in Study 2, it was expected that if recognition memory performance depends more on familiarity than on recollection in the speeded response condition, performance for the preterm children should be lower than that in the nonspeeded response condition. Accordingly, for the nonspeeded response condition, recognition memory performance should be higher than in the speeded condition because recognition depends on both recollection and familiarity.

Regarding the neural correlates elicited in the speeded and nonspeeded condition, the following predictions were made: Given selective hippocampal compromise in preterm children at early school-age, as suggested by the findings by Nosarti et al. (2002) or Peterson et al. (2000), it was predicted that in the speeded response condition preterm children show the same ERP pattern as the full-term control group of Study 2, that is, an early mid-frontally focused old/new effect, but no parietal effect should be present. In the nonspeeded condition, for preterm children, a reduced late parietal old/new effect as compared to the full-term control group was expected. On the basis of the mixed pattern of results regarding the ERP correlate of familiarity in standard item recognition tasks, no specific predictions were made regarding the frontal old/new effect for preterm children in the nonspeeded response condition.

If the degree of prematurity is associated with reduced recollective processing, the GA of the preterm children should positively correlate with the magnitude of the ERP correlate of recollection in the nonspeeded response condition. With regard to the relationship between the GA and the magnitude of the ERP correlate of familiarity in the speeded response condition, a negative correlation was predicted, supporting the view that within the brains of preterm children reduced recollective processing is compensated by familiarity-based processes. Moreover, if a compensatory mechanism exists in the brains of preterm children, it was expected that the magnitude of the ERP correlate of recollection in the nonspeeded condition should be negatively correlated with the magnitude of the ERP correlate of familiarity in the speeded response condition.

7.3 Methods

Participants

Twenty-four preterm children participated in this study. The children were recruited from archives of the Department of Pediatrics and Neonatology at the university hospital in Homburg. Inclusion criteria for this study were the same as in Study 1. Four preterm children had to be excluded from further analyses due to an insufficient number of artifact-free ERP trials that resulted from a combination of low performance levels and excessive movement artifacts. Two preterm children were excluded because of technical problems during recording. The mean GA of the remaining 18 preterm children was 30.03 weeks (range: 26-33) and the mean BW was 1252.22 g (range: 880-1540). The corrected age (corrected to 40 weeks gestation) and gender distribution was as follows: seven to ten years old (mean age = 8.99, range: 7;10-10;07; 10 female). Two subjects were left-handed. The SES was determined according to Ganzeboom et al. (1992). The mean value was 54.56 (range: 31-77).

The 18 children of Study 2 served as a full-term born control group (mean corrected age = 8.88, range: 8;00-10;11; 9 female, one left-handed). The mean GA of the controls was 39.67 weeks (range: 38-42) and the mean BW was 3312.78 g (range: 1950-4400). The mean value of the SES was 64.00 (range: 37-88) and thus significantly higher than in the preterm group, $t(34) = -2.03$, $p = .05$. To control for confounding influences of this factor on differences in memory variables and ERP old/new effects between preterm and full-term children, additional ANCOVAs with SES as a covariate were carried out in cases of group differences in any of the analyses.

The children received € 8.00/hour for participation. Additionally, the parents of all children received € 12.00 for travelling expenses. The study was approved by the Ethics Committee of the Saarland Medical Association (ID No. 151/07) and all children and parents gave written informed consent. All participants were native German speakers and reported themselves to be in good health.

Stimuli, Design, and Procedure

The experimental stimuli, design, and procedure were exactly the same as in Study 2. Each subject performed two study-test cycles, one with a speeded and one with a nonspeeded response condition. In both study phases, pictures were presented consecutively on a computer screen and subjects were instructed to make an indoor/outdoor judgment by pressing a corresponding key and to memorize the picture. Relative to an age-matched norm sample, the range of percent correct indoor/outdoor judgments was 0.48 to 0.87 for preterm children and 0.34 to 0.85 for control children. By this, task performance in the study phases was highly similar for both groups. After a retention interval of one minute, the test phase followed. In each of the two test phases, old and new pictures were presented and subjects were instructed to make old/new recognition decisions by pressing a corresponding key. In the speeded response condition, subjects were instructed to give their old–new responses during picture presentation (maximal response time = 1050 msec). In the nonspeeded response condition, subjects were given unlimited time to respond.

EEG Recording

EEG recording was also exactly the same as in Study 2. Trials were epoched and baseline corrected off-line with a 200-msec prestimulus period. The duration of the poststimulus period was 900 msec for the speeded and 1200 msec for the nonspeeded condition.

For each group, ERPs were averaged to correctly recognized old (Hits) and new items (CRs) for both response conditions. For preterm children, the mean trial numbers (range) in the speeded test block were 26 (19-36) for Hits and 25 (19-36) for CRs. In the nonspeeded response condition, one preterm child reached insufficient trial numbers (Hits: 15; CRs: 8) and was excluded from the analysis of the nonspeeded response condition. For the remaining 17 preterm children the mean trial numbers (range) in the nonspeeded test block were 27 (17-38) for Hits and 28 (18-40) for CRs. For the full-term children, the mean trial numbers (range) in the speeded test block were 27 (17-40) for Hits and 27 (17-45) for CRs. In the nonspeeded test block, the corresponding numbers were 28 (18-37) and 28 (20-42), respectively. In both groups, the number of trials used for ERP averaging was in the range used in previous developmental ERP studies (Czernochowski et al., 2005; Friedman et al., 2010) and was large enough to obtain equivalent signal-to-noise ratio across conditions. Furthermore, post hoc *t*-tests for independent samples indicate that both groups did not differ in their mean number of trials for each condition.

Data Analyses

SPSS 17.0 statistical package was used for all analyses. Memory accuracy was analyzed by means of the discrimination index (Pr). In the speeded test block, all trials with time-out responses or those in which no response was given were discarded from analysis. In addition, in both response conditions, trials with response times faster than 200 msec were discarded. Response bias (Br) was calculated according to Snodgrass and Corwin (1988) as Br = false alarms / (1-Pr). RTs were measured separately for Hits and CRs. To examine group effects, repeated-measures ANOVAs with the factor Group (full-term children, preterm children) were conducted.

For statistical analysis of the ERP data, nine electrodes over left, midline, and right frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal regions (P3, Pz, P4) were used. These recording sites were selected as they cover scalp regions on the anterior–posterior and the laterality dimension at which old/new effects can be reliably recorded. To quantify the mid-frontal and parietal old/new effects, mean amplitude measures were calculated in early (300-450 msec) and late (600-750 msec) time windows in both response conditions. The selection of these time windows was based on visual inspection of the waveforms.

ANOVAs with the factors Item Type (Hits, CRs), Anterior–Posterior (frontal, central, parietal), Laterality (left, midline, right), Response Condition (speeded vs. nonspeeded), and Group (full-term children, preterm children) were conducted separately for each time window. Interactions involving the factor Group, Response Condition, or Item Type were then followed-up in separate group- and response-condition-specific ANOVAs. Whenever appropriate, the Greenhouse–Geisser correction for nonsphericity (Greenhouse & Geisser, 1959) was used. Corrected *p* values are reported along with uncorrected degrees of freedom. Treatment magnitudes (η_p^2) (Tabachnick & Fidell, 2007) were calculated to assess effect sizes across electrode sites. For reasons of clarity, only effects involving the factors Item Type, Group, or Response Condition are reported.

To control for confounding influences of SES on differences in memory variables and ERP old/new effects between groups, additional ANCOVAs with SES as a covariate were carried out.

Within the preterm group, the relationships of GA (in days) with the magnitude of the ERP correlate of familiarity (old minus new difference at the electrode where the old/new effect is strongest in the early time window in the speeded response condition) and with the magnitude of the ERP correlate of recollection (old minus new difference at the electrode where the old/new effect is strongest in the late time window in the nonspeeded response condition) were examined by means of partial correlations (controlling for SES).

7.4 Results

Behavioral Data

Memory accuracy, response bias, and response times for the two groups and response conditions are illustrated in Table 6. Memory performance was high in both groups (performance did exceed chance performance) and the mean number of time-out responses in the speeded condition was highly similar across groups (1.1, range: 0-3, and 0.89, range: 0-4, for full-term and preterm children, respectively). The mean number of trials with response times faster than 200 msec in the speeded condition was also highly similar across groups (0.22, range = 0-2, and 0.06, range = 0-1, for full-term and preterm children, respectively). An ANOVA with the factors Group and Response Condition performed for the discrimination index Pr revealed a main effect of Response Condition, $F(1, 34) = 29.83$, $p < .001$, indicating that both groups responded more accurately in the nonspeeded than the speeded response condition. For response bias, the two-way ANOVA did not reveal any significant results (F values < 2, $p > .166$), indicating that both groups used a similar response criterion that also was not modulated by the response conditions.

For mean response times, an ANOVA with the factors Group, Item Type (Hits, CRs), and Response Condition revealed a main effect of Response Condition, $F(1, 34) = 75.58$, $p < .001$. This result indicates that both groups took more time for responding in the nonspeeded than in the speeded response condition.

Taken together, the lack of group differences in memory accuracy in both response conditions is consistent with prior reports of comparable performance for preterm and full-term children in episodic memory tasks (Curtis et al., 2006; Narberhaus et al., 2009). The results also show that the response condition manipulation was successful and comparable across groups, that is, both groups responded slower and more accurate in the nonspeeded than in the speeded response condition.

Table 6: Mean RTs in milliseconds for correctly recognized old and new pictures, proportions of Hits and CRs, discrimination index (Pr), and response bias (Br) for each group in the speeded and nonspeeded response condition. The standard errors of the means are given in parentheses.

	Control Group (N = 18)	*Preterm Group (N = 18)*
RT Speeded		
Hits	740 (14)	716 (11)
CRs	747 (10)	724 (14)
RT Nonspeeded		
Hits	1276 (104)	1128 (72)
CRs	1265 (72)	1185 (79)
Proportion Hits		
Speeded	0.71 (0.03)	0.72 (0.02)
Nonspeeded	0.82 (0.03)	0.80 (0.03)
Proportion CRs		
Speeded	0.78 (0.03)	0.73 (0.03)
Nonspeeded	0.87 (0.02)	0.83 (0.03)
Performance Estimate (Pr)		
Speeded	0.49 (0.04)	0.45 (0.05)
Nonspeeded	0.68 (0.04)	0.63 (0.06)
Bias Estimate (Br)		
Speeded	0.44 (0.03)	0.46 (0.03)
Nonspeeded	0.39 (0.04)	0.45 (0.03)

ERP Data

The grand mean ERP waveforms, separately for each group and response condition at three midline electrodes, are presented in Figure 11. Figure 12 shows the scalp topographies of the mean amplitude measures for early and late ERP effects in each group and response condition.

In the speeded condition, both groups showed an early old/new effect between 300 and 450 msec with a left frontal scalp distribution for full-term children and a mid-central distribution for preterm children. In the late time window (600-750 msec), no parietal old/new effect was evident for preterm children, albeit for full-term children a late effect, characterized by a larger positivity for old than new pictures, seemed to emerge at parietal recording sites.

In the nonspeeded condition, for full-term children, only a parietal old/new effect was obtained that started at around 400 msec but reached its maximum at around 700 msec at parietal recording sites. For preterm children, only an early effect, characterized by a larger positivity for old than new pictures, seemed to emerge at parietal recording sites. These observations were confirmed by a series of statistical analyses.

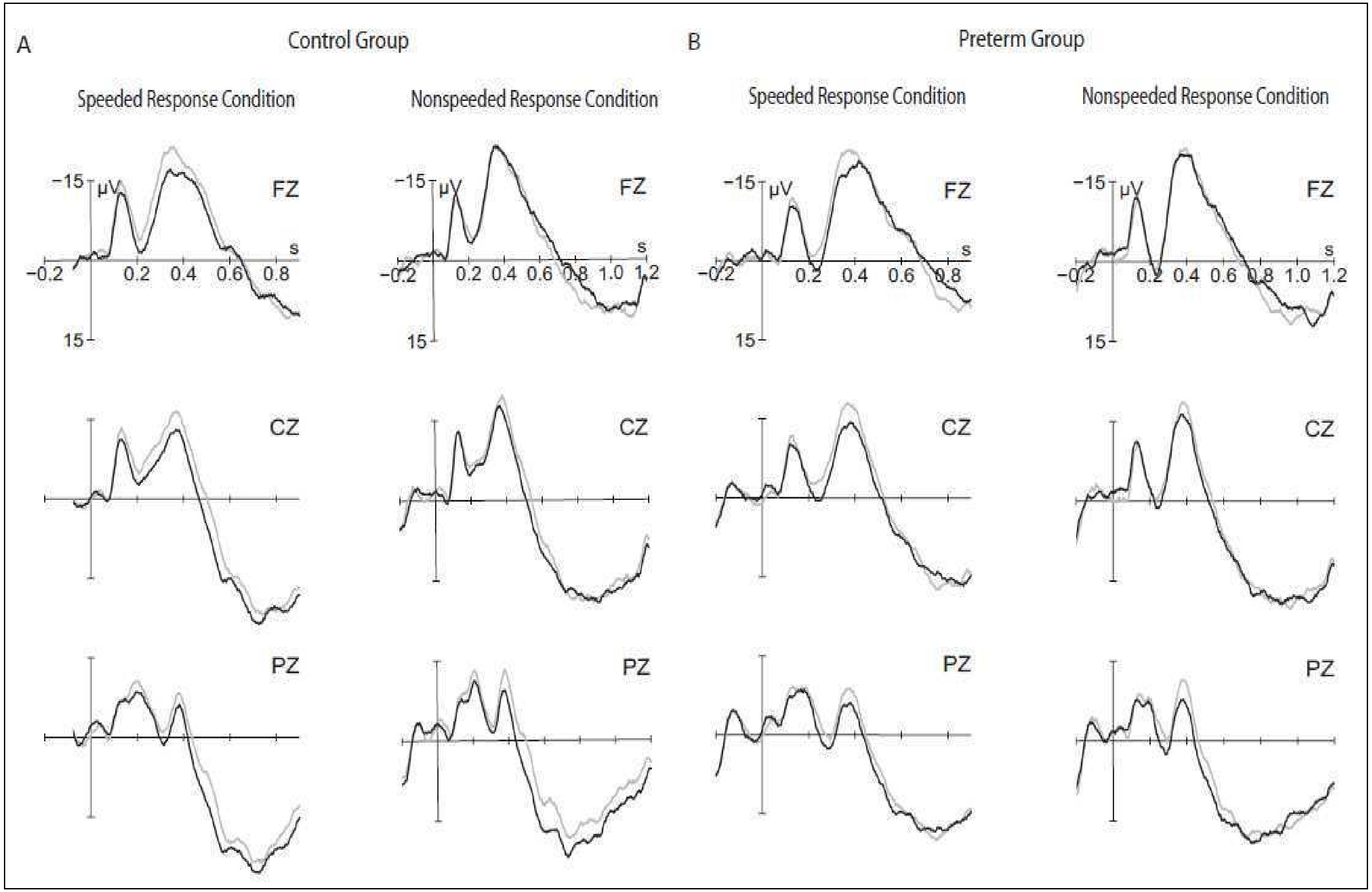

Figure 11: Grand mean ERPs elicited during the item memory task in the speeded and nonspeeded response condition for full-term control children (A) and preterm children (B). Correct Rejections of new items are depicted in gray lines and Hits are depicted in black lines.

Early Time Window (300-450 msec)

For the early time window, the ANOVA with the factors Group, Item Type, Anterior/Posterior, Laterality, and Response Condition revealed main effects of Item Type, $F(1, 33) = 19.12$, $p < .001$, and Response Condition, $F(1, 33) = 6.87$, $p < .020$. In addition, an interaction among Item Type and Laterality, $F(2, 66) = 4.08$, $p < .040$, was obtained. This interaction indicates that the early old/new (Item Type) effect differed as a function of recording sites, irrespective of group. As Study 2 revealed that in children the early old/new effect differed as a function of response condition, response condition-specific follow-up analyses were performed across both groups.

In the speeded condition, the ANOVA with the factors Item Type, Anterior/Posterior, and Laterality across both groups revealed an effect of Item Type, $F(1, 35) = 13.91$, $p < .010$, and an interaction of Item Type and Laterality, $F(2, 70) = 4.41$, $p < .030$. Follow-up analyses revealed that the old/new effect, although significant at left-sided, midline, and right-sided electrodes, was strongest at midline electrodes ($\eta_p^2 = .353$) compared with left-sided ($\eta_p^2 = .275$) and right-sided electrodes ($\eta_p^2 = .123$).

In the nonspeeded condition, the three-way ANOVA across both groups revealed a marginally significant main effect of Item Type, $F(1, 34) = 3.31$, $p = .078$, and a marginally significant interaction between Item Type and Anterior/Posterior, $F(2, 68) = 3.60$, $p = .055$. The interaction reflects the fact that the early old/new effect reach the significance only at parietal electrodes ($p < .010$, $\eta_p^2 = .205$), while it was marginally significant at central electrodes ($p = .081$, $\eta_p^2 = .087$).

To summarize, consistent with the prediction, the ERP effects in the early time window in the speeded condition were similar for preterm and full-term children. Both groups showed an early midline focused old/new effect, the putative ERP correlate of familiarity. In the nonspeeded condition, across both groups, a parietally distributed early old/new effect was obtained. This latter result is consistent with other studies that did not find mid-frontal old/new effects for children in standard item recognition memory tasks, but rather found an early parietal old/new effect (Kipp et al., 2010; Sprondel et al., in press; van Strien et al., 2009).

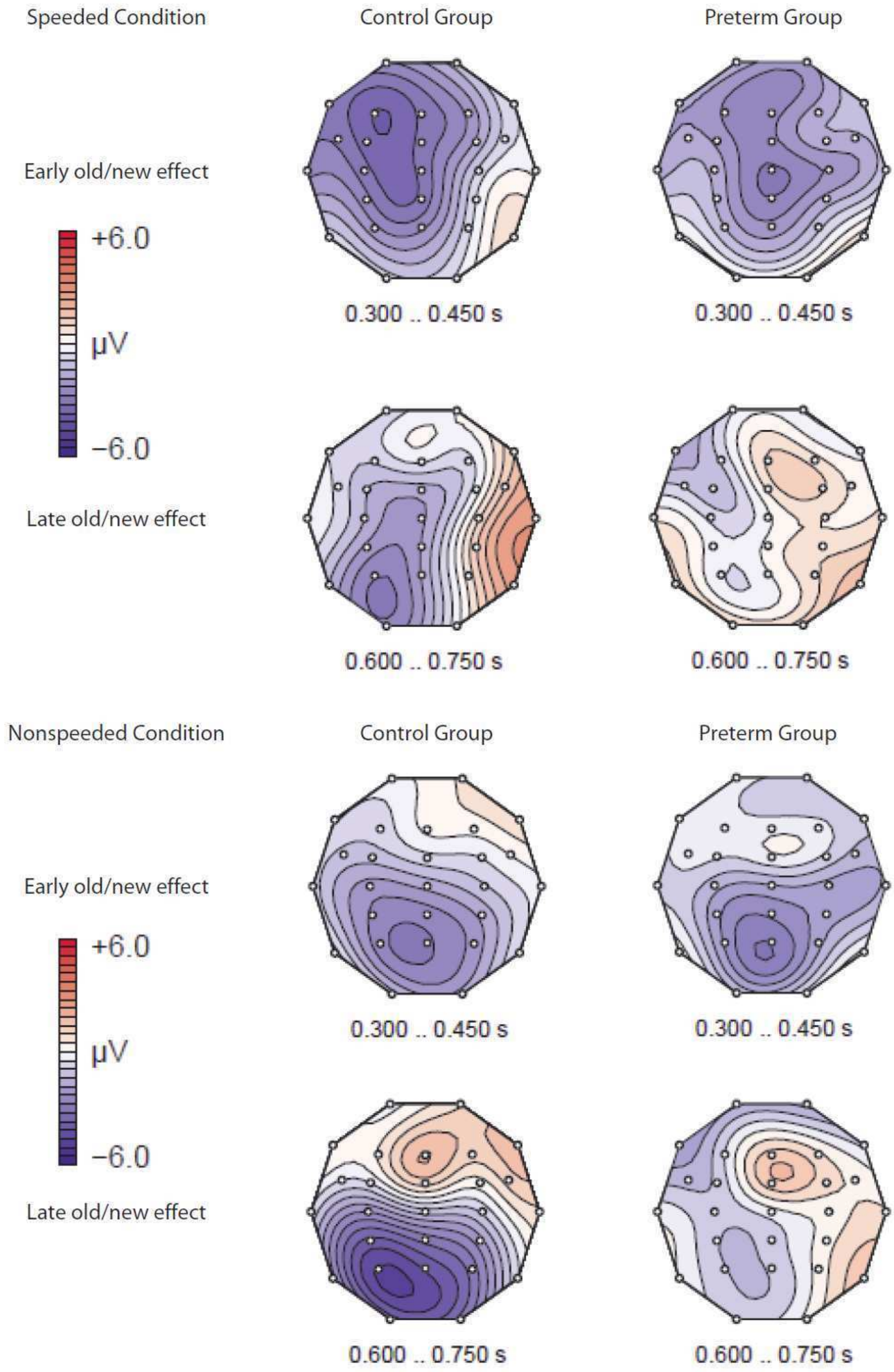

Figure 12: Scalp topographies of the early and late old/new effects (new minus old) for the full-term control group and preterm group in the speeded and nonspeeded response condition.

Late Time Window (600-750 msec)

In the late time window, the initial five-way ANOVA revealed no effects involving the factor Item Type (p values > .061). As this study was particularly interested in group-related patterns of retrieval activity in the late time window of the nonspeeded response condition, response condition- and group-specific analyses were performed.

In the speeded condition, for full-term children, there was a marginally significant interaction of Item Type, Anterior/Posterior, and Laterality, $F(4, 68) = 2.92$, $p = .062$. Follow-up analyses revealed that the old versus new differences did not reach significance at any electrode site (p values > .173). For preterm children, there was neither an effect of Item Type nor any interaction involving the Item Type factor (p values > .280).

In the nonspeeded condition, for full-term children, an Item Type x Anterior/Posterior interaction was found, $F(2, 34) = 8.89$, $p < .010$. Further analyses revealed an old/new effect at parietal, $F(1, 17) = 12.89$, $p < .010$, $\eta_p^2 = .431$, but not at central ($p = .243$) or frontal sites ($p = .428$). For preterm children, there was neither an effect of Item Type nor any interaction involving the factor Item Type (p values > .459).

To summarize, in the speeded condition, for full-term children, a marginally significant interaction was found, but the differences between old and new responses did not reach significance at neither recording site in the late time interval. For preterm children, no late parietal old/new effect was found when recognition decisions were required very quickly. Consistent with the prediction that recollection-based processes should be impaired in preterm children, without response deadline full-term children but not preterm children showed a parietally accentuated old/new effect, the correlate of recollective processing.

Relation between Gestational Age and ERP correlates of familiarity and of recollection. For preterm children, an early old/new effect was obtained in the speeded response condition, the putative ERP correlate of familiarity, but no late old/new effect was found in the nonspeeded response condition, the putative ERP correlate of recollection. The GA (in days, range: 187-234) of the preterm children was correlated with the old minus new difference at the electrode Cz in the early time window in the speeded response condition (i.e., magnitude of the ERP correlate of familiarity) and with the old minus new difference at the electrode Pz in the late time window in the nonspeeded response condition (i.e., magnitude of the ERP correlate of recollection) to assess if the degree of prematurity is associated with modulations in the neural systems underlying recognition memory retrieval. Partial correlations controlling for SES showed that the smaller the GA, the smaller the late old-new difference at Pz in the nonspeeded response condition (r = .57, *p* < .030; see Figure 13) and the greater the early old-new difference at Cz in the speeded response condition (r = -.61, *p* < .020; see Figure 14).

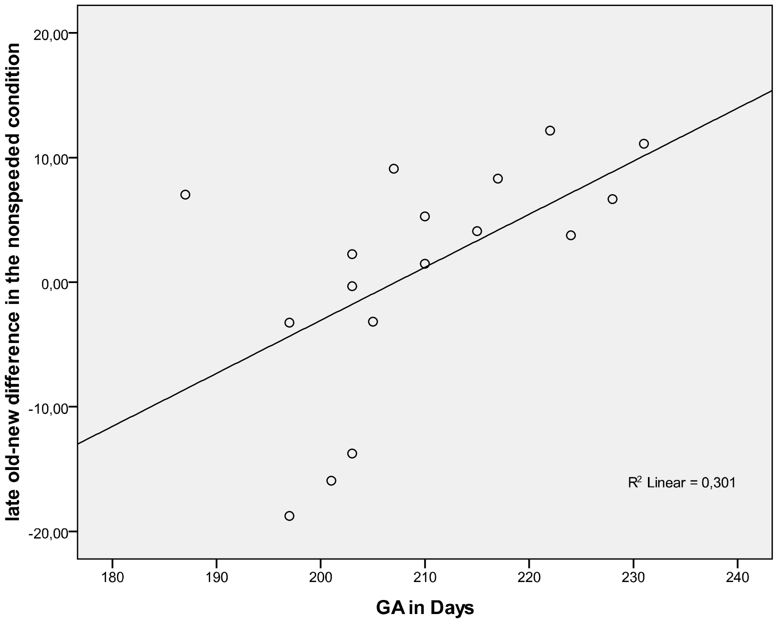

Figure 13: Correlation between the gestational age (GA) in days and the magnitude of the ERP correlate of recollection (late old/new difference at Pz in the nonspeeded condition).

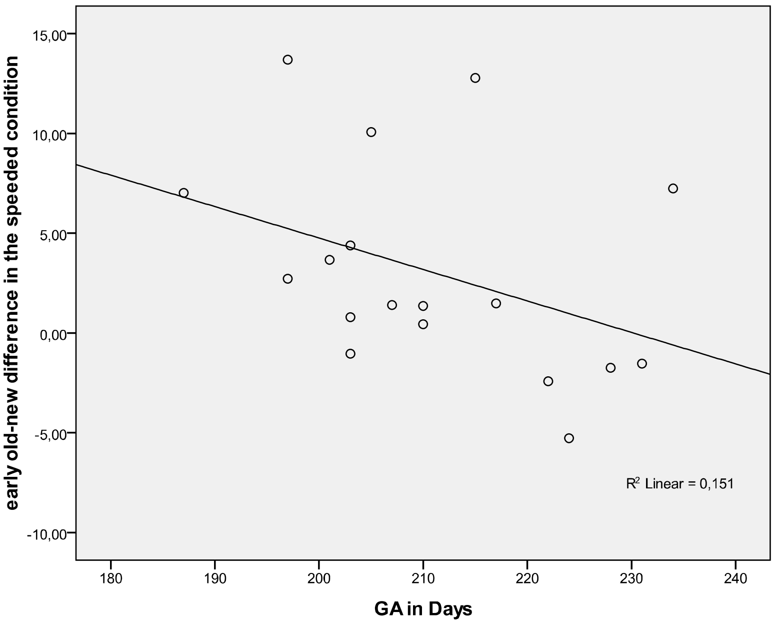

Figure 14: Correlation between the gestational age (GA) in days and the magnitude of the ERP correlate of familiarity (early old/new difference at Cz in the speeded condition).

As this study was particularly interested in potentially compensatory mechanisms within the brains of preterm children, the late old-new difference at Pz in the nonspeeded response condition was correlated with the early old-new difference at Cz in the speeded response condition. This analysis showed a negative correlation (r = -.40, *p* = .130), that is, the smaller the late old-new difference at Pz in the nonspeeded response condition, the greater the early old-new difference at Cz in the speeded response condition (see Figure 15). Thus, these results suggest that in preterm children, reduced recollective processing is possibly compensated by enhanced familiarity-based remembering.

For the full-term group, no correlation analyses were calculated, as the range of the GA in full-term children is too small to allow adequate testing of associations (range: 266-294 days).

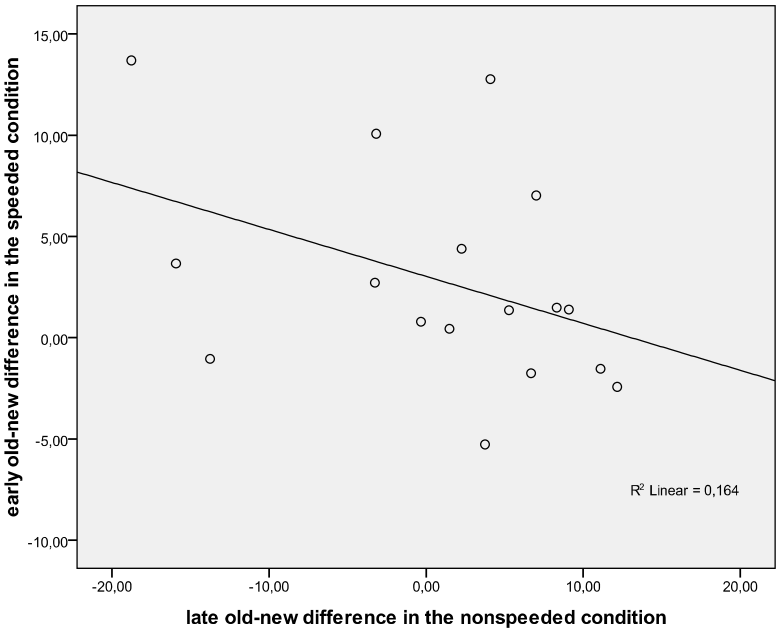

Figure 15: Correlation between the magnitude of the ERP correlate of recollection (late old/new difference at Pz in the nonspeeded condition) and the magnitude of the ERP correlate of familiarity (early old/new difference at Cz in the speeded condition).

7.5 Discussion

The main goal of Study 3 was to investigate the developmental trajectories of the ERP correlates of familiarity and recollection in preterm children with uncomplicated neonatal courses compared to the full-term control group of Study 2. In more detail, it was examined whether prematurity selectively affects the ERP correlate of recollection, as it would be expected if prematurity is associated with a decline in recollective processing due to reduced hippocampal volumes (Giménez et al., 2004; Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000; see also Study 1). For this purpose, the picture recognition memory task with a speeded and nonspeeded response condition of Study 2 was conducted with preterm children with uncomplicated neonatal courses. The ERPs of the preterm group were compared with those of the full-term sample of Study 2.

It was found that memory accuracy, response bias, and response times did not differ between groups, neither in the speeded nor in the nonspeeded response condition. This result is consistent with other studies that did not find group differences between preterm and full-term children in episodic memory performance (Curtis et al., 2006; Narberhaus et al., 2009; see also Study 1). As hippocampal volumes were found to be reduced in preterm children (Giménez et al., 2004; Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000; see also Study 1), this result possibly reflects functional compensation within the brains of preterm children. Support for this view comes from fMRI studies which indicate that structural damages in specific brain regions in preterm individuals are functionally compensated by other brain structures to reach a performance similar to those of full-term subjects (Curtis et al., 2006; Lawrence et al., 2009; Narberhaus et al., 2009; see also Ment & Constable, 2007).

As expected, in both groups, response times were faster and memory accuracy lower in the speeded compared to the nonspeeded response condition, suggesting that the effects of the response deadline manipulation were comparable across groups on the behavioral level. In addition, no differential effects of response conditions on setting the decision criterion (response bias) were found across groups, suggesting that similar decision strategies were used across response conditions and groups.

The analyses of the ERP data revealed a variety of results relevant for the understanding of the processes contributing to recognition memory and their developmental trajectories in preterm children. First, preterm and full-term children showed an early old/new effect in the speeded response condition. On the basis of its high resemblance with the mid-frontal old/new effect reported in other studies (Jäger et al., 2006; Opitz & Cornell, 2006; Rugg & Curran, 2007), this effect can be taken as the ERP correlate of familiarity. Notably, the observation that the mid-frontal old/new effect was highly similar in its temporal and topographic characteristics in full-term and preterm children suggests that familiarity-based processes are not affected by prematurity. The view that familiarity-based memory is not affected by prematurity is supported by a recent study by Rose et al. (2011). Using structural equation modeling, the authors assessed the dual-process theory of recognition memory in preterm and full-term infants longitudinally (at 1, 2, and 3 years). Familiarity was defined by measures of immediate and delayed recognition in visual paired-comparison tasks, recollection by these same measures plus those of recall memory, which was assessed with elicited imitation. The authors found that prematurity negatively affected recollection but not familiarity. Although these authors did not measure hippocampal volumes, they suggested that presumed hippocampal damage, in their study indexed by preterm birth, has selectively affected the recollection component of recognition memory.

Second, consistent with the prediction that recollection plays a negligible role when recognition judgments are given with a fast response deadline (Boldini et al., 2004, 2007), no parietal old/new effect was obtained for the late time interval, neither for preterm nor for full-term children (see Study 2 for further discussion of the late old/new difference in the speeded response condition in full-term children).

In the nonspeeded response condition, no early mid-frontal old/new effect, but an early parietally focused old/new effect was obtained across both children groups. This result is frequently found in standard item recognition memory tasks with children (Friedman et al., 2010; Kipp et al., 2010; Sprondel et al., in press; van Strien et al., 2009) and presumably reflects an early onset of recollective processing. However, this difference between old and new items in the early time interval diminished when group-specific analyses were performed.[5] This finding suggests that this effect is subtle, restricted to relatively large samples sizes (i.e., N = 35), and not reliable when smaller samples are analyzed (i.e., full-term group: N = 18, preterm group: N = 17). Further empirical data are required to disentangle the processing mechanisms reflected in this early old/new difference in children.

In accordance with previous studies that applied nonsensitive operational definitions of familiarity (Cycowicz et al., 2003; Czernochowski et al., 2005; Friedman et al., 2010; Hepworth et al., 2001; van Strien et al., 2009), there was no early mid-frontal old/new effect in the nonspeeded response condition for both children groups. However, the full-term children group showed a clear parietally focused late old/new effect, replicating a variety of former developmental ERP studies (Cycowicz et al., 2003; Czernochowski et al., 2005, 2009; Friedman et al., 2010; Sprondel et al., in press; van Strien et al., 2009). Notably, as it had been expected, there was no late parietal old/new effect in the nonspeeded response condition for preterm children. In light of the importance of hippocampal functioning for recollective processing (see Eichenbaum et al., 2007, for a review), this outcome may be taken as a reflection of the volume decline in the hippocampus in preterm children (Nosarti et al., 2002; Peterson et al., 2000; see also Study 1). Thus, as there was no group difference in the ERP correlate of familiarity, the reduced ERP correlate of recollection in preterm children can be taken to reflect a selective alteration in retrieval processing associated with prematurity.

Although the ERP correlate of recollection was reduced in preterm children, no group difference was found on the behavioral level. This finding implies a dissociation between memory performance and brain development. One possible reason for these diverging findings could be that ERPs are more sensitive in the detection of group differences. Another possibility for the observed dissociation between performance and the neural correlate of recollective

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[5] To examine whether the early parietally focused old/new effect in the nonspeeded response condition was modulated by group, group-specific analysis were performed in the early time window of the nonspeeded response condition. These analyses showed neither an effect of item type nor any interactions involving this factor for full-term (*p* values > .150) and preterm children (*p* > .250).

processing in preterm children is that other brain structures compensate for structural damages to the hippocampus (c.f. Narberhaus et al., 2009). Tentative support for this hypothesis of neural compensation was provided by the negative correlation between the magnitude of the ERP correlate of recollection and the magnitude of the ERP correlate of familiarity, suggesting that reduced recollective processing was associated with an increase in familiarity-based processing.

Importantly, the magnitude of the ERP correlate of recollection was also positively correlated with the GA at birth of the preterm children, while the magnitude of the ERP correlate of familiarity was negatively correlated with the GA. These results suggest that the degree of prematurity (i.e., GA at birth) is associated with the extent of modulation in the neural systems of preterm individuals. This is consistent with other studies using MRI (Davis et al., 2011; Peterson et al., 2000), which showed that the duration of gestation has lasting effects on neurodevelopment, and implies that the degree of prematurity is important for brain development.

An alternative interpretation for the observed group difference in recollection-based but not familiarity-based processes is a task-resource artefact (Ward, 2006). On the basis of a task-resource artefact, one might propose that recollection requires a greater amount of a cognitive resource or is the more difficult process than familiarity. Accordingly, it might be the case that increased processing difficulty has created the group difference between preterm and full-term children in recollection. Further empirical data are required to disentangle the processing mechanisms reflected in the reduced late parietal old/new effect in preterm children (see Study 4).

Taken together, the main goal of this study was to examine the developmental trajectories of the ERP correlates of familiarity and recollection in school-aged preterm children with uncomplicated neonatal courses compared to a full-term born control group. It has been shown that prematurity affects the ERP correlate of recollection but not the ERP correlate of familiarity. In addition, recognition memory performance was found to be preserved in preterm children. Moreover, for preterm children, a negative relationship between the magnitude of the ERP correlate of recollection and the magnitude of the ERP correlate of familiarity was found. This latter result suggests that in preterm children reduced recollective processing is compensated by enhanced familiarity-based remembering. Thus, it can be assumed that within the brains of preterm children at early school-age other brain structures compensate for reduced functioning of the hippocampus to reach a performance similar to those of full-term children.

8 Study 4

Closer Examination of the Task-Resource-Artefact-Hypothesis: Processing Difficulty Does Not Matter in Preterm Children

8.1 Background and Research Question

Study 4 aimed at a deeper understanding of the selective reduction in recollective processing in preterm children compared to full-term controls as found in Study 3. As mentioned in the discussion of Study 3, an alternative interpretation of the reduced magnitude of the ERP correlate of recollection but spared ERP correlate of familiarity in preterm children could be a task-resource artefact. This argument refers to the assumption that while recollection involves contextual retrieval of detailed information from a prior episode, familiarity reflects a fast assessment of the global similarity between study and test materials and is akin to automatic processing (Jacoby, 1991). By this, recollection can be assumed to require a greater amount of cognitive resources or is the more difficult process than familiarity. As mentioned in the aims of the present studies, the term task-resource artefact is used when two tasks (e.g., A and B) share the same neural/cognitive resource but one task (e.g., B) uses it more. If brain damage depletes this resource then task B may be selectively impaired (Ward, 2006). If the task-resource artefact holds true and preterm children perform worse compared to full-term children, then preterm children should be selectively impaired in tasks that require a greater amount of cognitive resources or that are more difficult compared to full-term children. In this study, processing difficulty was manipulated in two ways to directly examine whether preterm children are selectively impaired in tasks that are more difficult compared to a full-term control group.

To this end, a continuous recognition memory experiment with two runs was used. The critical manipulation of this task was that the first run of this experiment required relatively simple old/new recognition judgments (measure of item memory), whereas the second run served as a measure of source memory by means of an exclusion task. As source memory relies upon controlled memory processes to a greater degree than simple old/new recognitions (Johnson, Hashtroudi, & Lindsay, 1993), it can be assumed that the exclusion task requires a relatively greater amount of cognitive resources. As a second manipulation of processing difficulty, the exclusion task required the rejection of items repeated with either short or long item lags. In the short lag condition, items that were presented in the second half of the first run were presented again in the first half of the second run (short lag until these items were repeated in the second run). In the long lag condition, items that were presented in the first half of the first run were presented again in the second half of the second run (long lag until these items were repeated in the second run). As there are more intervening or distractor items across the repetition of an item in the long lag condition, a higher amount of interference is induced compared to the short lag condition. Thus, it can be assumed that memory retrieval in the long lag condition requires a relatively greater amount of cognitive resources.

To summarize, Study 4 aimed to contribute further evidence for the view that recollective processing is selectively reduced in preterm children compared to full-term controls by examining whether a task-resource artefact can alternatively explain the results of Study 3.

8.2 Hypotheses

If a task-resource artefact holds true, preterm children should perform lower in tasks that require a greater amount of cognitive resources compared to full-term children, that is, a group difference should emerge for source memory accuracy and for memory accuracy in the long lag condition. In contrast, simple old/new recognitions (i.e., item memory accuracy) and memory accuracy in the short lag condition should not differ between preterm and full-term children.

8.3 Methods

Participants

As this study was conducted several weeks after Study 3, four preterm children and six full-term control children of Study 3 could not be recruited once more. For the remaining 12 full-term children and 14 preterm children, there were no significant differences according to corrected age, gender, GA, BW, and SES compared to the initial samples of Study 3. The children received € 8.00/hour for participation and written informed consent was obtained from the parents of the children before the experiment. In addition, the children signed assent forms.

Stimuli

For this experiment, 140 stimuli from the black and white version of the Snodgrass and Vanderwart line drawings of common objects and animals were selected (Rossion & Pourtois, 2004). Of these 140 pictures, 20 pictures were used as practice items, 60 as filler items, and 60 as experimental items.

Procedure

The experiment consisted of two runs, which were separated by a ten-minute break (see Figure 16 for illustration of the design). Participants were given a practice phase with 14 items per phase prior to each of the two runs. The procedure in both runs was the same. Each picture was presented for 1000 msec at the center of the computer screen on a white background, preceded by a fixation cross (300 msec). Responses were recorded within a period of 1500 msec after stimulus onset. Following each response, visual feedback was presented for 500 msec in the form of a smiley face (correct) or a frown face (incorrect). After a fixed intertrial interval of 1000 msec, the next fixation cross appeared.

Before the first run, participants were told that they will see pictures that are repeated at various points. The task instructions were to attend to the pictures carefully and to judge each item for its repetition status by pressing the “new” button for first presentations with one of the two index fingers and the “old” button for repetitions with the other index finger. The response hands were counterbalanced across participants. In the first run, 60 pictures were presented in randomized order and repeated with lags varying between 10 and 15 intervening items. In order to include the lag manipulation and meet the experimental constraint that items featuring the same repetition status did not occur more than four times consecutively, 30 additional filler items were included. These items were also repeated at variable lags. The experimental conditions in the first run entering subsequent analyses were first presentations (new) and the repetitions (old) of the pictures.

Before the second run, participants were told that they will now see pictures, some of which either had already been presented in the first run or were new. The task instruction was to judge each item solely according to its within-run repetition status and to ignore across-run repetitions. That is, items repeated from the first run and presented for the first time in the second run had to be judged as “new” (non-targets). When these items were repeated within the second run, they had to be judged as “old” (targets). By this, each of the 60 pictures studied in the first run was repeated two more times in the second run in a pseudo-randomized order. In addition, 30 additional filler items were presented and repeated at variable lags. These filler items had also to be classified according to their “old-new” status within this second run. In order to include long and short lag conditions, different distances between the repetition of items across the two runs were used. In the long lag condition, items that were presented in the first half of the first run were shown again in the second half of the second run (long lag until these items were repeated in the second run). In the short lag condition, items that were presented in the second half of the first run were shown again in the first half of the second run (short lag until these items were repeated in the second run).

To ensure that the children had understood the procedure, they were asked to explain the instruction to the experimenter using their own words before each run and were corrected if necessary.

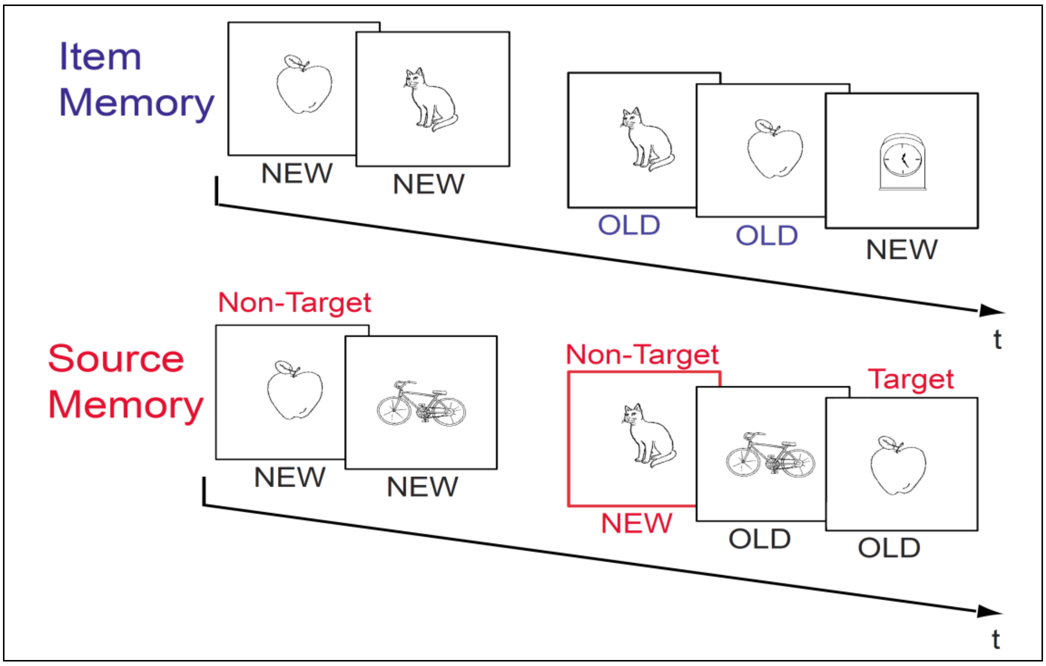

Figure 16: Illustration of the two runs of the continuous recognition memory experiment; Item Memory = first run; Source Memory = second run.

Data Analyses

SPSS 17.0 statistical package was used for all analyses. Trials that were not responded to and trials with filler items were removed from behavioral analysis. Memory accuracy was evaluated using the discrimination index Pr (the proportion of false alarms was subtracted from the proportion of hits of within-run repetitions). For item memory accuracy, false alarms to new items were subtracted from hits in the first run (Pr_Item = hits-false alarms). For source memory accuracy, false alarms to non-targets were subtracted from the target hit rates in the second run (Pr_Source = Target hits-Non-Target false alarms). For memory accuracy in the long lag condition, false alarms to long lag non-targets were subtracted from the target hit rates in the second run (Pr_long = Target hits-Non-Target false alarms_long). For memory accuracy in the short lag condition, false alarms to short lag non-targets were subtracted from the target hit rates in the second run (Pr_short = Target hits-Non-Target false alarms_short). RTs were measured separately for new, old, non-target, target, non-target_short, and non-target_long items. Response bias (Br; Snodgrass & Corwin, 1988) was calculated separately for the item memory task (Br_Item = false alarms / (1-Pr_Item)), the source memory task (Br_Source = Non-Target false alarms / (1-Pr_Source)), the long lag condition (Br_long = Non-Target false alarms_long / (1-Pr_long)), and the short lag condition (Br_short = Non-Target false alarms_short / (1-Pr_short)). To examine group effects, repeated-measures ANOVAs with the factor Group (full-term control children, preterm children) were conducted.

8.4 Results

Memory accuracy, response bias, and response times for both groups are illustrated in Table 7. The ANOVA with the factors Memory Task (Item vs. Source) and Group on the Pr-measures yielded only a main effect of Memory Task, *F*(1, 24) = 18.08, *p* < .001. Both groups showed poorer source discrimination performance compared to item memory performance. As this study was particularly interested in group-related patterns of task difficulties, an ANOVA with the factors Lag Condition (short vs. long) and Group on the Pr-measures was additionally calculated. This ANOVA showed only a reliable effect of Lag Condition, *F*(1, 24) = 15.88, *p* < .010, indicating that both groups showed poorer discrimination performance in the long lag condition compared to the short lag condition.

Regarding response bias, the ANOVA with the factors Memory Task and Group revealed a main effect of Memory Task, *F*(1, 24) = 11.15, *p* < .010, and an interaction among Memory Task and Group, *F*(1, 24) = 5.22, *p* < .040. Follow-up analyses revealed that for full-term children the criterion for “old” judgments was more liberal in the source compared to the item memory task (*p* < .010), while this difference was not found for preterm children (*p* > .490). The ANOVA with the factors Lag Condition (short vs. long) and Group on the Br-measures revealed only a reliable effect of Lag Condition, *F*(1, 24) = 10.95, *p* < .010, indicating that the criterion for “old” judgments was more liberal across both groups in the long compared to the short lag condition.

Table 7: Mean RTs (msec) for correctly recognized New, Old, Non-Target, Non-Target_short, Non-Target_long, and Target items. The discrimination index (Pr) and response bias (Br) were calculated for item and source memory as well as for the short and long lag condition. The standard errors of the means are given in parentheses.

	Control Group (N = 12)	*Preterm Group (N = 14)*
RT Correct Rejections		
New	757 (22)	741 (19)
Non-target	800 (23)	765 (18)
Non-target_short	793 (28)	753 (19)
Non-target_long	806 (20)	777 (19)
RT Hits		
Old	756 (22)	738 (17)
Target	759 (22)	745 (21)
Performance Estimate (Pr)		
Pr_Item	0.82 (0.03)	0.78 (0.03)
Pr_Source	0.69 (0.05)	0.68 (0.04)
Pr_short	0.72 (0.04)	0.73 (0.03)
Pr_long	0.67 (0.06)	0.63 (0.05)
Bias Estimate (Br)		
Br_Item	0.38 (0.02)	0.47 (0.05)
Br_Source	0.58 (0.04)	0.50 (0.05)
Br_short	0.56 (0.03)	0.44 (0.05)
Br_long	0.60 (0.04)	0.57 (0.05)

The ANOVA on RTs with the factors Item Type (New vs. Old vs. Non-Target vs. Target) and Group yielded a main effect of Item Type, $F(3, 72) = 7.06$, $p < .010$. In both groups, correct responses to new items were of the same speed as correct responses to old items ($p = .530$) and Targets ($p = .599$). In contrast, in both groups, correct responses to new items were reliably faster than correct responses to Non-Targets (*p* < .001). The ANOVA with the factors RT-Lag-Condition (Non-Target_short vs. Non-Target_long vs. Target) and Group yielded a main effect of RT-Lag-Condition, *F*(2, 48) = 8.12, *p* < .010. In both groups, correct responses to Targets were reliable faster than correct responses to Non-Targets_long (*p* < .010) and to Non-Targets_short (*p* < .050).

Taken together, in showing comparable memory accuracy for preterm and full-term children in the item and source memory task as well as in the conditions with long and short lag manipulations, the present results provide no evidence for the view that preterm children are more impaired on tasks that require a greater amount of cognitive resources compared to full-term children.

As the lack of significant group differences in more difficult tasks might be attributed to the small preterm sample size in this experiment (N = 14), the same analyses were repeated with nine additional preterm children. These preterm children were also recruited from archives of the Department of Pediatrics and Neonatology at the university hospital in Homburg. Again, for these 23 preterm and 12 control children, there were no significant differences according to corrected age, gender, GA, BW, and SES compared to the initial samples of Study 3. The behavioral data for these samples are summarized in Table 8. All analyses replicated each of the former results. Thus, the present outcomes provide no evidence for the view that preterm children are disproportionally impaired on tasks that presuppose a relatively high amount of cognitive resources compared to full-term children.

Table 8: Mean RTs (msec) for correctly recognized New, Old, Non-Target, Non-Target_short, Non-Target_long, and Target items. The discrimination index (Pr) and response bias (Br) were calculated for item and source memory as well as for the short and long lag condition. The standard errors of the means are given in parentheses.

	Control Group (*N = 12*)	*Preterm Group* (*N = 23*)
RT Correct Rejections		
New	757 (22)	753 (17)
Non-target	800 (23)	783 (21)
Non-target_short	793 (28)	772 (23)
Non-target_long	806 (20)	795 (19)
RT Hits		
Old	756 (22)	760 (18)
Target	759 (22)	762 (20)
Performance Estimate (Pr)		
Pr_Item	0.82 (0.03)	0.72 (0.03)
Pr_Source	0.69 (0.05)	0.62 (0.03)
Pr_short	0.72 (0.04)	0.67 (0.03)
Pr_long	0.67 (0.06)	0.57 (0.04)
Bias Estimate (Br)		
Br_Item	0.38 (0.02)	0.46 (0.04)
Br_Source	0.58 (0.04)	0.51 (0.03)
Br_short	0.56 (0.03)	0.44 (0.04)
Br_long	0.60 (0.04)	0.57 (0.04)

8.5 Discussion

Study 4 aimed at investigating whether a task-resource artefact is an alternative interpretation of the selectively reduced recollective processing in preterm children compared to full-term controls found in Study 3. Hence, in this study, task difficulty was manipulated to examine whether preterm children are disproportionally impaired in tasks that are more difficult or require a greater amount of cognitive resources compared to a full-term control group. To do this, a continuous recognition memory experiment with short and long repetition lags across two runs was used. In this paradigm, task difficulty was manipulated, first, between an item memory task (easier task) and a source memory task (more difficult task). While the first run of this experiment served as a measure of item memory, in the second run source memory was operationalized by means of a memory exclusion task. The second manipulation of task difficulty was achieved by using short lags (easier task) and long lags (more difficult task) for the repetition of items across both runs. As there are more intervening items across the repetition of an item in the long lag condition, a higher amount of interference should be induced compared to the short lag condition. In case that a different processing of task difficulty between preterm and full-term children can explain the results of Study 3, it was hypothesized that a group difference should emerge for source memory accuracy and for memory accuracy in the long lag condition, as these are the tasks that are assumed to require a greater amount of cognitive resources. By contrast, no group difference should emerge for item memory accuracy and for memory accuracy in the short lag condition, as these are the tasks that are assumed to require a lower amount of cognitive resources.

Contrary to the prediction of a task-resource artefact, the groups did not differ in their memory accuracy, neither in their item and source memory performance nor in their performance in the short and long lag condition. The lack of group differences in the more difficult retrieval conditions can be taken as a support for the view that the group difference in recollective processing found in Study 3 cannot be accounted for by poorer cognitive resources of preterm children.

Consistent with previous reports that children show a selective attenuation of memory performance in a condition requiring controlled episodic memory retrieval (Czernochowski et al., 2005, 2009; Sprondel et al., in press), memory accuracy in the source memory task relative to the item memory task was lowered to 84% and 87% in the full-term and preterm group, respectively (see Table 7). In a similar vein, memory accuracy in the long lag condition relative to the short lag condition was lowered to 93% and 86% in the full-term control and preterm group, respectively. As in addition both children groups showed prolonged response times to non-targets in the source memory task, it can be concluded that the effects of the task difficulty manipulation were highly comparable across groups. In light of the fact that participants in both groups used a more liberal response criterion in the long lag compared to the short lag condition, it could be suggested that there were differential effects of task difficulty on setting the decision criterion (response bias) in both groups. Notably, while the full-term children used a more liberal response criterion in the source compared to the item memory task, this difference was not found for preterm children. As apparent from Table 7, preterm children used a rather neutral response criterion in both the item and source memory task. However, this group difference did not affect the memory accuracy, as the preterm children did not differ from controls in their memory performance. Further empirical data are required to disentangle the processing mechanisms reflected in the group difference on setting the decision criterion in both memory tasks.

As one could argue that the lack of significant group differences was caused by the small sample size, the same analyses were repeated with nine additional preterm children. Yet even there was no group difference for the source memory task or the condition with the long lag manipulation, replicating the former results that did not show differences between preterm and full-term children in the more difficult tasks.

As one could further argue that the sample size of the full-term control group was too small as well, the question of power was further explored by estimating the critical sample size for the memory accuracy for the source memory task (Pr_Source) and the condition with the long repetition lag (Pr_long).

For this analysis the program G*Power was used (Faul et al., 2007). The effect size (*d*) was calculated on the basis of the group mean values and standard deviations of the Pr_Source and Pr_long. Alpha and 1-β were set to .05 and .80, respectively. This analysis revealed that, given the between-group differences in Pr_Source and Pr_long obtained in this latter analysis, sample sizes of 58 and 43 participants per group would have been required to reject the null hypothesis of no group differences in Pr_Source and Pr_long, respectively. Thus, due to the relatively small sample sizes in the present study, the conclusions are only preliminary and must await reassessment in a follow-up study with larger sample sizes.

In conclusion, by showing no group differences in memory accuracy between preterm and full-term children, the present data suggest that a task-resource artefact does not seem to provide an alternative explanation for the selective reduction in recollective processing in preterm children as compared to full-term controls. It has been shown that preterm children reach performance similar to those of full-term children, irrespective of the difficulty of the task. By this, Study 4 provided evidence that the findings of Study 3 were not confounded or influenced by the level of task difficulty. In addition, the present findings add to the gradually growing body of evidence showing that on the behavioral level, preterm children with uncomplicated neonatal courses do not differ from full-term children in episodic memory performance.

9 General Discussion

The global aim of the four studies reported in the present thesis was to investigate the development of declarative long-term memory and its subsystems in school-aged preterm children with uncomplicated neonatal courses as compared to age-matched full-term control children by applying different methods and approaches of cognitive psychology. In particular, the focus was on the development of episodic memory and its specific retrieval processes in these children groups. Through different measurement methods, this thesis sought to gain converging evidence for developmental differences between preterm and full-term children, as any method per se has unique strength and limitations. To this end, four experiments were conducted. The goals of Study 1 were firstly to explore developmental differences in the two subsystems of declarative long-term memory (episodic and semantic memory) between the preterm and full-term group and secondly to address the question about the relationship between these subsystems and hippocampal volume in both groups. For these purposes, standardized neuropsychological tests, a recognition memory experiment, and structural MRI were used. Study 2 and Study 3 investigated the development of the two episodic memory retrieval processes, familiarity and recollection, in both children groups and a group of young adults by means of ERPs, capitalizing on the sensitivity of ERPs to the neural correlates underlying familiarity and recollection. Finally, Study 4 aimed to rule out the alternative hypothesis that reduced recollective processing in preterm children as revealed by Study 3 is confounded with potentially poorer cognitive resources of preterm children. In this way, Study 4 aimed to substantiate the view that recollective processing is selectively reduced in preterm children as compared to full-term controls. In the following, the main findings and converging results will be summarized and discussed to draw more general conclusions.

The results of Study 1 provide evidence for changes in declarative long-term memory in preterm children as compared to full-term controls. Specifically, while there were no group differences in episodic memory performance, preterm children showed lower performance in semantic memory tasks relative to full-term controls. Importantly, after controlling for the influence of IF and SES on semantic memory performance, the group difference in performance in the HAWIK-R subtest vocabulary diminished, whereas the group difference in performance in the subtests general knowledge and general comprehension remained statistically significant. This pattern indicates that preterm children are not generally impaired in their declarative long-term memory performance, but rather show selective deficits in semantic memory that are not fully explainable by IF and SES. Through the application of structural MRI, it was possible to estimate structural changes in the hippocampi of the children groups and to combine these neuroimaging findings with the behavioral data of the neuropsychological tests and the recognition memory experiment. This allowed to investigate the relationship between the hippocampal volume and declarative long-term memory performance in both groups.

With regard to structural changes in the brains of preterm children with uncomplicated neonatal courses relative to an age-matched full-term control group, the findings of Study 1 support recent findings with preterm individuals which showed both reduced cerebral volumes as well as hippocampal volume reductions (Nosarti et al., 2002; Peterson et al., 2000). Although the pathophysiological mechanisms for the disproportionate hippocampal volume loss are still unresolved and a matter of debate, recent studies indicate that damage to the hippocampus may lead to altered neural activation within the brains of preterm individuals, which presumably functionally compensates for the consequences of prematurity to maintain competent performance (Narberhaus et al., 2009). The functional compensation hypothesis in preterm children is compatible with the assumption of the existence of neural plasticity following early brain injury, as is suggested by functional neuroimaging findings (see Nosarti & Rifkin, 2010, for a review). Plasticity refers to the capacity of the nervous system to modify its organization and ultimately its functions throughout the lifetime of individuals. Such modifications can be caused by positive (e.g., responsive caregiving, appropriate stimulation and learning) and negative (e.g., stress, drug, malnutrition, brain injury) experiences (Kolb, Gibb, & Robinson, 2003). Following this line of thought, the brains of preterm individuals may be substantially different in structure and function as compared to full-term individuals because they presumably have acquired experiences which are different from those of full-term individuals.

For full-term children, a positive relationship between hippocampal volume and general episodic memory performance (i.e., delayed recall performance in the Rey-Osterrieth Complex Figure) was found. This result is compatible with the view that the hippocampus is an important mediator of episodic long-term memory (Tulving & Markowitsch, 1998). Moreover, the fact that in full-term children the posterior two-thirds of hippocampal volume were related to memory accuracy in the nonspeeded response condition in the recognition memory experiment converges with the view that the posterior two-thirds of the hippocampus are more involved in recollection-based memory retrieval (Daselaar, Fleck, & Cabeza, 2006; Ludowig et al., 2008).

Study 1 also suggests that semantic memory performance is not related to hippocampal volume in full-term children. This result is consistent with the view of a neuroanatomic distinction between episodic and semantic memory, which proposes that episodic memories are hippocampus-dependent, whereas semantic memories can exist independently of the hippocampus (see Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006, for a review). In this context, a considerable body of evidence has emerged over the past decades that favors the view of a distinction between the acquisition and retrieval status of semantic and episodic memory (see Ryan et al., 2008, for a review). The hippocampus appears to play an important role in the acquisition, but not retrieval, of semantic memories, while supporting both the acquisition and retrieval of episodic memories. Consistent with this view, the present findings provide further evidence that at least for the retrieval of semantic and episodic memory, there seems to be a distinction for the hippocampal involvement.

With regard to the relationship between hippocampal volume and semantic and episodic memory performance in preterm children, the picture is less obvious. Although hippocampal volumes were reduced in preterm children relative to the age-matched full-term group even after correcting for reduced cerebral volume, no relationship of hippocampal volume with episodic or semantic memory performance was obtained. This result may be consistent with the assumption of a functional compensation within the brains of preterm individuals (Curtis et al., 2006; Narberhaus et al., 2009). Due to neural compensation for the consequences of prematurity, reduced functioning of the hippocampus may not affect memory performance. Following this line of thought, altered patterns of structure-function relationships may be observed following early brain injury because functions are remapped onto other undamaged areas of the brain (see Stiles, Reilly, Paul, & Moses, 2005, for a review). This dovetails with the fact that although several studies have revealed reduced hippocampal volume in preterm individuals (Narberhaus et al., 2009; Nosarti et al., 2002; Peterson et al., 2000), memory performance is often unimpaired (Curtis et al., 2006; Narberhaus et al., 2009). However, the results of Study 1 do not provide the substantiation for a compensation mechanism, that is, it remains unclear which other brain structures may compensate for hippocampal compromise. Nevertheless, the pattern of findings suggests that recovery from structural damage can occur in the brains of preterm children. For instance, Narberhaus et al. (2009) showed reduced absolute amounts of gray matter bilaterally in the hippocampus in preterm as compared to full-term adults. In addition, these authors did not find any group differences in episodic memory performance, even though the preterm adults were found to activate different neural networks than controls during task completion. By this, the study by Narberhaus et al. (2009) even provided direct evidence for the activation of different neural networks in preterm individuals as compared to full-term controls to reach performances similar to those of full-term participants.

The findings of Study 3 added further evidence for the assumption of functional compensation within the brains of preterm children. In particular, this study focused on the subprocesses of recognition memory that can be situated within the framework of episodic memory. From a dual-process point of view, recognition memory involves two qualitatively distinct memory retrieval processes – familiarity and recollection. Evidence for the dissociation of both processes has come from studies on neurological patients, neuroimaging studies, and behavioral studies. These investigations indicate a division of labor within the medial temporal lobes, with the recollective process depending largely on the hippocampus and familiarity on the anterior part of the parahippocampal region centered around the perirhinal cortex (Aggleton & Brown, 1999, 2006; Eichenbaum et al., 2007; Norman & O'Reilly, 2003; Yonelinas, 2002).

Before discussing the results of Study 3, it is important to sum up the results of Study 2, which was conducted in anticipation of Study 3. While ERP studies have revealed that the late parietal old/new effect, the putative ERP correlate of recollection, is highly similar for children and adults, the early mid-frontal old/new effect, the putative ERP correlate of familiarity, has not been reported for children so far, even though some behavioral studies suggest that children at early school-age use familiarity. To elucidate this latter issue, a response-deadline procedure was used to examine whether full-term children of early school-age show a mid-frontal old/new effect, the putative ERP correlate of familiarity, under a speeded response condition that encouraged familiarity-based remembering and diminished recollective processing. More specifically, capitalizing on the different temporal dynamics of familiarity and recollection, two experimental response conditions were created that differed from each other in the degree to which they promote familiarity-based (speeded response condition) and recollection-based (nonspeeded response condition) processes. Additionally, to examine age differences in the ERP correlates of familiarity and recollection, the results of the full-term children were compared with the results of young adults.

Consistent with the behavioral data of other studies (Billingsley et al., 2002; Ghetti & Angelini, 2008), the ERP results of Study 2 support the view that familiarity is available for recognition judgments at early school-age under specific circumstances. Both groups showed an early mid-frontal old/new effect, the putative ERP correlate of familiarity, in the speeded response condition, whereas in the nonspeeded response condition a late parietal old/new effect, the putative ERP correlate of recollection, was found for both groups. Considering the generally lower memory accuracy of the children, this result pattern indicates that children at early school-age use a weaker and less matured version of the same explicit memory network used by adults.

Turning to the discussion of the results of Study 3, it is important to refer back to the findings of Study 1. As in Study 1, developmental differences between preterm children with uncomplicated neonatal courses and full-term children were tried to be identified in Study 3. As the results of Study 1 suggested that preterm children at early school-age recruit a neural network for episodic memory that differs from the one used by full-term children, Study 3 focused on the developmental trajectories of the ERP correlates of familiarity and recollection in preterm children as compared to the full-term children of Study 2. To this end, the same experimental design with a speeded and nonspeeded response condition as in Study 2 was used. It was hypothesized that prematurity selectively affects the ERP correlate of recollection, as the hippocampus, which showed a reduced volume in preterm children, is assumed to be critical for recollection (Rose et al., 2011).

Consistent with this view, recollective processing was diminished in preterm children compared to full-term controls. Moreover, the behavioral data replicated the findings of Study 1, showing no impairments in episodic memory performance in preterm children relative to full-term controls. Thus, while hippocampal dysfunction may affect retrieval processing, – and especially recollective processing – it does not seem to disrupt episodic memory performance. In other words, in preterm children, episodic memory performance did not conform to the pattern of ERP correlates, which indicated a selective reduction of recollective processing. It is conceivable that this dissociation between brain function and memory performance reflects the fact that retrieval processing in preterm children is altered in a relatively subtle way. The current findings suggest that ERPs provide sufficient sensitivity to detect these changes.

Consistent with the view that the duration of gestation has lasting effects on neurodevelopment (Davis et al., 2011; Peterson et al., 2000), Study 3 revealed that within the preterm children group the GA at birth is positively correlated with the magnitude of the ERP correlate of recollection and is negatively correlated with the magnitude of the ERP correlate of familiarity. Together with the finding that the magnitude of the ERP correlate of recollection was negatively correlated with the magnitude of the ERP correlate of familiarity, tentative direct support is provided for the proposed functional compensation within the brains of preterm children. This means that within the brains of preterm children reduced recollective processing may be compensated by enhanced familiarity-based remembering. In this context, the findings of Study 4 were especially relevant because they ruled out that a task-resource artefact can explain the results of Study 3, and by this substantiated the reduction in recollective processing in preterm children. Investigating the preterm and full-term group of Study 3 with an item and source memory task as well as with the application of short and long lags between the repetition of items across two runs, it was possible to demonstrate that preterm children reach performances similar to those of full-term participants, irrespective of the difficulty of the tasks. By this, Study 4 extended the knowledge on the proposed association between prematurity and reduced recollective processing, because this selective reduction was not confounded or influenced by the level of task difficulty.

Further support for the view that preterm birth results in the engagement of alternative or additional neural systems comes from a recent study by Gozzo et al. (2009). Using an fMRI passive auditory language task, these authors examined the connectivity between language regions in preterm and full-term children at early school-age. The preterm children showed different patterns of functional connectivity from Wernicke’s reference region (left-sided) with increased connectivity to right-sided regions as compared to full-term controls. These findings again suggest that neural plasticity in the preterm brain permits the recruitment of alternative pathways for neural processing involved in specific cognitive functions.

To summarize, the reported findings shed light on the developmental differences in declarative long-term memory between preterm and full-term born children at early school-age. While hippocampal volume was significantly correlated with episodic but not semantic memory performance in full-term children, neither relationship was shown in preterm children, even though hippocampal volumes were reduced in the preterm group. The reported impairments in semantic memory in preterm children relative to full-term controls suggest that semantic memory is affected by prematurity. With respect to episodic memory performance, full-term and preterm children did not differ, although the ERP correlate of recollection was selectively reduced in preterm children. These findings add to the considerable body of evidence within the research on preterm individuals, which indicates that alterations in key brain regions following preterm birth may result in functional changes in distributed brain systems. It is especially the change in recollective processing in preterm children with uncomplicated neonatal courses which is supported by the results of the present thesis. These changes are most likely due to hippocampal volume reductions. They may underlie the development of alternative neural pathways which enable the preterm children to reach performance similar to those of full-term participants. Given these results, for the first time electrophysiological evidence is provided for the assumption of the development of compensatory mechanisms in the preterm brain.

10 Perspectives

The results of the studies reported in the present thesis speak for the existence of processes of neural plasticity within the brains of preterm children. In other words, compensatory neural processes may facilitate the reorganization of existing brain tissue – at least in the brain systems underlying episodic memory. This conclusion was drawn on the basis of ERPs, in particular, on the basis of the negative correlation between the magnitude of the ERP correlate of recollection and the magnitude of the ERP correlate of familiarity. However, this conclusion could be further strengthened by applying functional MRI, which allows the monitoring of metabolic changes in specific brain structures, for instance, in the brain regions thought to support episodic memory. By this, it would be possible to specify the exact brain structures underlying episodic memory in preterm and full-term children.

It can also be speculated whether developmental delays in the maturation of neural circuits which underlie episodic memory retrieval processing provide an alternative explanation for the present findings in preterm children (Luciana, 2003), as the present conclusion of neural plasticity within the preterm brain merely refers to a preterm sample with a restricted age range (7-11 years) and by this do not provide comparative data of younger and older preterm participants. Notably, Rose et al. (2011) found that recollection is selectively affected in one- to three-year-old preterm children, even if only behavioral data are used. One could speculate that the potential compensatory mechanisms in the brains of preterm individuals have not fully evolved until the early school-age. In other words, younger preterm children (i.e., children less than four years old) with hippocampal damage might still be unable to access other matured and presumably optimal brain circuits. By this, age differences on the behavioral level in preterm children might reflect developmental delays (Luna, Padmanabhan, & O'Hearn, 2010). Thus, longitudinal assessments might provide more evidence for the suggestion that neural plasticity in the preterm brain permits the recruitment of alternative pathways for memory retrieval processing to reach performances similar to those of full-term participants. Moreover, longitudinal neurodevelopmental research combining structural and functional neuroimaging may help to provide a better support for the cognitive development of preterm children in the earlier periods of life.

In addition, it is necessary to replicate the present ERP results in preterm children, as according to the current state of knowledge, this was the first time that recognition memory processes were assessed in preterm children at early school-age by means of ERPs. In this context, it might be worthwhile to use a source memory task, as this allows deriving a more sensitive estimate of recollection.

Further research is also needed to investigate the neural mechanisms which underlie the reported selective deficits in semantic memory in preterm children, as the present findings merely suggest that the hippocampus is not involved in this form of memory but cannot elucidate which other brain structures are critical. Given the relationship between language processing and verbal comprehension IQ scores as reported in the study by Peterson et al. (2002), one could speculate that semantic memory deficits are caused by alterations in the brain systems which are important for language processing and that these neural networks have not fully recovered in preterm children until the early school-age.

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