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Neuroimaging of episodic memory development during childhood

A multi-component approach

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Thèse de doctorat de Neurosciences

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Titre : *Neuroimagerie du développement de la mémoire épisodique pendant l'enfance*

Résumé :
Nous avons peu de souvenirs avant l'âge de 6 ans : ce phénomène, appelé « amnésie de l'enfance », illustre le développement considérable de la mémoire épisodique (ME) au cours des premières années de la vie. La ME est une fonction cognitive multiforme comprenant des « composantes » cognitives aux corrélats cérébraux différents. Le développement de la ME pourrait donc résulter de trajectoires développementales propres à ses composantes, une question qui reste mal comprise. Notre objectif était d'examiner le développement de la ME via l'étude des associations entre ses composantes et leurs corrélats cérébraux pour différents stades de développement. Nous avons acquis des données comportementales de ME et de neuroimagerie multimodale chez 50 enfants âgés de 4 à 12 ans. Nos principaux résultats sont: (1) Deux études ont montré que les axes transversal (sous-champs) et longitudinal (antéropostérieur) de l'hippocampe étaient associés respectivement aux tâches de *pattern separation* et de rappel épisodique. (2) Deux autres études ont montré que la connectivité structurelle et fonctionnelle au sein d'un réseau cérébral à large échelle était associée aux tâches de rappel épisodique et épisodique-autobiographique, respectivement. Nos résultats mettent en évidence une spécialisation précoce du cerveau pour différentes composantes de la ME. De plus, la relation entre l'axe transversal de l'hippocampe et les performances de *pattern separation* était modérée par l'âge, ce qui n'était pas le cas pour les relations entre les tâches de rappel et la connectivité. Des dynamiques développementales différentes, l'une spécifique à l'hippocampe et l'autre à la connectivité entre aires cérébrales, pourraient donc contribuer ensemble au développement des composantes de la ME et, de la sorte, à l'arrêt progressif de l'amnésie de l'enfance.

Mots-clefs : Mémoire épisodique, hippocampe, amnésie de l'enfance, imagerie par résonance magnétique, développement cérébral, connectivité cérébrale, pattern separation.

Title : *Neuroimaging of episodic memory development during childhood*

Abstract
We have few memories before the age of 6: this phenomenon, called "childhood amnesia", illustrates the considerable development of episodic memory (EM) during the first years of life. EM is a multifaceted cognitive function comprising cognitive "components" with different brain correlates. Thus, the development of EM may result from developmental trajectories specific to its components, an issue that remains poorly understood. Our goal was to examine the development of EM via the study of the associations between its components and their neural correlates for different developmental stages. We acquired behavioral EM and multimodal neuroimaging data from 50 children aged 4-12 years. Our main results are as follows: (1) Two studies showed that the transversal (subfields) and longitudinal (anteroposterior) axes of the hippocampus were associated with pattern separation and episodic recall tasks, respectively. (2) Two other studies showed that structural and functional connectivity within a large-scale brain network was associated with episodic and episodic-autobiographical recall tasks, respectively. Our results highlight early brain specialization for different components of EM. Furthermore, the relationship between the hippocampal transversal axis and pattern separation performance was moderated by age, which was not the case for the relationships between recall tasks and connectivity. Different developmental dynamics, one specific to the hippocampus and the other for connectivity between brain areas, might therefore contribute together to the development of EM components and, consequently, to the progressive offset of childhood amnesia.

Keywords : Episodic memory, hippocampus, childhood amnesia, magnetic resonance imaging, brain development, cerebral connectivity, pattern separation**.**

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The goal of this thesis - to understand the development of episodic memory in children - required MRI acquisitions from a sufficiently large number of young individuals. This objective would not have been achieved without Christine Doublé and Gaëlle Mediouni, whose unfailing involvement made it possible to recruit the subjects of the "Memodev" cohort studied in this work. I would like to thank them warmly. Thanks, also, to the radiology technicians of Neurospin, who conducted the MRI acquisitions in a masterly manner, with expertise and patience. A special thanks to Chantal Ginisty for her involvement in the elaboration of sequences for the imaging of the hippocampus.

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Cette thèse est dédiée, si cela veut dire quelque chose, à mes parents et à mes frères.

List of main abbreviations

CA : *Cornu Ammonis*.

DG : Dentate Gyrus.

DWI: Diffusion-weighted imaging.

EAM: Episodic Autobiographical Memory.

fMRI: functional Magnetic Resonance Imaging.

MRI: Magnetic Resonance Imaging.

MTL : Medial temporal lobe.

PFC: Prefrontal Cortex.

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Chapter 1. Introduction

1.1 General introduction

Why study the development of episodic memory?

Can you recall memories from before the age of two? Can you vividly recall many memories from before the age of six? (A good way to define "many" and "vivid" would be to compare these early memories with memories of events experienced as an adult). To both of these questions, your answer is probably no. Our early childhood is usually obscure to us, and we often know more about it through photographs and family stories than through direct mnemonic re-experiences of past events. The forgetting of all memories of events lived before the age of about two, and of most memories of events lived between the ages of two and six, are generally referred to as infantile amnesia and childhood amnesia, respectively (Alberini & Travaglia, 2017; Bauer, 2015a, 2015b; Bauer & Larkina, 2014b; Bouyeure & Noulhiane, 2020b; Carver & Bauer, 2001; Josselyn & Frankland, 2012). These phenomena have intrigued researchers for over a century (Freud, 1953 [1905]) and their causes are still debated to this day (Alberini & Travaglia, 2017; Bauer, 2015a, 2015a; Josselyn & Frankland, 2012).

Traumatic events experienced in early childhood, or child development in an adverse context, are known to have a long-lasting influence on psychological, cognitive and cerebral development (Bick & Nelson, 2016; Heim & Nemeroff, 2001). Thus, events experienced during early childhood can mark an individual, even if they have no memory of these events. How can we be influenced by something we do not remember? This conundrum or paradox (Alberini & Travaglia, 2017; Li et al., 2014; Ramsaran et al., 2019) of infantile and childhood amnesia highlights the fascinating aspects of the study of memory development.

We must begin by defining what we mean by “memories”. One of the most robust conclusions of the scientific investigations on memory is that what we call memory is not a unitary construct. There are different types of memory, which can be referred to as memory systems (Squire & Dede, 2015; Squire & Zola, 1996; Tulving, 1972), which

are, at least to some extent, behaviorally and cerebrally independent of one another. Episodic memory is the mnemonic system concerned with the phenomena of infantile and childhood amnesia and is defined as the long-term memory system dedicated to the memorization of specific *episodes*. Episodic memories can be defined as composite representations associating the memory of an event (factual content about the event: what happened) with information on the contextual framework of this event (spatio-temporal context, but also perceptual, emotional or cognitive context: where and when it happened, how did it look, feel, and so on). This implies that an episodic memory is bounded in space and time, and highlights two fundamental characteristics of episodic memories: they are contextual (they are memories of specific episodes) and relational (they are composite representations integrating various contextual information). Episodic memory is also often identified with autonoetic consciousness, the ability to re-experience past events from the first-person perspective (Tulving, 1972, 2002; Wheeler et al., 1997).

Thus, memories forgotten during infantile and childhood amnesia are episodic memories. However, they are a particular kind of episodic memory as they have some degree of personal self-relevance and involve the subject as the agent of the action (i.e., a sense of self). Such memories are called episodic autobiographical memories (Lin et al., 2016; Squire & Zola, 1996; Tulving, 1972, 2002; Wing et al., 2021). This implies that all episodic memories are not necessarily autobiographical. Indeed, episodic memory is generally investigated through laboratory-based experiments that involve the recall of information that may be contextual and relational, but not autobiographical, and which have no degree of self-relevance.

Research on the ontogeny of episodic memory over the past decades has shown that children's episodic memory abilities at a given age (e.g., when one *is* four years old) is closely related to the ability to recall events that occurred at that age (when one *was* 4 years old). In other words, the progressive development of episodic memory abilities during childhood is related to the recall of episodic autobiographical memories from childhood (Bauer, 2015a; Mullally & Maguire, 2014; Newcombe et al., 2007; Olson & Newcombe, 2013). During the period concerned with infantile amnesia (before age

two), episodic memories in the strict sense, i.e. that are contextual and relational, cannot be observed with absolute certainty in experimental paradigms (Hayne, 2004; Newcombe et al., 2007; Olson & Newcombe, 2013; but for discussion see Bauer, 2006, 2015a; Bauer et al., 2011; Carver & Bauer, 2001). During the period concerned by childhood amnesia, i.e. from age 2 to 6 approximately, episodic memories abilities as measured in experimental settings become evident. These abilities develop strongly during this period, and qualitative changes in the content of episodic memories are also observed around the offset of childhood amnesia. This suggests that there are, to some extent, distinct periods in the development of episodic memory (Newcombe et al., 2007). Furthermore, the offset of infantile and childhood amnesia correspond to maturational transitions in the main neural substrate of episodic memory, the hippocampus. Converging evidence thus indicates that **infantile and childhood amnesia**, in addition to referring to the absence of episodic memories from early childhood, also reflect **significant periods of episodic memory development** (Alberini & Travaglia, 2017; Bouyeure & Noulhiane, 2020b; Donato et al., 2021; Newcombe et al., 2007; Olson & Newcombe, 2013).

Other factors could contribute to the immaturity of episodic memory in the early years of life and the forgetting of early memories. For example, immaturity of language skills or lack of the sense of self have been proposed as important, even central, factors to infantile and childhood amnesia (Fivush, 2011; Nelson, 1993; Nelson & Fivush, 2004). However, infantile and childhood amnesia are also observed in non-human mammals (e.g., rodents, monkeys). There are also close parallels between the development of “episodic-like” memory abilities in animals and the development of episodic memory in humans (e.g., Alberini & Travaglia, 2017; Josselyn & Frankland, 2012; Lavenex & Banta Lavenex, 2013). Therefore, although the importance of “non-mnemonic” factors should not be overlooked, the study of episodic memory development and of infantile/childhood amnesia would first and foremost benefit from a focus on the biological and cognitive factors specific to the development of episodic memory.

Some important discoveries on episodic memory development have been brought by neuroimaging, notably by Magnetic Resonance Imaging (MRI) studies, which

investigated *in vivo* how episodic memory processes were related to distinct brain mechanisms and underpinned by distinct neural correlates that have their own developmental trajectories. In this dissertation, our aim was to try to contribute to the study of the development of episodic memory. More specifically, our approach was focused on **examining how the relationship between episodic memory and its neural substrates in the developing brain can highlight important aspects of episodic memory development**, and potentially contribute to our understanding of the phenomena of infantile and childhood amnesia.

To address this general objective, we acquired and analyzed neuroimaging and behavioral data on a **cross-sectional cohort** comprising both children during and after the childhood amnesia period (50 children aged 4-12 years). We sought to determine how **interindividual differences in episodic memory abilities were related with interindividual differences in structural and functional brain properties**. We also examined whether we could find **distinct patterns of brain-behavior relationships for children during the childhood amnesia period compared to children after the childhood amnesia period,** which could putatively be interpreted as "neuroimaging markers" of memory development.

Given its importance for the function and development of episodic memory, we particularly focused on how the **hippocampus was structurally and functionally related to episodic memory abilities in the developing brain**. But the importance of the hippocampus in episodic memory is also explained by its central role within a larger network of brain areas involved in memory-guided behavior (Kragel et al., 2021; Qin et al., 2014; Ranganath & Ritchey, 2012; Riggins et al., 2020; Ritchey et al., 2015). Therefore, we also examined how the **structural and functional connectivity within this larger network was related to episodic memory abilities during development**. Thus, we studied the hippocampus, as well as the connectivity between brain areas involved in episodic memory, both at the structural and functional levels.

As mentioned above, memory is not a unitary capacity; but the same observation could apply to episodic memory, although to a much lesser extent. Perhaps more than for

other memory systems, several components within episodic memory have been described in the scientific literature. These include, for instance, source/context memory, relational/associative memory, item memory, recognition memory, or memory discrimination/pattern separation (e.g., Cycowicz et al., 2001; Hassevoort et al., 2020; Ngo et al., 2018, 2019; Riggins, 2014; Sprondel et al., 2011). In addition, episodic memories can be autobiographical or non-autobiographical, a distinction that has a particular importance given the phenomena of infantile and childhood amnesia. Thus, there is a certain multiplicity within episodic memory; and the idea that some "types" or "components" of episodic memory might contribute to its overall development in different ways and with distinct timings is found throughout the developmental literature. This idea is also supported by the observation that different episodic memory components have different neural correlates, which have their own developmental trajectories (e.g., Benear et al., 2020; Hassevoort et al., 2020; Ngo et al., 2018, 2019; Olson & Newcombe, 2013; Riggins, 2014; Sluzenski et al., 2006; Sprondel et al., 2011). Thus, we studied distinct components of episodic memory which were chosen based on their complementarity and relevance in a developmental context. **This allowed us to examine whether components of episodic memory were associated with specific, non-overlapping brain areas during development, and whether these brain-behavior relationships differed between younger and older children.**

***

This dissertation is composed of 5 chapters. The following sections of Chapter 1 (Introduction) constitute our theoretical contribution to the topic of episodic memory development. Sections 1.2 and 1.3 present the development of memory systems and episodic memory. Their content has been published separately as chapters in academic books. Section 1.4 presents the developmental trajectories of several components of episodic memory. Section 1.5 presents the developmental trajectories of the main neural correlates of episodic memory. Section 1.6 presents the aims and hypotheses of this dissertation.

Chapter 2 (Methods) presents the materials and methods. Chapter 2 also contains a methodological contribution of our dissertation that has been published in a scientific journal.

Chapter 3 (Results) presents our experimental contributions that aim to address the hypotheses presented at the end of the Introduction chapter. Chapter 3 is composed of 5 studies. Study 2 has been published in a scientific journal. Study 4 was, at the time of writing, under revision. Studies 3 and 5 are in preparation and will be submitted to scientific journals.

Chapter 4 is the general discussion of this dissertation.

1.2 Development of memory systems

To understand the specifics of episodic memory development, it is required to compare the ontogeny of episodic memory to the ontogeny of other memory systems. This is addressed in the present section, which has been published separately as a chapter in the 173rd volume of the Handbook of Clinical Neurology (Elsevier).

Chapter highlights (also serving as a short updated discussion) follow the content of the chapter.

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Chapter highlights and additional discussion

- **Memory systems have distinct developmental trajectories**. Differences in these developmental trajectories are largely related to differences in the maturation of their neural correlates (e.g., Elward & Vargha-Khadem, 2018; Ghetti & Bunge, 2012; Klingberg, 2006; Newcombe et al., 2007; Olson & Newcombe, 2013; Willoughby et al., 2012).
- **The development of episodic memory is protracted, extending from birth to adolescence.** Distinct periods can be distinguished within episodic memory development, which correspond to the offsets of infantile and childhood amnesia.
- The cited boundaries of infantile amnesia (0-2 years) and childhood amnesia (2-6 years) are not used with exactness by all authors in the literature. As the offset of these phenomena is progressive and not set in stone, these boundaries are necessary approximations. For example, Bauer & Larkina (2014b) use the 1-3 years period to define infantile amnesia, and 4-7 years to define childhood amnesia. However, as we will elaborate further in the next section, we used the age 0-2 and age 2-6 boundaries as they correspond to meaningful transitions in the maturation of the hippocampus (Newcombe et al., 2007; Olson & Newcombe, 2013).

1.3 Development of episodic memory

The purpose of this section is to present in more detail the development of episodic memory, the relationship between its development and the maturation of its neural correlates, and how the study of episodic memory development can shed light on the paradox of infantile and childhood amnesia. The content of this section has been published separately as a chapter in the book Factors Affecting Neurodevelopment (Academic Press).

Chapter highlights (also serving as a short updated discussion) follow the content of the chapter.

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Chapter highlights and additional discussion

- **Infantile and childhood amnesia reflect separate periods in episodic memory development.** The offset of infantile amnesia corresponds to the age at which the first episodic memories start to appear. The offset of childhood amnesia corresponds to a qualitative shift in episodic memory development, which is demonstrated by the analyses of recall errors made by children in the childhood amnesia period compared to older children (Newcombe et al., 2007).
- **The hippocampus is comprised of several cellular layers,** called **hippocampal subfields**, that have distinct functions for the processing of episodic memories (Azab et al., 2014; Bonnici et al., 2013; Canada et al., 2019; Dalton et al., 2019; Yassa et al., 2011; Yassa & Stark, 2011).
- **The maturation of the hippocampus largely reflects periods of episodic memory development**, both at the **macrostructural** (e.g., total volume) and **microstructural** (hippocampal subfields) levels (Gómez & Edgin, 2016; Mullally & Maguire, 2014; Olson & Newcombe, 2013; Ramsaran et al., 2019).
- Infantile and childhood amnesia arguably correspond to **critical periods** in hippocampal development, i.e. periods during which cerebral plasticity in the hippocampus is particularly important and reactive to the environment (Alberini & Travaglia, 2017; Ramsaran et al., 2019; Travaglia et al., 2016).

1.4 Developmental trajectories of the components of episodic memory

In the previous sections, we saw that episodic memory development is organized in three main periods, which are closely related to transitions in the maturation of the hippocampus: infantile amnesia (age 0-2), childhood amnesia (age 2-6), and the emergence of adult-like episodic memory – since memories formed after the age of 6 loose the fragility and rapid forgetting observed during childhood amnesia.

The development of episodic memory therefore takes place in several stages. However, what we call episodic memory is not unitary but can be broken down into a variety of distinct "components" with complementary functions. The notion that episodic memory can be decomposed into multiple components has been used in the literature in a variety of theoretical contexts (e.g., (Diana et al., 2007; Eichenbaum, 2004; Eichenbaum & Cohen, 2014; Keresztes et al., 2018; Ngo et al., 2019; Picard et al., 2012; Wais et al., 2006; Yassa & Stark, 2011). Here, we will use the term “component” in a theory-neutral manner to refer to the idea that distinct aspects can be distinguished within what we call episodic memory, based on behavioral and/or cerebral evidence, without reference to a specific theoretical framework.

Components of episodic memory have distinct developmental trajectories, which are related to the heterogeneous maturation of their neural correlates (e.g., Ghetti & Angelini, 2008; Ghetti & Bunge, 2012; Meier et al., 2013; Ngo et al., 2019; Sluzenski et al., 2004, 2006). This opens the hypothesis that the components of episodic memory contribute to the development of episodic memory with distinct timings. For example, if a component of episodic memory matures rapidly during the period of childhood amnesia, then the development of that component, underpinned by the maturation of its neural correlates, could play a particular role in the offset of childhood amnesia. Furthermore, it used to be a well-established idea in the field of episodic memory development that the hippocampus is a relatively early maturing structure compared to neocortical regions (such as the prefrontal and parietal areas), which are also critical

for episodic memory. Thus, age-related improvements in episodic memory have been hypothesized to depend primarily on hippocampal maturation during early memory development, and to be supported by neocortical maturation from childhood or adolescence onward (reviewed in Ghetti & Bunge, 2012). For the hippocampus, this assumption has been challenged by studies showing that its maturation is in fact protracted (Callaghan et al., 2021; Gogtay et al., 2006; Krogsrud et al., 2014; Lee et al., 2014; Tamnes et al., 2018). But the relative contributions of the hippocampus and neocortical regions to episodic memory during development remain unclear. One way to address this question would be to examine the developmental trajectories and brain-behavior relationships of components of episodic memory that have been specifically linked to either the hippocampus or to extra-hippocampal (e.g., neocortical) areas.

Thus, the goal of this section was not to exhaustively describe the multiple components of episodic memory, but to discuss components that may be particularly relevant in the context of memory development because of their association with distinct neural correlates. This may provide insight into how the heterogenous maturation of the brain contributes to memory development. Because the literature on the subject is vast and its organization often unmapped, we used criteria related to the differences in the neural correlates of episodic memory components to "systematize" our descriptions: (a) components of episodic memory that have been primarily linked to the hippocampus (relational memory, pattern separation); (b) components of episodic memory that have been primarily linked to neocortical regions, or hippocampo-neocortical interactions (components of episodic retrieval). Moreover, we specifically examined (c) episodic autobiographical memory, which has been linked to a large-scale network of brain areas (the hippocampus, neocortical regions, subcortical regions, and the cerebellum). The cognitive development of these components is described here and the maturation of their neural correlates is the subject of the next section (1.5).

1.4.1 Episodic memory components associated with the hippocampus

The hippocampus is undoubtedly the main neural substrate of episodic memory. As such, its contribution to many aspects or components of episodic memory has been described. However, some components of episodic memory have been specifically linked to the hippocampus.

Relational memory

For example, relational memory is commonly referred to as a key function of the hippocampus (Ngo et al., 2018a, 2019; Olson & Newcombe, 2013). Relational memory consists of the ability to bind separate elements into a combined representation. Because a core trait of episodic memory is its relational nature, relational memory is generally seen as a key component of episodic memory (Ngo et al., 2019; Olson & Newcombe, 2013; Sluzenski et al., 2006) There is strong evidence that the hippocampus is essential for relational binding (Olson & Newcombe, 2013). However, other brain areas are also involved in relational memory, such as the MTL, and the ventromedial and dorsolateral parts of the prefrontal cortex (PFC) (Blumenfeld et al., 2011; McCormick et al., 2010; Wing et al., 2021).

Relational memory improves significantly during early childhood (Lloyd et al., 2009; Ngo et al., 2018, 2019; Sluzenski et al., 2006), suggesting that its development could contribute to the offset of childhood amnesia. Young children's poor performance at relational memory tasks has been reported to result a higher probability of falsely recognizing new relationships (Lloyd et al., 2009). An absence of age-improvements of relational memory after age 6 has been reported when children were asked to remember relations between items learned in unrelated or dissimilar contexts (Ngo et al., 2018, 2019). However, Ngo et al. (2019) also showed that when the relationships to be learned involved items presented in highly similar contexts, significant improvements in relational memory were observed. This suggests that relational memory development is also modulated by the ability to discriminate similar contexts.

Pattern separation

At the neural level, the ability to discriminate similar information is underpinned by pattern separation, a component of episodic memory also strongly associated with the hippocampus. Pattern separation is a neural computation mechanism implemented by hippocampal neurons aiming at discriminating similar (overlapping) information by assigning them orthogonal memory representations (Figure 1). Pattern separation thus maximizes the specificity of memory representations. This reduces potential interference between similar memories, and enables the retrieval of specific memories (Marr & Brindley, 1971; Norman & O'Reilly, 2003; Yassa & Stark, 2011). For example, from a child's point of view, a trip to school may look like any other trip to school done in the past; in order to retain a specific memory of a particular trip, it is necessary for these memories to be pattern-separated. Pattern separation has been shown to be underpinned almost exclusively by the hippocampus, specifically by hippocampal subfields Dentate Gyrus (DG) and CA3 (Berron et al., 2016; Bakker et al., 2008; Doxey & Kirwan, 2015; Kirwan & Stark, 2007; Mankin et al., 2015; Nakashiba et al., 2012; Yassa & Stark, 2011). Some fMRI studies provided marginal evidence for a role of MTL regions such as the perirhinal cortex (Stevenson et al., 2020) but this has not always been replicated (Doxey & Kirwan, 2015; Kirwan & Stark, 2007).

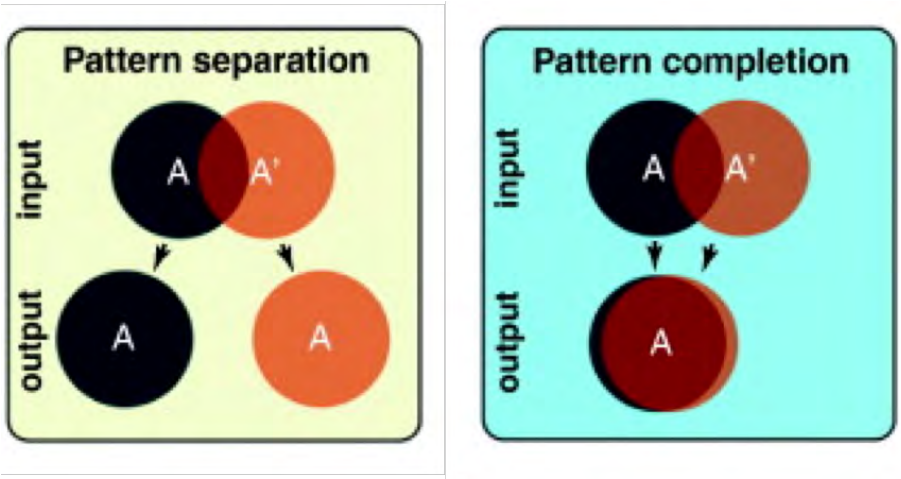

Figure 1. Illustration of pattern separation (left) and of the opposite process, pattern completion (right). Pattern separation consists in making similar (overlapping) information (A and A') more distinct, ensuring memory specificity. On the other hand, pattern completion consist in making overlapping information more overlapping. Pattern separation is a mechanism for memory specificity, and pattern completion for memory generalization. Adapted from Yassa & Stark (2011).

A characteristic of everyday memories reported by young children is their lack of specificity. Indeed, these recalled events are generally made of unspecific details (e.g., the story of a day at school could be hardly distinguishable from the story of another school day). This lack of specificity could depend on a variety of causes, such as a general impairment in information encoding (see Sluzenski et al., 2004), impairment in relational binding (Sluzenski et al., 2006), or an impairment in the ability to relate information to the context (source) in which it was acquired (Cycowicz et al., 2001; Lindsay et al., 1991; Sprondel et al., 2011). However, this lack of specificity could also be related to impaired pattern separation: the impaired orthogonalization of similar information into distinct representations would also lead to a lack of memory specificity. More generally, the link between relational memory and pattern separation-mediated memory discrimination abilities mentioned above (Ngo et al., 2019) is an indication that the development of pattern separation during childhood may contribute to the development of episodic memory as a whole.

Impaired pattern separation has been reported in young children, as well as rapid development of pattern separation during the childhood amnesia period (Ngo et al., 2018, 2019). Age-related improvements of pattern separation for the discrimination of single (non-relational) items after early childhood are more unclear, as they have been reported by some, but not all, studies (Ngo et al., 2018, 2019; Rollins & Cloude, 2018). More generally, it has been suggested that young children exhibit a bias towards the generalization of new information, relating it to previously learned information (e.g. through pattern completion), rather than preserving its specificity (Keresztes et al., 2017, 2018). This developmental lag between generalization and specificity during childhood could be explained by the idea that it would be more ontogenically relevant to identify regularities in one's environment before remembering specific details (Keresztes et al., 2018).

Beyond impaired pattern separation, this developmental lag is also suggested by the observation that young children are less impaired in tasks requiring retrieval of general information (semantic memory, familiarity-based recognition memory) than in tasks requiring recall of specific information (pattern separation, episodic recollection,

context memory) (reviewed in Keresztes et al., 2018). Relatedly, there is a developmental lag between the neural correlates of specificity and generalization: neural structures essential for specificity (e.g., the DG) have a more protracted maturation than the neural correlates supporting generalization processes or memory for general information (e.g. subfield CA1 of the hippocampus, the perirhinal cortex). The DG has the most protracted maturation across hippocampal subfields, and reaches maturation approximately around the offset of childhood amnesia (Lavenex & Banta Lavenex, 2013). However, the development of pattern separation during childhood has only been an object of study since the recent years (first paper on the topic: Ngo et al., 2018). Further research is hence needed to determine its role during episodic memory development, its relationship with other components of episodic memory, and with hippocampal maturation.

Hippocampus-related components: summary

Relational memory and pattern separation are two components of episodic memory that have been closely associated with the hippocampus. In particular, **impaired pattern separation could be a factor contributing to the fragility of early memories and its maturation could support the overall development of episodic memory.**

1.4.2 Episodic memory components associated with neocortical areas

While the role of the hippocampus in episodic memory is pivotal, its importance is also explained by its central place in a network of brain areas which all contribute to episodic memory. In particular, neocortical regions have been shown to contribute decisively to episodic memory, particularly the PFC. Here, we will review some components of episodic memory associated with neocortical areas.

Episodic retrieval: recall and recognition

Retrieval of episodic information has, generally speaking, repeatedly been associated with the activity of neocortical regions, and particularly the PFC, as well as the

hippocampus and hippocampo-neocortical interactions (DeMaster & Ghetti, 2013; Henson et al., 1999; Jin & Maren, 2015; Kesteren et al., 2010; Lepage et al., 2000; McCormick et al., 2010, 2020; Wing et al., 2021). However, this would ultimately depends on the nature of the retrieval process. Broadly, two forms of memory retrieval are distinguished in the literature: the first is recall, which refers to the process by which information stored in the brain is consciously searched and accessed. The second is recognition, in which a memory is accessed following re-exposure to information (e.g., an item in the external world) contained by this memory. Thus, in recognition, an item is recognized by establishing a correspondence between two given pieces of information, one of which is stored in memory; whereas in recall, the retrieval of information does not need to follow re-exposure.

Recognition: recollection and familiarity

Recognition is often further decomposed into two components. For the dual-process signal detection theory, recognition of information can be achieved through recollection, in which recognition occurs through the recall of information related to that item. Recollection can thus be understood as a form of recall triggered by re-exposure. On the other hand, recognition can also occur through familiarity, a rapid process producing a feeling of "knowing" an item without recollecting specific information about this item. According to the dual-process signal detection theory, recognition occurs through recollection if the strength of the memory trace exceeds a threshold; otherwise, recognition occurs through familiarity (Yonelinas, 1994, 2002; Yonelinas et al., 2010). Recollection and familiarity are often disambiguated through paradigms asking participants to provide a subjective report of their retrieval experience. For example, the "Remember/Know" paradigm involves asking the participant to indicate if he recognized information through recollection ("I remember") or by a sense of familiarity ("I know"). However, because it is based on subjective self-reports, this paradigm has often been criticized (e.g., Umanath & Coane, 2020; Wixted, 2009). Furthermore, an alternative explanation of recognition memory argues that recognition occurs through a single recognition process and that recollection and familiarity judgments are dependent of the strength of the memory trace without reflecting distinct processes at the cognitive level (Wixted, 2007).

Neural correlates of recall, recollection, and familiarity

A vast literature has examined the similarities and differences between the neural correlates of recall and recognition, as well as between recollection and familiarity. Overall, recall and recollection have been associated with the hippocampus, the lateral and medial areas of the prefrontal cortex, and parietal regions (posterior cingulate cortex, angular gyrus). On the other hand, feeling of familiarity has been associated with the perirhinal cortex, and more ventral prefrontal areas (Diana et al., 2007; Ranganath et al., 2004; Ranganath & Ritchey, 2012; Ritchey et al., 2015; Yonelinas et al., 2005). While the involvement of the hippocampus in recall and recollection is uncontroversial, its role in familiarity has been an important object of debate, particularly given the fact that the recollection/familiarity distinction has been an object of debate (Wais et al., 2006; Wixted & Squire, 2004a, 2004b; Yonelinas et al., 2002, 2010). On a more general level, the problem of recognition paradigms is that they need to disambiguate how the memory trace is accessed, which can be methodologically problematic, especially in young children. Therefore, studying episodic recall could be a better option to examine how the maturation of neocortical regions contribute to the development of a fundamental component of episodic memory.

Development of episodic recall and its relation to neocortical areas

The fact that young children are impaired in their ability to recall memories is known since a long time (Ackerman, 1985). Recall performance has been shown to increase over childhood and adolescence. Age-related differences have been reported to be more important when they are greater retrieval demands, requiring the use of recall strategies that is typical PFC-mediated function (Gee & Pipe, 1995; Hasselhorn, 1990; also Ghetti & Bunge, 2012). Overall, age-related improvements of recall during middle childhood and adolescence have been associated with the greater use of strategies and other control behaviors, which are mediated by neocortical areas such as the PFC, and also by some parietal areas (reviewed in Ghetti & Bunge, 2012). It has also been shown that school-age children and adults recruit differently their hippocampus and PFC during recall tasks, which could account for differences of memory performance (DeMaster & Ghetti, 2013).

Overall, because neocortical regions such as the PFC and the parietal cortex have a protracted development (see section 1.5), it is often thought that the contribution of neocortical regions to episodic memory unfolds progressively over developmental time (e.g., Ghetti & Bunge, 2012; Ngo et al., 2017). More specifically, it is often assumed that the locus of episodic memory development 'switches' from hippocampal maturation to neocortical maturation during middle childhood or adolescence (DeMaster & Ghetti, 2013; Ghetti & Bunge, 2012; Ofen et al., 2007; Selmeczy et al., 2019). Studying the development of episodic memory recall could thus constitute a relevant example for understanding how the protracted maturation of neocortical regions, particularly the PFC, and of hippocampo-neocortical interactions, progressively contribute to episodic memory development.

Neocortical-related components: summary

Episodic memory recall has been associated with the activity of the hippocampus and of neocortical areas, particularly the PFC. Evidence suggests that the contribution of the PFC to episodic memory unfolds progressively during development, with a more important 'role' from middle childhood and adolescence. **Thus, studying the neural correlates EM recall could uncover distinct brain-behavior relationships over developmental time. Quantitatively or qualitatively different brain-behavior relationships could be observed between older and younger children if neocortical regions play a more important role in episodic memory over the course of development.**

1.4.3 The case of episodic autobiographical memory

As discussed in section 1.1, some episodic memories are autobiographical, meaning that they have some form of personal self-relevance and involve the self as the agent of the event. Episodic autobiographical memory, i.e. the system for memories that are both episodic and autobiographical, can thus either be understood either as a specific component of episodic memory (episodic autobiographical memories), or as component of Autobiographical Memory, the memory system dedicated to the

remembering of one's personal life (Conway et al., 2004; Conway & Pleydell-Pearce, 2000; Newcombe et al., 2007). Here, for simplicity, we will refer to episodic autobiographical memory as being a 'component' of episodic memory, while acknowledging the specificities of autobiographical memory (e.g., relation to the concept of self).

There are two main reasons for specifically studying episodic autobiographical memory during childhood. The first one is related to childhood amnesia, since it is first and foremost defined by the forgetting of early episodic autobiographical memories. The second reason is that the particular nature of autobiographical memories entail that they are associated with neural correlates that partly overlap with the correlates of other episodic memory components, but also have their own specificities. Thus, dtudying the relationship between the development of episodic autobiographical memory and the maturation of its neural correlates is a privileged approach to study episodic memory in a more 'ecological' way, as well as to uncover factors that could contribute to the offset of childhood amnesia.

Development of episodic autobiographical memory

The earliest autobiographical memories recalled by children and adults are generally reported to date around age 3 to 4 (Bauer, 2006; Bauer et al., 2011; Bauer & Larkina, 2014b; Tustin & Hayne, 2010). It has been suggested that children often postdate their earliest memories, meaning that earliest memories could actually date around age 2 to 3 (Peterson et al., 2018), i.e. around the offset of infantile amnesia. Studies have shown that memories from early childhood (before 6 years of age) recalled during later development are scarcer than what would be expected given only the passage of time (Bauer & Larkina, 2014b), and also lack specificity and detail (Hayne & Imuta, 2011; Hayne & Jack, 2011). Importantly, it has been shown that childhood amnesia is a progressive process: as they grow older, children progressively forget the memories that used to be their earliest (Bauer & Larkina, 2014a; Peterson et al., 2018).

Many studies have used paradigms allowing the "objective" rating of the richness and specificity of autobiographical memories recalled by children, assessing the number of

episodic autobiographical details recalled, or whether the recalled memories meet a certain threshold for "episodicity" (e.g., whether it contains specific contextual details). Such studies have shown continuous improvements of the ability to recall episodic autobiographical memories over middle childhood and adolescence. Overall, older children or adolescents are able to recall autobiographical memories that are richer, more coherent, and more organized, than their younger counterparts (Bauer & Larkina, 2019; Picard et al., 2009; Piolino et al., 2007; Willoughby et al., 2012).

Neural correlates of episodic autobiographical memory

At the cerebral level, episodic autobiographical memory is underpinned by a large-scale cortical network that mainly includes the hippocampus, neocortical regions, but also subcortical regions and the cerebellum (Addis et al., 2017; Cabeza & St Jacques, 2007; Svoboda et al., 2006). To this date, only two studies investigated the neural correlates of episodic autobiographical memory in the developing brain (Bauer et al., 2017; Østby et al., 2012). Given the importance of episodic autobiographical memory for the understanding of infantile and childhood amnesia, the current state of literature would benefit from further explorations of this relationship.

Episodic autobiographical memory: summary

Studying the autobiographical nature of episodic memories is crucial to **understand episodic memory development in an ecological fashion** as well as to understand the relationships between episodic memory, episodic autobiographical memory, and childhood amnesia.

1.4.5 The role of the different components of episodic memory in episodic memory development

As discussed in above, episodic memory is a complex construct that can further be broken down into a variety of components, some of which are summarized Table 1 below.

Component name	Putative developmental trajectory	Main neural correlates
Episodic recall	Early childhood to adolescence	Medial and dorsal PFC, parietal cortex, Hippocampus
Recognition memory	Familiarity earlier than recollection. Relatively early for familiarity	Familiarity: perirhinal cortex, ventral PFC; recollection: hippocampus, medial PFC, dorsal PFC, parietal areas
Relational memory	Early childhood to middle childhood (relations in dissimilar contexts), or further (relations in similar contexts)	Hippocampus, medial PFC
Pattern separation	Single items: early to middle childhood? Relations: adolescence?	Hippocampus (DG, CA3)
Episodic autobiographical memory	Early childhood to adolescence	Large-scale network: hippocampus, PFC, parietal cortex, MTL, cerebellum…

Table 1. Episodic memory components and their neural correlates.

Thus, it is necessary to characterize the developmental trajectories of distinct components to understand the timing of their contribution to the overall development of episodic memory, and to the offset of childhood amnesia in particular. As discussed, components with a rapid development during childhood amnesia, such as pattern separation, could contribute to its offset. On the contrary, components with a continuous and linear development until adolescence (such as recall) could reflect more “evenly distributed” contributions to memory development.

In other words, the qualitative transitions in episodic memory observed around the offset of childhood amnesia could be caused by the fact that some episodic memory components reached a "critical mass" of maturity, while components with a linear development would contribute more evenly to the protracted development of episodic memory. In the latter case, since brain maturation is heterogenous, distinct factors could underpin age-related improvements over the course of development (e.g. hippocampal maturation during early childhood, followed by neocortical maturation in later development). Indeed, the development of episodic memory components is ultimately underpinned by the maturation of their neural substrates, which is the focus of the next section.

1.5 Maturation of the neural correlates of episodic memory

In the previous section, we saw that episodic memory could be described with a variety of components that each have their own developmental courses and neural correlates. Here, we will describe the developmental trajectories of the neural correlates of episodic memory and examine how they could contribute to episodic memory development.

1.5.1 The hippocampus

As previously discussed (sections 1.1-1.4), the hippocampus is the main neural correlate of episodic memory and its maturation is closely related to the development of episodic memory as a whole. However, the hippocampus a highly organized structure, which entails that there is a specialization within the hippocampus itself for distinct components of episodic memory. Moreover, the maturation of the hippocampus is heterogenous, as all areas do not develop at the same rate, or follow the same developmental trajectories.

The complexity of hippocampal organization can be summarized with two main axes of variation. The first is the transversal (or transverse) axis of organization of the hippocampus, which spans the medial-lateral direction in humans. This axis of organization corresponds to hippocampal subfields, as they are “stacked” to each other on the medial-lateral (transverse) direction. The second is the longitudinal axis of organization, which corresponds to the anterior-posterior axis in humans. An important question is therefore to understand the contribution of the maturation of these axes of hippocampal organization, as well as their interaction, to memory development.

Transversal axis of organization : hippocampal subfields

On the transversal (medial-lateral) direction, the hippocampus is composed of distinct cellular layers called subfields. As mentioned in section 1.3, hippocampal subfields are interconnected through distinct circuits, such as the monosynaptic and trisynaptic circuits. The function of a hippocampal subfield could be interpreted in relation with its place in the internal circuitry of the hippocampus. For example, single-cell recordings and computational models suggest that the function of CA3 cells is influenced by the nature of their Dentate Gyrus (DG) inputs (Neunuebel & Knierim, 2014; Rennó-Costa et al., 2014; Rolls, 2007, 2016; Yassa & Stark, 2011). The monosynaptic and trisynaptic circuits, and the subfields within them, have been associated with distinct episodic memory components, e.g. pattern separation and completion (Figure 2). Thus, the transversal axis of hippocampal organization (hippocampal subfields) represent the organization of the **internal connectivity of the hippocampus**.

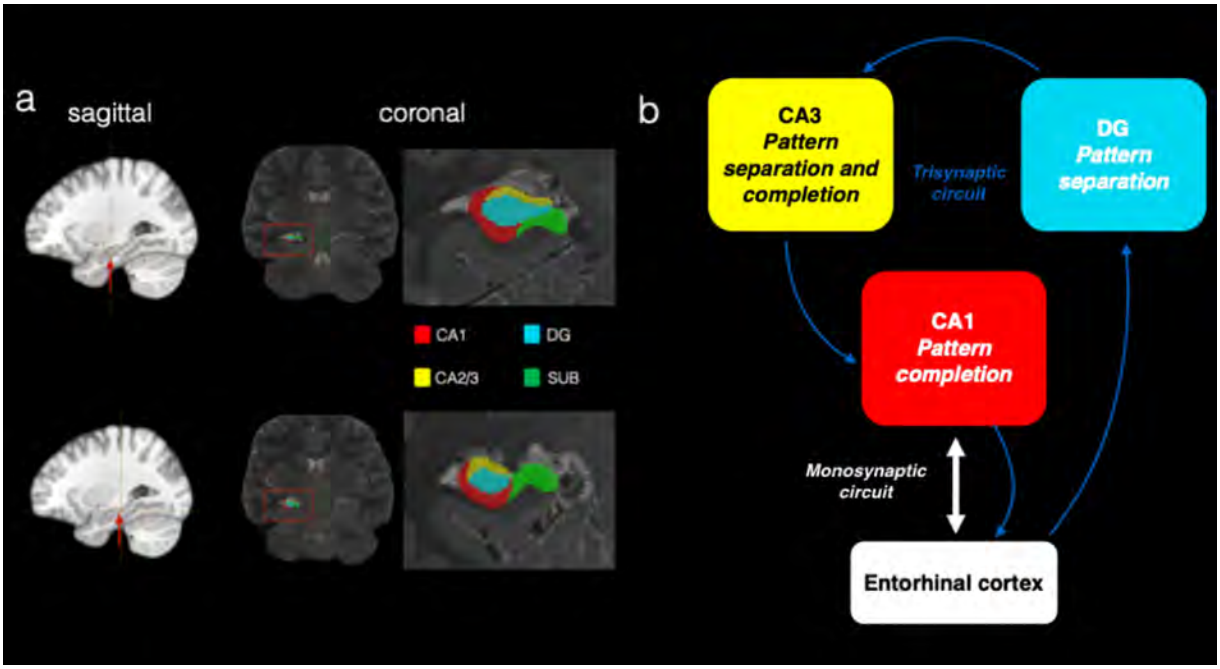

Figure 2. Hippocampal subfields, monosynaptic and trisynaptic circuits, and example of their functions in episodic memory. Adapted from Bouyeure & Noulhiane (2020a).

As discussed in section 1.3, there is a clear relationship between the maturation of the internal connectivity of hippocampal subfields and the main stages of episodic memory development. The monosynaptic circuit reaches maturation around the offset of infantile amnesia, and CA1 reaches adult-like morphology around age 3 (Gómez & Edgin, 2016; Lavenex & Banta Lavenex, 2013; Seress et al., 2001). By contrast, subfields specific to the trisynaptic circuit (CA3 and DG) have a more protracted developmental trajectory. The DG has the most protracted maturation and does not reach adult-like morphology until age 6 to 7, i.e. around the offset of childhood amnesia (Lavenex & Banta Lavenex, 2013; Olson & Newcombe, 2013).

Further, but less important age-related differences in the structure (volume) of hippocampal subfields have been observed until adulthood. These age-related differences have been associated with improvements in episodic memory performance after the childhood amnesia period (Canada et al., 2020, 2021; Krogsrud et al., 2014; Riggins et al., 2018; Tamnes et al., 2018). Thus, contrarily to a long-held view (discussed in Ghetti & Bunge, 2012), the maturation of the hippocampus extends beyond the rapid maturation of the infantile and childhood amnesia years, and continue to contribute to episodic memory development after these stages. However, the methodological advances allowing the study of hippocampal subfields *in vivo* in humans, and particularly in children, are fairly recent. Thus, further research is required to understand how the protracted maturation of hippocampal subfields contribute to the development of episodic memory components from early childhood to adulthood.

Longitudinal axis of hippocampal organization

Complementarily to its transversal organization, the hippocampus is also organized over its longitudinal (anterior-posterior) axis. Numerous studies have shown differences in gene expression, cell morphology, connectivity and function between the anterior and posterior areas of the hippocampus (for reviews: Poppenk et al., 2013; Strange et al., 2014). Since many functional dissociations between the anterior and posterior hippocampus have been described, there is no consensus in the current literature regarding how these should be summarized. However, popular frameworks based on numerous multimodal data collected in animal models and humans suggest

that the anterior hippocampus is mainly involved in the formation and recall of broader and more coarse-grained memory representations, while the posterior hippocampus is associated with sharper and more fine-grained memory representations (Poppenk et al., 2013; Ranganath & Ritchey, 2012; Ritchey et al., 2015) (Figure 3).

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Figure 3. Summary of functional and connectivity differences between the anterior and posterior hippocampus from the popular model of Poppenk et al. (2013). Adapted from Poppenk et al. (2013).

These functional differences over the longitudinal axis of the hippocampus are directly related to differences of connectivity of the anterior and posterior areas of the hippocampus with the rest of the brain (Poppenk et al., 2013; Strange et al., 2014). Indeed, if the inputs and outputs of two brain regions, or of two areas within a given structure, are different, then their function will likely differ as well.

As previously illustrated in Figure 2, the entorhinal cortex is the main gateway of information to the hippocampus. Tracer studies on animal models, but also recent high-resolution fMRI studies in humans (Navarro Schröder et al., 2015; Poppenk et al., 2013; Strange et al., 2014), have shown that the anterior hippocampus is preferentially connected with the medial band of the entorhinal cortex, while the posterior

hippocampus is preferentially connected with the lateral band of the entorhinal cortex (Figure 3). These areas of the entorhinal cortex are, in turn, preferentially connected with distinct regions: the medial band (connected with the anterior hippocampus) is connected with the perirhinal cortex, to which converges mainly information from the orbitofrontal cortex, the temporal pole and the inferior temporal gyrus; on the other hand, the lateral band of the entorhinal cortex mostly receives inputs from the parahippocampal cortex, which is preferentially connected with posterior cingulate cortex, the angular gyrus, and the precuneus. Thus, the anterior/posterior division of the hippocampus is also found at the cerebral level: the anterior and posterior areas of the hippocampus are preferentially connected with distinct cortical networks, one more anterior and the other more posterior (Blankenship et al., 2017; Dalton et al., 2019; Diana et al., 2007; Poppenk et al., 2013; Przeździk et al., 2019; Ranganath & Ritchey, 2012; Ritchey et al., 2015).

The PMAT framework summarizes these connectivity differences by positing the existence of two distinct systems for memory-guided behavior: the posterior medial (PM) system, preferentially involved in recollection and the processing of specific (sharp) information, and the anterior temporal (AT) system, preferentially involved in familiarity and the processing of general (broad) information (Ranganath & Ritchey, 2012; Ritchey et al., 2015) (Figure 4). Data also suggest that the ventromedial PFC is equally connected to the two systems, integrating information from both networks.

Thus, while differences over the transversal axis of organization of the hippocampus (subfields) represent differences of internal connectivity, differences over the longitudinal axis represent differences of external connectivity.

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Figure 4. Connectivity differences between the anterior and posterior hippocampus as summarized by the PMAT framework. Regions connected preferentially to the anterior hippocampus are in red (AT system), and to the posterior hippocampus in blue (PM system). Adapted from Ranganath & Ritchey (2012).

Developmental differences over the hippocampal longitudinal axis have been mainly studied from a structural (volumetric) perspective. Previous studies showed distinct developmental trajectories of the anterior and posterior areas of the hippocampus, which have often been related with age-improvements of episodic memory abilities (DeMaster et al., 2014; Gogtay et al., 2006; Riggins et al., 2015). Some studies have also integrated both axes of organization, showing that the developmental trajectories of hippocampal subfields and their association with memory development differed between the anterior and posterior areas (Canada et al., 2021; Riggins et al., 2018). However, fewer studies have examined the longitudinal organization of the hippocampus from a developmental perspective (Blankenship et al., 2017; Riggins et al., 2016), and the relationship between both of these axes of organization during memory development remains elusive.

Hippocampal organization: summary

The transversal and longitudinal axis of hippocampal organization reflect the internal and external connectivity of the hippocampus, respectively. **The maturation of these two axes could contribute to distinct components of memory development, with distinct developmental timings; but this remains largely unknown to this date, as few studies sought to integrate these two aspects of hippocampal organization.**

1.5.2 Neocortical regions

Besides the hippocampus, episodic memory has been shown to be supported by neocortical regions: among them, a particularly important role is attributed to the PFC (e.g., Ankudowich et al., 2019; Bowman & Zeithamova, 2018; Ciaramelli et al., 2020; Ghetti & Bunge, 2012; Jin & Maren, 2015; Wing et al., 2021).

Prefrontal cortex

The PFC is often considered as one of the main neural correlates of episodic memory with the hippocampus (Henson et al., 1999; Lepage et al., 2000; Tulving, 2002; Wheeler et al., 1997). Distinct areas within the PFC have been associated with distinct aspects of episodic memory, such as processing the affecting value of episodic memories, self-referential processes, episodic inference, strategic retrieval, information selection, and maintaining online search results (Bowman & Zeithamova, 2018; Gagnon et al., 2010, 2011; Javadi and Walsh, 2012; Lin et al., 2016; Sandrini et al., 2003; Wing et al., 2021). In particular, the PFC has been shown to be decisive during episodic recall, mainly by its 'monitoring' role based on strategic and control processes for search and access of information (e.g., Henson et al., 1999)

The PFC is one of the later-developing brain regions, with age-related changes extending into adolescence. Age-related changes of cortical thickness, grey matter volume, and white matter volume in the PFC have been reported, and related to memory development (Lenroot & Giedd, 2006; Ofen et al., 2007; Paus, 2005; Sowell et al., 2001, 2004). With age, older subjects tend to recruit more their PFC during

memory tasks, in relation with better episodic memory performance; by contrast, an absence of age-related differences, or even age-related decreases, of hippocampal recruitment has often been reported (DeMaster & Ghetti, 2013; Ghetti & Bunge, 2012; Ofen et al., 2007; Selmeczy et al., 2019). Improvements of episodic memory in middle childhood and adolescence have been related to an increased importance of encoding and retrieval strategies and other mnemonic control processes which are mediated by the PFC (reviewed in Ghetti & Bunge, 2012). Overall, this suggests that the locus of memory improvements progressively switches from the hippocampus to the PFC during middle childhood or adolescence; but as recent studies have shown that hippocampal maturation is in fact protracted, how maturational processes in the PFC and in the hippocampus both contribute to episodic memory development remains unclear.

Parietal cortex

Two subdivisions of the parietal cortex are important to episodic memory: the posterior parietal cortex (PPC), composed of the inferior and superior parietal lobules, and the precuneus. The PPC is mainly known for its role in attention, but converging evidence have demonstrated its importance in episodic encoding and retrieval. Various accounts have been proposed to explain the nature of its role in episodic memory (e.g., Cabeza et al., 2008). On the other hand, the precuneus has been mainly associated to the recollection of episodic memories, particularly to mental imagery (Trimble & Cavanna, 2008). The parietal cortex also has a protracted development that extends into adolescence. The contribution of the parietal cortex to episodic memory development is relatively poorly known, but evidence suggest, as for the PFC, that increasing recruitment of the parietal areas with age are related to improvements of episodic memory (e.g., DeMaster & Ghetti, 2013; Paz-Alonso et al., 2008; discussed in Ghetti & Bunge, 2012).

Neocortical regions: summary

The prefrontal and the parietal cortices play key functions in episodic memory and particularly after middle childhood, but their **role during early childhood needs to be further elucidated.**

1.5.3 Brain maturation and episodic memory development

The development of episodic memory is closely related to the maturation of its neural correlates, both at the structural and functional levels. From what precedes, we can **organize maturational changes of the brain critical for episodic memory into two categories.**

The first concerns the structural and functional changes affecting the hippocampus. These changes can either concern its **transversal organization** (subfields), which is reflective of its internal connectivity and is crucial to some components of episodic memory, such as pattern separation and completion; or its **longitudinal organization** (anterior-posterior axis), which is reflective of its external connectivity, i.e. the integration of the hippocampus to cortical networks.

The **second category concerns structural and functional changes affecting extra-hippocampal regions**, particularly neocortical areas such as the PFC.

Given that brain maturation is heterogenous, we could expect age-related differences in functional and structural properties of the hippocampus to be particularly important during the childhood amnesia period. Hippocampal maturation after childhood amnesia is less dramatic, but still noteworthy; therefore, its maturation could still contribute to the development of some episodic memory components. By contrast, because the maturation of neocortical areas is particularly protracted, we could expect to observe a greater association between episodic memory function and neocortical areas in older, compared to younger, children.

1.6 Aims and hypotheses

1.6.1 General objective

Our general objective was to **examine how the relationship between episodic memory and its neural substrates in the developing brain can highlight the main characteristics of episodic memory development**, and potentially contribute to the understanding of the phenomena of infantile and childhood amnesia.

We used a multi-component approach to discover how specific components of episodic memory components could be associated with specific brain areas. We also sought to describe **age-related differences in these brain-behavior associations**, which might reflect distinct states of episodic memory maturation.

1.6.2 Studied episodic memory components

In that order, we mainly studied three components of episodic memory: pattern separation, episodic recall, and episodic autobiographical recall. These components were chosen because the literature indicates that they are related to distinct neural substrates: pattern separation is mainly associated to specific hippocampal subfields (section 1.4.1); episodic recall to the hippocampus and to neocortical regions (section 1.4.2); episodic autobiographical recall to the hippocampus, neocortical regions, and a large-scale cortical and subcortical network (section 1.4.3).

1.6.3 Studied aspects of brain maturation

To specifically associated components of episodic memory with brain maturation, we studied the transversal (subfields) and longitudinal axes of organization of hippocampal development (section 1.5.1), as well as the connectivity within cortical networks, notably comprising neocortical regions involved in episodic memory (section 1.5.2). This reflect, respectively, hippocampal maturation and the maturation of the

integration (measured with connectivity) between the hippocampus and extra-hippocampal areas, as well as between extra-hippocampal areas themselves.

Given that brain maturation is heterogenous, it is possible that brain maturation contributes to episodic memory development with developmental timings that are different for episodic memory components and brain regions:

(a) **The rapid development of pattern separation during early childhood**, in relation with the fast maturation of the transversal axis of hippocampal organization, **could importantly contribute to episodic memory development during the childhood amnesia years**.

(b) On the other hand, **the continuous development of episodic recall** could depend more on the hippocampus during early childhood, and on **neocortical maturation during middle childhood and adolescence**.

(c) **Episodic autobiographical memory** could follow an **intermediate pattern**: as suggested by childhood amnesia, it could follow a **rapid development** during early childhood, in relation with **hippocampal maturation**; **later gains** would be related to **neocortical maturation**.

1.6.4 Aims and hypotheses

We saw (sections 1.2 and 1.3) that the development of episodic memory follows distinct stages, and that episodic memory is comprised of a variety of components (section 1.4) that might have different developmental trajectories. Therefore, our first aim was to describe and compare the developmental trajectories of distinct components of episodic memory and to examine their relationships in the developing brain.

***

Aim 1. Examining the developmental trajectories and relationships between components of episodic memory in the developing brain.

Hypothesis: Pattern separation will show important age-related differences during early childhood, followed by more moderate improvements. The development of episodic recall will be linear. The development of episodic autobiographical memory will be linear from middle childhood, but might show important age-related differences during early childhood, given the phenomena of childhood amnesia. Performance at episodic recall and episodic autobiographical recall will be correlated as they neural correlates overlap, but as pattern separation depends on specific subfields, it will be behaviorally independent from the other components of episodic memory.

Experimental contribution: this aim was the focus of Study 1 of our dissertation.

***

We also saw (section 1.5.1) that the hippocampus could be described either by its transversal or longitudinal organization. Understanding how both types of hippocampal organization contribute to episodic memory development remains to be elucidated. This consideration defines our second aim:

Aim 2. Describing hippocampal organization contributes to episodic memory development.

Aim 2.1. Describing how hippocampal subfields contribute to episodic memory development.

Aim 2.2. Describing how the longitudinal organization of the hippocampus contribute to episodic memory development.

Hypothesis: The transversal organization of the hippocampus will be related to pattern separation. The longitudinal organization of the hippocampus will also be related with episodic memory. But as it reflects the integration of the hippocampus to cortical networks, it will be related with measurements of episodic recall or of episodic autobiographical recall rather than with pattern separation. Importantly, we expect to

find age-moderated effects on these brain-behavior relationships, showing distinct relations of hippocampal maturity and episodic memory function over development.
Experimental contribution: Aim 2.1 was the focus of Study 2 of our dissertation. Aim 2.2 was the focus of Study 3.

***

Besides the hippocampus, episodic memory is supported by a large-scale cortical network that closely interact with the hippocampus through structural and functional connectivity (section 1.5.2). This defines our third aim:

Aim 3. Describing the how connectivity within large-scale networks contribute to episodic memory development.
Aim 3.1. Describing how structural connectivity between and within the hippocampus and extra-hippocampal regions contribute episodic memory development.
Aim 3.2. Describing how structural connectivity between and within the hippocampus and extra-hippocampal regions contribute episodic memory development.
Hypothesis: Connectivity within large-scale networks will be related with episodic recall and episodic autobiographical recall, but not pattern separation. Specifically, connectivity of neocortical regions such as the PFC should be more associated with memory performance in older children compared to younger children.
Experimental contribution: Aim 3.1 was the focus of Study 4 of our dissertation. Aim 3.2 was the focus of Study 5.

***

1.6.5 Summary of the approach

To address these three questions, we studied 50 children aged from 4 to 12 years old, i.e. in a developmental period comprising both children during and after the childhood amnesia period. The extent of this sample allowed us to study a period covering most of childhood (the infant/toddler years excepted), and therefore to potentially identify

developmental moments where some components (e.g. pattern separation) reach adult-like maturation. We examined cerebral maturation using high-resolution structural MRI to describe the integrity of hippocampal subfields; diffusion-weighted imaging (DWI) to describe the maturity and integrity of white matter tracts connecting the hippocampus and extra-hippocampal areas; and task-free fMRI to describe the longitudinal organization of the hippocampus, as well as the functional connectivity between the hippocampus and extra-hippocampal areas, and, more generally, within large-scale brain networks.

1.6.6 Experimental contributions

The results of our approach are presented in Chapter 3 of this manuscript, and are organized in three main parts (Figure 5).

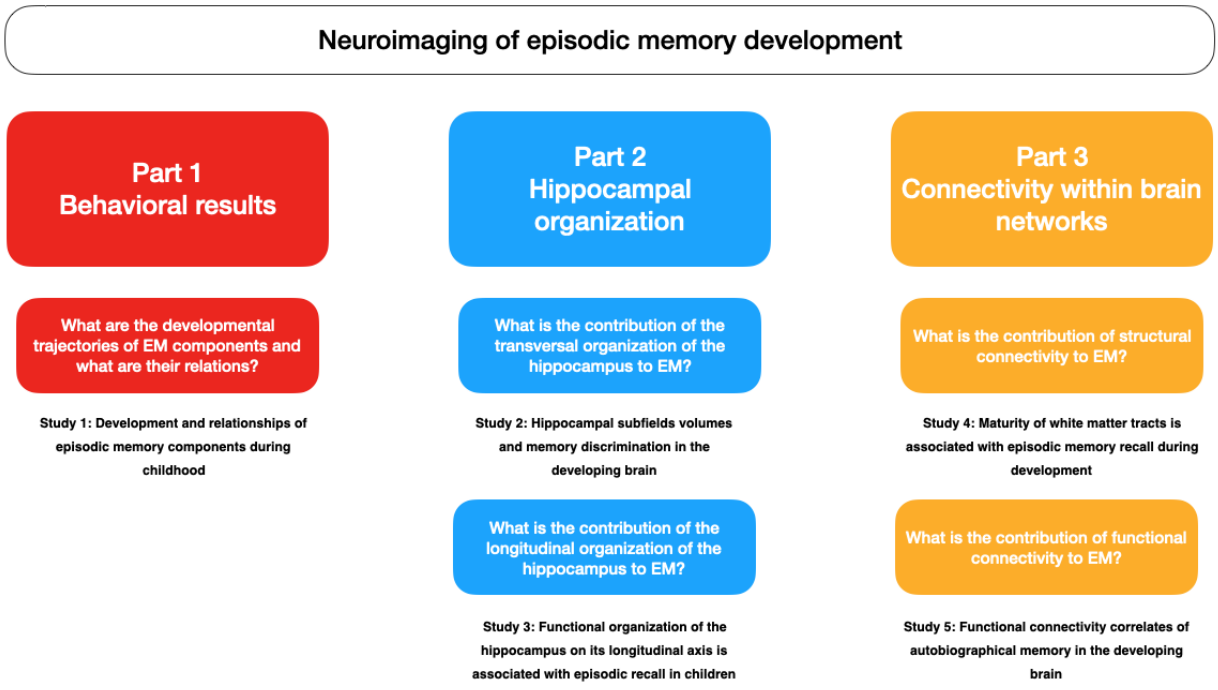

Figure 5. Summary of our 3 aims and the experimental contributions addressing these aims.

Part 1 of the results is composed **Study 1** (section 3.1) which **presents the age-related differences of episodic memory components as well as their relationships**. This study addresses Aim 1.

Part 2 focuses on describing the relationship between **hippocampal organization** and episodic memory in the developing brain, addressing Aim 2. **Study 2** (section 3.2) present results regarding the **transversal** organization of the hippocampus (Aim 2.1). **Study 3** (section 3.3) present results regarding the **longitudinal** organization of the hippocampus (Aim 2.2).

Part 3 presents the relationship between **brain connectivity** and episodic memory in the developing brain (Aim 3). **Study 4** (section 3.4) presents results regarding structural connectivity (Aim 3.1). **Study 5** (section 3.5) presents results regarding functional connectivity (Aim 3.2).

Chapter 2. Methods

2.1 Population

For the objectives of this thesis, we studied 50 healthy children aged from 4 to 12 years old (mean age=8.1, standard deviation=2.28, 22 females). Data acquisition was performed in NeuroSpin, Gif-sur-Yvette, France, and consisted in neuroimaging (MRI) acquisitions and behavioral assessments. Among the 50 studied subjects, 2 refused to take part to the neuroimaging acquisitions, and 3 were excluded because of a past history of learning disabilities or structural anomalies detected on the MRI. They were therefore not included in our analyses.

2.2 Behavioral assessments

Children underwent a behavioral assessment protocol outside of the scanner. This protocol consisted of tasks measuring different components of episodic memory, and a task measuring fluid intelligence that was used as a control task. The tasks measuring episodic memory were chosen based on their validity in measuring the components of episodic memory of interest for our dissertation. We also chose tasks based on their ability to provide multiple measures of interest related to the components of episodic memory, in order to avoid developing a behavioral protocol that included too many different tasks, so as not to inflate protocol duration and cognitive demand.

Thus, the following tasks were selected :

- The children version of the California Verbal Learning Test (CVLT-c, Delis, 1994). This test was chosen as a measurement of **episodic memory recall**. The CVLT-c was chosen as it provides several measurements of episodic recall (free or cued, with short or long delay). Moreover, it is a tool of reference for assessing episodic memory in the context of healthy and pathological development, meaning that its use could facilitate the comparison of our results with those of other studies, notably in the context of pathological development (see the Annexes section).
- The Mnemonic similarity task (MST) (Ngo et al., 2018; Stark et al., 2019) is a tool of reference to measure memory discrimination, a behavioral outcome of **pattern separation**. The MST also provides a measurement of **recognition memory** for single items.
- The Child Autobiographical Interview (CAI) (Willoughby et al., 2012) is a measurement of **episodic and semantic autobiographical memory.** This task was chosen among other autobiographical memory tasks because it provides a precise and objective rating of autobiographical recall. Morever, it allows to distinguish between **episodic and semantic aspects of autobiographical**

memory. It provides separate measurements for **distinct types of episodic autobiographical information** (e.g., event information, context information).

- Raven's progressive colored matrices (PM47), a measurement of fluid intelligence, was included as a domain-general measurement of cognitive performance.

These tasks were selected after conducting a pilot study on 28 children aged 6 to 12 years. The main purpose of the pilot study was to test the feasibility of using the CAI on children younger than age 8, to which we concluded positively, as the study of Willoughby et al. (2012) was performed on age 8-16 subjects. The pilot study also included a measure of language (the WISC-IV or WPPSI "comprehension" subtest, depending on the age of the children) to test potential relationships between language skills and measures of autobiographical memory recall. Because we found no significant correlation between language skills and autobiographical recall (see details in Study 5), we did not include a language task in our final protocol to avoid excessive protocol duration. The duration of the final behavioral protocol was 45 minutes to 1 hour, depending on the child.

The memory tasks used in our final protocol, the components of episodic memory they measure, and the number of subjects with usable data for each of these tasks are presented Table 2 below.

Task	Measured EM component	% of subjects with usable data (N)
CVLT-c	Episodic verbal recall	86% (43)
MST	Pattern separation, recognition memory	74% (37)
CAI	Episodic and semantic autobiographical memory	76% (38)
Raven PM47	Fluid intelligence	90% (45)

Table 2. Tasks used in our protocol and data attrition for each task.

Behavioral data attrition was caused by four factors: 1) data was not analyzed in the following cases: if subjects were excluded because of a past history of learning disabilities; if they showed structural anomalies on their MRI images; if they refused to take part to the neuroimaging acquisitions (N=5). 2) For the MST test, the first subjects of our cohort did not perform this task because the MST task was not operational at the time (N=6). 3) For the CAI, the audio file containing the recordings of the reported narratives was lost or corrupted and thus unusable in some cases (N=6); 4) Some subjects were excluded because they showed poor compliance during the overall behavioral assessment or during some tasks (N=2).

The procedure for each task is briefly described below. Detailed descriptions are reported in the studies of the Results section (CVLT-c: Study 4; MST: Study 2; CAI: Study 5).

2..2.1 CVLT-c

We used the French adaptation of the children's version of the CVLT-c (Delis, 1994). Briefly, the procedure of the CVLT-c consists in presenting a list of words (list A) to the

participant 5 times. Each trial is immediately followed by the free recall of the words of list A. Then, a distractor list (list B) is presented to the participant and followed by free recall of words of list B. Then, the participant is asked to recall words from list A. This free recall is followed by a cued recall of words from list A based on the semantic categories to which list A words belong. After a 20 minutes delay, the participant is again asked to recall words from list A (free recall, then cued recall). The task ends with a recognition test for list A words among a list comprising list B distractors and new words (lures). In our analyses, to avoid committing multiple comparisons between statistical tests, we chose to focus on three scores: Short-Delay Free recall, Long-Delay Free Recall, and Long-Delay Cued recall. These tests were chosen as measures of episodic recall and because they allowed to contrast two types of conditions: delay duration (short or long) and recall type (free or cued).

2.2.2 Pattern separation

The MST (see Ngo et al, 2018) for an application in children), was used to assess memory discrimination, which is a behavioral proxy for pattern separation (see Results chapter, Study 2 for details). In short, the MST consists of an initial incidental encoding phase in which images are presented to the participant who must perform a semantic task (indicate whether the images represent objects that can be used indoors or outdoors). As soon as the incidental encoding phase is over, the test phase begins, during which images are presented to the participant again: among them, 33% are images that were identical to images presented in the first phase (target trials), 33% are similar to images of the first phase (foil trials), and 33% are novel images (lure trials). Memory discrimination (and thus pattern separation) is assessed as the percentage of correctly identified “target” trials, from which is subtracted the percentage of responses in which subjects incorrectly identified target trials as lure trials (similar is confused for identical). Additionally, recognition memory for single items is computed with the Item memory index, which is the percentage of correctly identified target trials, from which is subtracted the percentage of responses in which subjects incorrectly identified target trials as foil trials (identical is confused for new).

2.2.3 Child Autobiographical Interview (CAI)

We administered a modified version of the CAI (Willoughby et al. (2012) which is described in more details in Study 5. In short, the CAI is an autobiographical interview based on a cue-word paradigm: participants are provided with cue words, which they use to recall a personal memory that happened to them in relation with the cue (e.g., if the cue word is 'toy', they have to recall an autobiographical memory related to a toy). Children were trained to understand that they should recall specific episodes (episodic autobiographical memories). Narratives were recorded and transcribed. We counted the number of episodic and semantic details reported in each narrative. Within recalled episodic details, we distinguished between details related to events ("I was playing with a friend") and details related to context ("it was at my house last Thursday").

2.2.4 Raven's Progressive Matrices 47 (PM47)

The PM47 is a measurement of fluid intelligence (Raven, 2000). In each trial, the child is are shown a set of several figures. They have to select the figure that logically completes the set among several choices. Trials are of increasing difficulty. Raw scores were converted in standard scores using the PM47's norms.

2.3 MRI acquisitions

We developed a multimodal MRI acquisition protocol including a T1-weighted (T1w) image, a hyper-resolute T2-weighted (T2w) image centered on the hippocampus (for hippocampal subfields segmentation), a DWI sequence to study the structural connectivity, and a resting-state fMRI sequence to study resting-state functional connectivity. Images were acquired on a Siemens PRISMA 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil.

Several MRI sequences parameters, varying in spatial or temporal resolution, were initially assessed in a pilot study conducted on 4 subjects. The goal of this study was to determine which sequence parameters were best fitted to minimize sequence duration (for children, shorter is better) and sensitivity to motion, while maximizing signal-to-noise ratio (SNR). Another objective was to verify that the selected sequences had good SNR coverage in the medial temporal lobe (MTL) region, given that this region is subject to magnetic susceptibility artifacts causing drop of signal (Olman et al., 2009). Sequences were selected based on analyses of their SNR (for T1w/T2w), temporal SNR (for fMRI), or on the estimation of the quality of the eigenvectors reconstructed with diffusion tensors (for DWI). The selection of MRI sequences was performed with the help of Alexis Amadon, Marie Chupin, Jessica Dubois, David Germanaud, Franck Mauconduit, and Lucie-Hertz Pannier, which are all researchers at the NeuroSpin Imaging Centre, Centre d'Etudes de Saclay, Gif-sur-Yvette, France. Chantal Ginisty (radiology technician at NeuroSpin) also provided precious help for the parametrization of T2w images.

The selected sequences are reported in Table 3 below.

Anatomical/functional	Modality	Parameters	% of subjects with usable data
Anatomical	T1-weighted	TR=300ms, TE=2.98ms, 0.9mm isotropic resolution, 175 slices	90%(45)
Anatomical	Diffusion Weighted Imaging	b=1500, 60 directions, + b=1000, 30 directions, TE = 55.2ms; 1.8mm isotropic resolution, 78 slices	78%(37)
Anatomical	T2-weighted	TR=3970ms, TE=89ms, FOV 256mm, 0.45 x 0.45 mm in-plane resolution, 2.1 mm thru-plane resolution, 92 slices	56%(28)
Functional	T2*	TR=1.81, TE=30.4, 2mm isotropic resolution, 69 slices	78% (39)

Table 3. MRI sequences used in our protocol and data attrition for each sequence.

During the neuroimaging protocol, sequences were acquired in the order shown Figure 6 below. Given the number of sequences and the overall duration of the neuroimaging protocol (approximately 45 minutes), data attrition was variable among sequences. The sequence acquired at the end of the protocol (T2w images) had more attrition than the ones acquired at the beginning (T1w images). The studies of the Results chapter provide a detailed description of sequence parameters, factors of data attrition, and preprocessing methods.

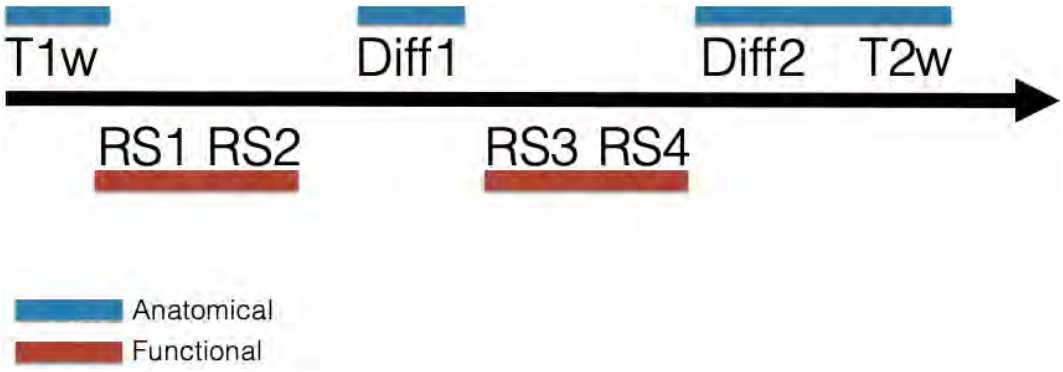

Figure 6. Order of the acquisition of MRI sequences. The arrow represent the passage of time. T1w=T1-weighted. RS=resting-state. Diff=Diffusion-weighted imaging. T2w=T2-weighted. The numbers represent the number of the session (for resting-state) or of the sequence (for diffusion: Diff1=60 directions and Diff2=30 directions).

During the anatomical sequences (in blue in Figure 6), children watched an animation movie while being scanned. For the functional sequences, children watched a clip displaying abstract shapes and deprived of narration, which was conceived specifically for resting-state neuroimaging (Vanderwal et al., 2015); see Study 5 for details.

2.4 Methodological study: Anatomical variability in the medial temporal lobe region

Given our interest in the medial temporal lobe (MTL) region and in the hippocampus to study episodic memory, a prerequisite to our investigations was to determine the anatomical variability of the MTL/hippocampus region as well as the factors potentially influencing this variability. Indeed, if the anatomical organization of the MTL is influenced by systematic factors of anatomical variability, then our investigations of hippocampal structure and function, as well as of the parahippocampal gyrus, would have to take these factors into account in order to perform accurate anatomical (e.g., segmentation) or functional analyses.

A factor potentially influencing the anatomy of the MTL is the morphology of the collateral sulcus. The collateral sulcus is a brain sulcus along the parahippocampal gyrus. Previous research on adults have suggested that different types of collateral sulcus conformation could impact the location of the neighboring parahippocampal cortices as well as of the hippocampus. Differences in sulcal conformation could also be related to functional or behavioral differences.

To examine the relation between colateral sulcus morphology and the anatomical variability of MTL structures, we conducted a study that was published in *Frontiers in Neuroanatomy.* The aim of this study was to quantify the anatomical variability of MTL structures in the developing brain using three-dimensional probabilistic maps representing their average location. Analyses were conducted in a previously acquired dataset, which was not used in our other studies.

We analyzed the relationship between the collateral sulcus and MTL structures by developing a new method for analyzing factors influencing anatomic localization. We grouped subjects according to their collateral sulcus morphology and compared the extrema of each subject's segmented MTL structure in the x, y, and z directions using

permutation tests. We concluded that the shape of the sulcus did not significantly influence the average location of MTL structures in the developing brain. We made available to the scientific community the probabilistic maps of MTL structures, which have been used by some studies to assess structure-function relationships within the MTL. As we have developed a new method to analyze the factors influencing the localization of brain areas, this study can be considered as a methodological contribution to our thesis. We present the published manuscript below.

The DOI link of the publication is: https://doi.org/10.3389/fnana.2018.00098

Article title: Three-dimensional probabilistic maps of mesial temporal lobe structures in children and adolescents' brains

Authors: Antoine Bouyeure, David Germanaud, Dhaif Bekha, Victor Delattre, Julien Lefèvre, Charlotte Pinabiaux, Jean-Francois Mangin, Denis Rivière, Clara Fischer, Catherine Chiron, Lucie Hertz-Pannier, Marion Noulhiane.

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Three-Dimensional Probabilistic Maps of Mesial Temporal Lobe Structures in Children and Adolescents' Brains

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The hippocampus and the adjacent perirhinal, entorhinal, temporopolar, and parahippocampal cortices are interconnected in a hierarchical MTL system crucial for memory processes. A probabilistic description of the anatomical location and spatial variability of MTL cortices in the child and adolescent brain would help to assess structure-function relationships. The rhinal sulcus (RS) and the collateral sulcus (CS) that border MTL cortices and influence their morphology have never been described in these populations. In this study, we identified the aforementioned structures on magnetic resonance images of 38 healthy subjects aged 7–17 years old. Relative to sulcal morphometry in the MTL, we showed RS-CS conformation is an additional factor of variability in the MTL that is not explained by other variables such as age, sex and brain volume; with an innovative method using permutation testing of the extrema of structures of interest, we showed that RS-SC conformation was not associated with differences of location of MTL sulci. Relative to probabilistic maps, we offered for the first time a systematic mapping of MTL structures in children and adolescent, mapping all the structures of the MTL system while taking sulcal morphology into account. Our results, with the probabilistic maps described here being freely available for download, will help to understand the anatomy of this region and help functional and clinical studies to accurately test structure-function hypotheses in the MTL during development.

Free access to MTL pediatric atlas: http://neurovault.org/collections/2381/.

Keywords: medial temporal lobe, probabilistic maps, development, hippocampus, parahippocampal gyrus

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INTRODUCTION

The medial temporal lobe (MTL) plays a pivotal role in memory and learning. During childhood and adolescence, memory abilities undergo a continuous development in relation to the anatomical maturation of MTL structures. These structures are the hippocampus (HC), divided along its rostrocaudal axis between the hippocampal head (HH), body (HB), and tail (HT), and the

adjacent cortical areas of the parahippocampal gyrus (i.e., temporopolar, perirhinal, entorhinal, and parahippocampal cortices) to which the HC is reciprocally connected (Squire et al., 2004; Gogtay et al., 2006; Poppenk and Moscovitch, 2011; Poppenk et al., 2013; Strange et al., 2014). Together, HC subparts and adjacent cortices form a hierarchically organized system with both integrated functioning and structure-related specificities. Our understanding of the functional maturation of MTL structures during childhood and adolescence is, however, limited (e.g., DeMaster and Ghetti, 2013; DeMaster et al., 2013; Paz-Alonso et al., 2013; Pinabiaux et al., 2013; Riggins et al., 2016) compared to what is known in adults.

Taking into account the anatomical variability of MTL structures is a prerequisite to the study of their functional maturation during early years of life. Current anatomical and functional investigations of MTL in children and adolescents are constrained by the use of adult-based maps and landmarks that have not, or only partially, been adapted or confirmed in younger populations yet (e.g., DeMaster et al., 2013, 2014). Meanwhile, the complex sulcal pattern of the MTL defines a framework of anatomical landmarks to be used for locating the adjacent cortices (Insausti et al., 1998; Huntgeburth and Petrides, 2012; Augustinack et al., 2013a; Kivisaari et al., 2013). In fact, the rhinal sulcus (RS) and the collateral sulcus (CS) display various morphological conformations (Ono et al., 1990; Kim et al., 2008; Feczko et al., 2009; Huntgeburth and Petrides, 2012; Cikla et al., 2016). One of the most visible sulcal variation in the MTL is that the RS and CS can be either connected or separated (at a level slightly caudal to the caudal tip of the entorhinal cortex), which may impact the boundary localization, and the volume, surface area and cortical thickness of the adjacent cortices (Pruessner et al., 2002; Feczko et al., 2009). Still, these relations are poorly understood in adults and remain unexplored in children and adolescents. While in adults, probabilistic maps have already been proposed for the HC subfields, the perirhinal cortex and the entorhinal cortex (Amunts et al., 2005; Fischl et al., 2009; Augustinack et al., 2013a; Iglesias et al., 2015; Yushkevich et al., 2015), and for sulcal morphological variants (RS and CS proper) (Huntgeburth and Petrides, 2016), probabilistic description of the anatomical variability of all MTL structures (hippocampus, adjacent cortices, and sulci) in a group of children and adolescents has not been made. Such an atlas would be useful in several regards. First, using an adult atlas in children is limited by anatomical variation induced by development. The hippocampus is known to have a protracted structural maturation until adulthood that affects distinctly its head (anterior part) and tail (posterior part) (e.g., Gogtay et al., 2006), while the structural maturation of MTL cortices is almost unknown (see Hu et al., 2013). Second, mapping the anatomical variability of MTL sulci is relevant to understand the anatomical variability of the cortices they border. For example, the location of a functional region such as the parahippocampal place area is closely related to the morphology of the Collateral Sulcus (Huntgeburth and Petrides, 2016; Weiner et al., 2018). Third, an atlas of all MTL structures using a unified set of segmentation rules has never been made available. Therefore, a pediatric of all MTL structures, thereby taking into account age-related anatomical variability, would be useful to test structure-function relationships during development.

Here, we provide a detailed structural description of the MTL region in children and adolescents aged 7 to 17 years old, following automatic segmentation with the BrainVisa pipeline and according to a set of unified MTL manual segmentation rules for specific cortices that have been extrapolated from adult anatomical histological correlates as proposed in Hu et al. (2013) and Pinabiaux et al. (2013). For this purpose, we followed several steps, investigating successive hypotheses: (1) we confronted the RS-CS conformation observed in children and adolescents to that reported in adults to determine developmental characteristics of sulcation in the MTL; (2) we investigated whether the sulcal conformation in children and adolescents was related to age, sex and brain size; (3) we searched for an effect of the RS-CS conformation on morphometrical features of these sulci; (4) we searched for a difference in sulci location between the two RS-CS conformations at the group level, in the normalized space; (5) we generated probabilistic maps of each structure (RS, CS, cortices of the parahippocampal gyrus and HC subparts), *i.e.,* maps representing the variability of the location of anatomical structures after normalization in the MNI space, based on relative occurrence at the voxel level across subjects (Amunts et al., 2005; Eickhoff et al., 2005) to obtain an atlas of MTL structures during childhood. These maps are freely available for visualization and download on NeuroVault[1].

MATERIALS AND METHODS

Population

We studied 38 healthy subjects aged from 7 to 17 years ($M = 11.71$, $SD = 3.03$). There were 19 girls ($M = 12.93$, $SD = 3.13$) and 19 boys ($M = 10.15$, $SD = 2.15$). All subjects were right-handed and none had any history of medical condition. The study was approved by an appropriate research ethics board (CPP number 11-008). All subjects agreed to participate and their parents gave their informed consent to the study.

Neuroimaging Data

MRI data were acquired on a 3T scanner device (Tim Trio, Siemens Medical Systems, Erlangen, Germany) with a 3D MPRAGE T1-weighted high-resolution sequence (TR: 2300 ms; TE: 2.98 ms; FOV: 256 mm; 64*64 matrix; 160 sagittal slices, 1 mm3 isotropic) and analyzed with BrainVisa (v.4.4.0)[2] including the Anatomist visualization module and the Morphologist segmentation pipeline (Rivière et al., 2009).

Sulcal Analysis

Extraction, Correction, and Classification Into Morphological Sulcal Types

The Morphologist pipeline performs the automatic segmentation of both hemispheres, gray matter (GM) and white matter (WM)

[1]http://neurovault.org/collections/2381/

[2]http://brainvisa.info

masks, then computes the inner cortical surface (GM-WM interface) and the outer cortical surface (pial surface) meshes, and finally sulcal proxies that are casts of the sulci with both a surfacic (mesh) and volumetric (voxel cluster) representation. The last step of the pipeline consists in anatomical labeling of the sulci through a localization-based probabilistic method named Statistical Probabilistic Anatomy Map (SPAM) (Perrot et al., 2011).

Automatical labeling of CS and RS was corrected manually when necessary in each hemisphere; the SPAM method often mislabels collateral branches or segments of the CS and RS, mistaking them, for instance, with parts of the neighboring occipito-temporal sulcus. Indeed, following nomenclature of MTL sulci, we distinguished between RS and CS rather than labeling the RS as the 'rostral part' of the CS (see Insausti et al., 1995; Pruessner et al., 2002; Huntgeburth and Petrides, 2012 for review). Both manual correction of CS-RS boundary and labeling relied on a reference atlas (Ono et al., 1990) and on a recent study (Huntgeburth and Petrides, 2012), based on which we further distinguished two components to the CS: the CS proper and the CS post. Basically, the RS is more rostral and medial, delineating the entorhinal cortex (ERC) and the rostral perirhinal cortex (PRC) (see **Figure 1A**). The CS proper is more caudal and lateral, delineating the PRC and the parahippocampal cortex (PHC), while the CS post starts caudally to the caudal bit of the CS proper, extending into the occipital lobe (Ono et al., 1990; Huntgeburth and Petrides, 2012; Kivisaari et al., 2013; Chau et al., 2014; Lehman et al., 2016). The caudal border of the uncus was used to delimit the caudal border of the RS. For the CS (taken as whole), the caudal border of the uncus and the position of the amygdala delineated its rostral border, while the most caudal tip of its main medial bank delineated the caudal border. The CS was then separated into rostral (CS proper) and caudal (CS post) segments. The caudal tip of the body of the HC, at the level of the splenium of the corpus callosum as seen in coronal view in the MNI coordinates system, was used as a transition landmark between CS proper and CS post (Huntgeburth and Petrides, 2012). This landmark was also used to delineate the caudal border of the PHC. Hence, the limit between CS proper and CS post (Huntgeburth and Petrides, 2012) is deemed to coincide with the transition from memory-allocated cortices in the parahippocampal gyrus to vision-related cortices in the lingual gyrus.

After extraction and correction, we categorized the MTL sulcal patterns into two types based on either the connection (Type 1) or the separation (Type 2) between RS and CS proper (**Figure 1B**). In the same fashion, CS post was labelized as Type 1 when it followed caudally a Type 1 CS proper, and Type 2 otherwise. Morphometric measurements (maximum depth of the sulcus, mean depth of the sulcus, and length of the sulcus) were performed for each sulcus in the native space with the dedicated BrainVisa tool.

Probabilistic Maps of MTL Sulci

Masks of the accurately labeled RS, CS proper and CS post in each hemisphere of each subject were extracted with BrainVisa's module Anatomist The masks were then normalized in the MNI stereotaxic space with SPM12 using the 'old normalize' tool[3]. Each mask was smoothed with a 3 mm Gaussian kernel to increase the continuousness of the map. Mean volumes were computed over all subjects for each sulcus of interest, separately for each hemisphere. Therefore, in the obtained maps, the voxels intensities range from 0 (voxel absent in every individual mean map) to 1 (voxel present in every individual mean map). Finally, a threshold of 5% was applied to get rid of outlier voxels (*i.e.*, to keep voxels that were present in at least 5% of subjects corresponding to at least one subject over the whole group). These maps were superimposed on the MNI152 1 mm brain mask.

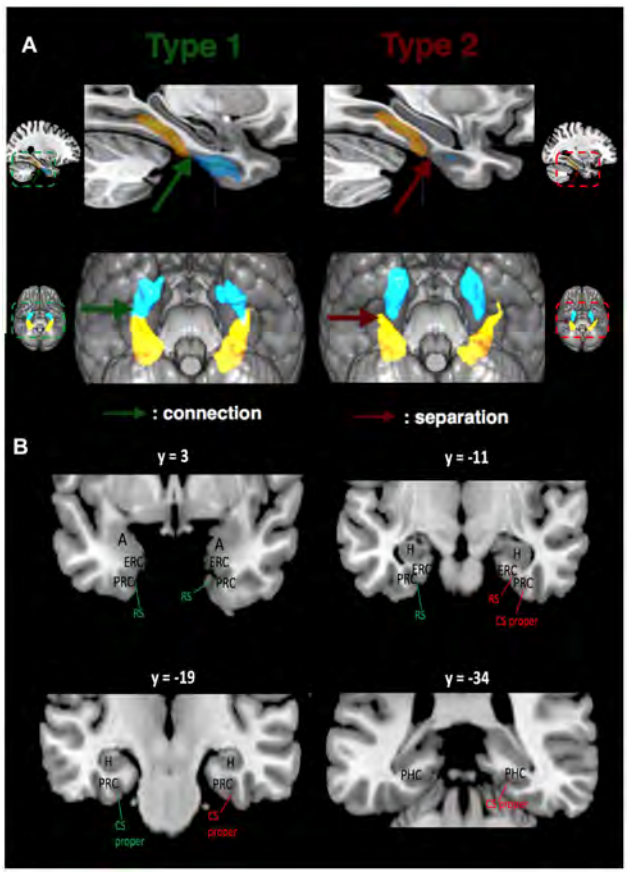

FIGURE 1 | Relations between CS proper (in yellow) and RS (in blue) for both sulcal Types shown with mean sulcal maps. **(A)** Left: Mean Type 1 RS and CS proper are connected (shown by green arrow). Right: Mean Type 2 RS and CS proper are separated (shown by red arrow). Mean RS and CS proper (at the population level) for Types 1 and 2 are surimposed on the MNI152 template of MRIcro. **(B)** Location of MTL structures. MNI coordinates are provided for the y-axis. The same color code is used: green indicates connection between RS and CS proper, while red indicates separation. Abbreviations: A, amygdala; H, hippocampus; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex.

[3]https://www.fil.ion.ucl.ac.uk/spm/software/spm12/

Mesial Temporal Structures Analyses

Manual Segmentation of MTL Cortices and HC Subparts

Medial temporal lobe cortices (ERC, PRC, PHC, and TPC) and HC subparts (HH, HB, and HT) were manually delineated on both sides in each subject (**Figure 2**). Manual segmentation of MTL regions was done accordingly to the Insausti et al. (1998) protocol, except for the PHC that was segmented in reference to the protocol of Pruessner et al. (2002), as we did in some of our previous works (Noulhiane et al., 2006, 2007; de Vanssay-Maigne et al., 2011; Pinabiaux et al., 2013). The HC subparts were segmented according to criteria detailed in Kivisaari et al. (2013). Details are provided in **Supplementary Table 1**. Given our population of children and adolescents, we adjusted our criteria of HC segmentation according to hippocampal development (see Insausti et al., 2010). The translation of these criteria for the segmentation of MTL cortices and HC subparts in children and adolescents has already been proposed (e.g., Hu et al., 2013; Pinabiaux et al., 2013) and is deemed valid in the absence of conflicting data on anatomical histological correlation at that age.

Probabilistic Maps of MTL Cortices and HC Subparts

Probabilistic maps of MTL cortices and of HC subparts were generated with the same method than for sulcal probabilistic maps, at the exception of the smoothing step, which was not applied because cortical structures and HC subparts are larger than brain sulci, and therefore don't need smoothing to reach important inter-subject overlap.

Statistical Analyses

The following analyses were conducted, with a p-value of 0.05 as the threshold for significance for each analysis:

(1) We computed the proportion of Type 1 and Type 2 RS-CS proper conformations (which were observed in subject space for each sulci) and tested it against the proportions reported in adult literature with a one-proportion z-test ("proportion_z-test" function from python's StatsModels package).

(2) We tested whether age, sex, brain size (volume and surface) and sulcal morphometric features, as measured in subject space, were correlated to RS-CS proper conformation, with t-tests (t-test_ind function Python's SciPy package), corrected for multiple comparisons with FDR ("fdr correction" function from python's statsmodels package).

(3) We assessed the effect of the RS-CS proper conformation on the MLT sulcal and cortical spatial locations in normalized space. To that purpose, we located the extrema along the mediolateral, rostrocaudal and dorsoventral axes of each sulcus or cortex probabilistic blob, *i.e.,* the volume defined by the non-null voxels of the corresponding statistical map (already thresholded at 5%). This can be seen as a bounding box for the blob of the structure. For each extremum, we then computed the difference between Type 1 and Type 2 RS-CS proper conformation groups and tested its significance using permutation test: we simulated the distribution of differences between each extremum for 1000 pairs of groups of the size of Type 1 and Type 2 groups but randomly generated by permutation. The difference observed between real Type 1 and Type 2 groups was considered significant if superior to the 95th centile of the simulated random distribution. To test the sensitivity of the 5% threshold applied to the statistical map defining the blobs, we repeated the analysis with a 25% threshold, *i.e.,* excluding voxels that are present in less than 25% of the subjects. This analysis was performed with MATLAB's permutation function "randperm."

(4) We searched for differences between sulcal variations in the location of the center of mass of each sulcus in normalized space. Namely, we computed the center of mass of each sulcus (via Python's package NumPy), separately for Type 1 and Type 2. We used permutation testing to assess the differences in the location of the center of mass for each axis (x, y, and z) between Type 1 and Type 2 sulci. Then, we analyzed the variability of these center of mass in terms of direction. For each MTL sulcus, we projected individual center of mass in 3D space separately for Type 1 and Type 2, and fitted the cloud of points with an orthogonal distance regression line using singular value decomposition (via MATLAB's function 'svd'). We thus obtained a parametric equation $P = p0 + t^*d$ where p0 is the average position of the vector, d the directions of the vector in 3D space, and t the parametrical value for each point. We then compared the direction parameters between Type 1 and Type 2, for each sulcus, using paired t-test. This analysis is complementary to the previous one as it describes the variability of sulcal center of mass between Type 1 and Type 2 sulci regarding their principal direction.

RESULTS

RS-CS Proper Conformation

Among the 76 analyzed hemispheres, 29 had a Type 1 pattern (38.15%) and 47 a Type 2 pattern (61.85%). The inter-hemispheric correlation between types was high (r = 0.71), meaning that both hemispheres of a same subject tended to share the same type. The differences in type proportions between the present study and previous studies were not significant using proportions z-tests: comparison between the present study with Ono et al. (1990): p = 0.16; with Novak et al. (2002): p = 0.86; with Kim et al. (2008): p = 0.40; with Huntgeburth and Petrides (2016): p = 0.89; with Chau et al. (2014): p = 0.75; and with Cikla et al. (2016): p = 0.58. More details about comparison with previous studies are to be found in the Discussion section of this paper.

Age, Sex, and Brain Size Effects on RS-CS Proper Conformation

Age

No age effect was found on RS-CS proper conformation (left hemisphere: t = 1.14, p = 0.29, right hemisphere: t = 0.01, p = 0.98). Therefore, subjects were distributed into sulcal types regardless of age.

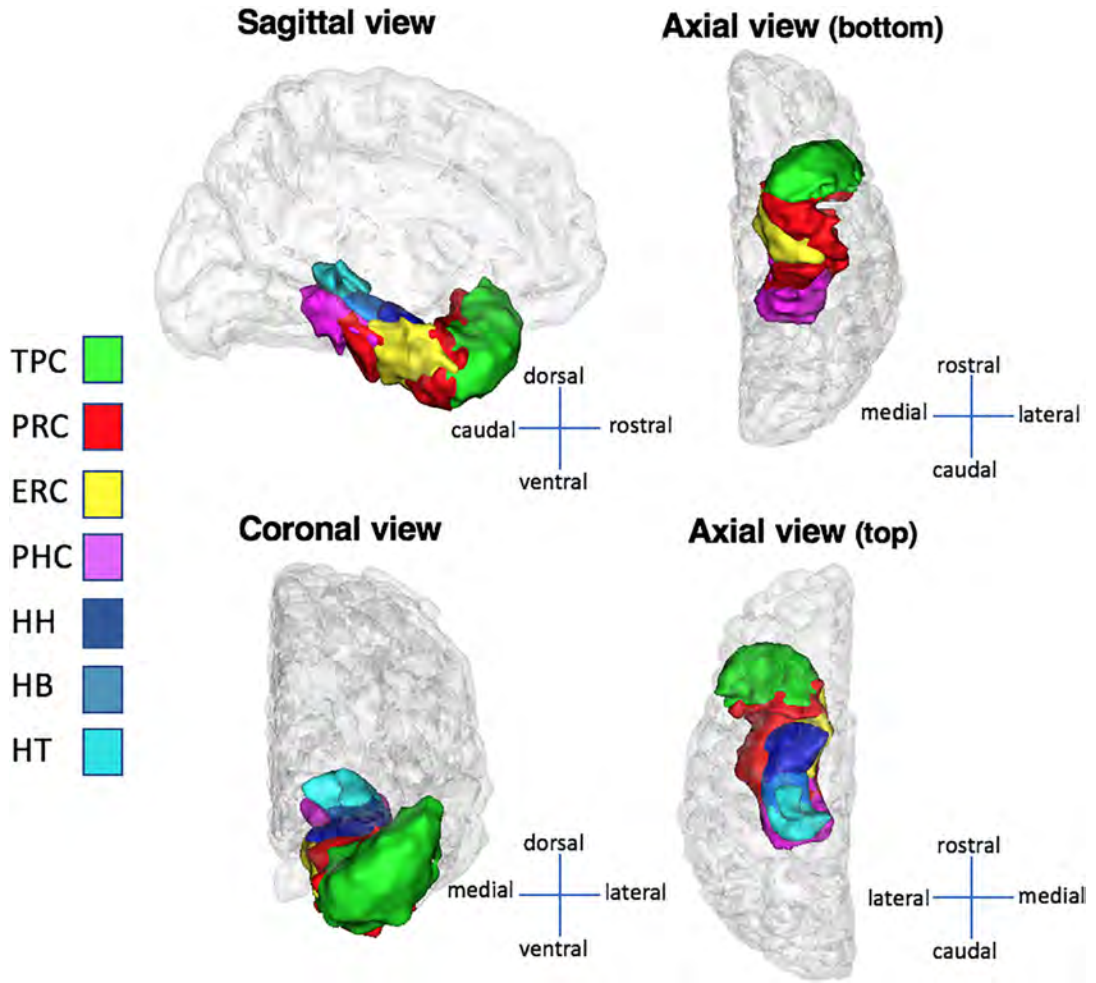

FIGURE 2 | Medial temporal lobe structures in sagittal, coronal, and axial views. The structures presented here are computed over the whole population and converted to surfaces with BrainVisa's AimsMesh function. A threshold of 5% (the same used volumes visualization) was applied on the surfaces to keep voxels present in at least 95% of subjects. Abbreviations: TPC, temporopolar cortex; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex; HH, hippocampus head; HB, hippocampus body; HT, hippocampus tail.

Sex

No sex effect was found on RS-CS proper conformation, both in the left ($t = 0.01$, $p = 1$) and right ($t = 0.12$, $p = 0.74$) hemispheres.

Brain Size

No hemispheric size effect was found on RS-CS proper conformation on both sides, neither on volumes (left hemisphere: $t = 0.10$, $p = 0.74$; right hemisphere: $t = 0.06$, $p = 0.79$) nor on surface [left: $F(1,36) = 0.49$, $p = 0.48$; right: $F(1,36) = 0.14$, $p = 0.71$].

Morphometrical Measurements of the RS and CS According to RS-CS Proper Conformation

A summary of the morphometrical measurements of the RS and CS according to RS-CS proper conformation is presented in **Table 1**.

In Type 1, the maximum depth of the RS was significantly larger than in Type 2, in the right hemisphere ($t = -3.08$, $p < 0.01$, corrected) but not in the left ($t = -1.36$, $p = 0.36$). For the mean depth of the RS, the right hemisphere was significant after correction ($t = -5.76$, $p < 0.005$, corrected), but not the left ($t = -2.40$, $p = 0.02$ before correction, $p = 0.14$ after correction).

For the CS proper, no significant differences between Types 1 and 2 were found for the maximum depth (left hemisphere: $t = -1.34$, $p = 0.38$; right hemisphere: $t = -0.69$, $p = 0.54$). However, the mean depth of the CS proper was significantly greater in Type 1 than in Type 2 in the right hemisphere ($t = -2.8$, $p < 0.01$, corrected). In the left hemisphere, no significant difference was observed after correction ($t = -2.82$, $p = 0.008$ before correction, $p = 0.11$ after correction).

No significant differences of the CS post were found between Types 1 and 2 for maximum and mean depth for both hemispheres.

TABLE 1 | Morphological measurements of the MTL sulci as measured in native space.

Sulcus name	Rhinal sulcus				Collateral sulcus proper				Collateral sulcus post			
Hemisphere	Left		Right		Left		Right		Left		Right	
Sulcal variant	Type 1	Type 2	Type 1	Type 2	Type 1	Type 2	Type 1	Type 2	Type 1	Type 2	Type 1	Type 2
Max depth in mm (SD)	15.27 (3.71)	13.60 (2.58)	16.17 (2.37)	13.64 (2.50)	16.48 (2.96)	15.16 (3.01)	16.93 (1.93)	16.45 (2.15)	16.15 (2.15)	16.17 (1.50)	16.40 (1.63)	16.36 (1.81)
Mean depth in mm (SD)	9.21 (1.54)	8 (1.52)	10.45 (1.24)	8.06 (1.26)	12.41 (2.18)	10.11 (2.18)	12.42 (2.16)	10.96 (2.17)	10.36 (1.10)	10.23 (0.95)	11.15 (1.43)	10.74 (1.07)

The mean and maximum depth of each sulcus are given separately for Type 1 and Type 2. For each sulcus of each type of each hemisphere, the mean value is indicated (in mm) with its SD.

Effect of RS-CS Proper Conformation on Sulci Location: Permutation Tests

To complete the analyses of the effect of sulcal conformation on sulcal features, we tested weather the observed conformations (i.e., Type 1 vs. Type 2) was related to different locations of Type 1 and Type 2 sulci of RS, CS and CS proper sulci in normalized space. The location of each mean sulcus (the sulcus computed over all subjects) was thus defined on each axis (i.e., x, y, and z axes) by pair of extrema, i.e., a minimum and a maximum location for each axis in the x, y, and z directions (**Figure 3**). Hence, the minima of a sulcus on the x-axis corresponds to the most medial point of the sulcus, while its maxima corresponds to the most lateral point; on the y-axis, the minima corresponds to the most rostral/anterior point, while the minima corresponds to its most caudal/posterior point; and for the *z*-axis, the maxima corresponds to the most dorsal point, while the minima corresponds to the most ventral point. The extrema were computed at two thresholds regarding the voxels included in the mean map of each sulcus: the 5% threshold, which was also used for visualization of the probabilistic maps (see section below), and a 25% threshold, to look at differences in location between mean sulci for each types that were present in at least 75% of subjects.

Regarding the minima of each sulcus along each axis, we found no significant differences between Type 1 and Type 2 RS, CS proper and CS post, at the 5 and 25% thresholds (**Table 2**). For the maxima (maximal coordinate of the blob along each axis), we found a significant difference between Type 1 and Type 2 RS for the x-axis in the right hemisphere at the 5 and 25% map thresholds. The observed difference in distance between Type 1 and Type 2 right RS maxima was of −5 mm at the 5% map threshold, a difference outside the 95% of the random distribution interval ranging from −2 to 3 mm. This means that in Type 1, the location of the right RS maxima is located significantly more laterally than in Type 2 RS at the 5% threshold. Similarly, the observed distance difference between Type 1 and Type 2 maxima was of 7 mm (outside the 95% of the random distribution interval ranging from −4 to 5 mm) at the 25% threshold, showing that in Type 1, the right RS maxima is located at a significantly less lateral level at the 25% threshold. The opposite sides of these differences suggested that, although Type 1 right RS extends more laterally than Type 2 right RS when looking at the mean map comprising nearly all subjects, the opposite is observed at the 25% threshold because the subject overlap of Type 1 right RS is less important laterally than for Type 2 right RS. No other significant differences were found for both hemispheres at both thresholds. Hence, overall, the location of the RS, CS proper and CS post was not greatly different between Type 1 and Type 2 patterns, with only one difference observed, regarding the location of RS maxima coordinates in the right hemisphere. These findings showed that the RS is deeper in the right hemisphere than in the left, as already shown by morphometrical measurements (see section "Morphometrical Measurements of the RS and CS According to RS-CS Proper Conformation"). We also tested differences

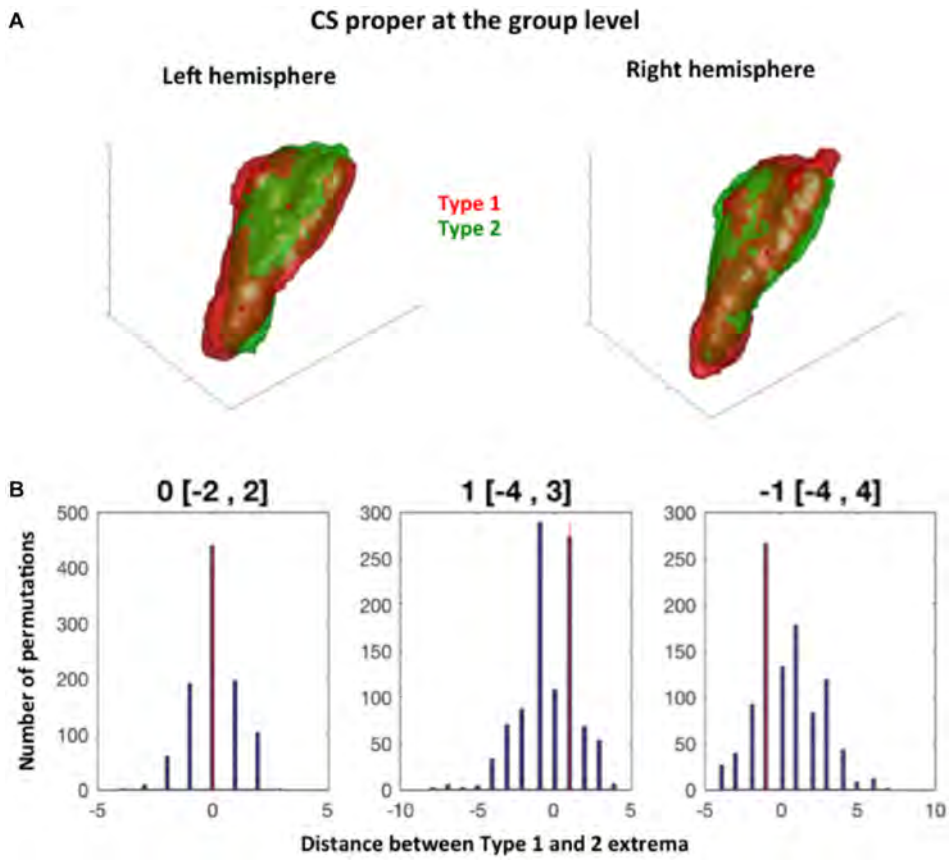

FIGURE 3 | Permutation test procedure. **(A)** Two blobs are defined at the group level by merging the sulci of Type 1 and Type 2 subjects for a given sulcus (here illustrated with the collateral sulcus proper for both hemispheres). Here, the group-level Type 1 collateral sulcus proper is in red, and the group level Type 2 collateral sulcus in green. A bounding box illustrates the coordinates of these group sulci. **(B)** The extrema coordinates on the x, y, and z axis between the observed group sulci (shown in **A**) and 1000 group sulci generated randomly are compared.

in minima locations for each MTL cortex, finding accordingly no significant differences between the cortices bordered by Type 1 sulci, and those bordered by Type 2 sulci (data not shown).

We completed our analyses of sulcal extrema by testing differences in center of mass between Type 1 and Type 2 sulci. For each sulcal structure, we computed the individual center of mass of each sulcus and tested differences of the center of mass' coordinates separately for each axis (x, y, and z) between Type 1 and Type 2 sulci. We found no significant differences between the center of mass of Type and Type 2 variants (**Supplementary Table 2**). Then, we tested the variability of sulcal center of mass in terms of direction. For each sulcus, we projected individual center of mass in 3D space separately for Type 1 and Type 2, and fitted the cloud of points with an orthogonal distance regression line using singular value decomposition. We compared the direction parameters of the line between Type 1 and Type 2 using paired *t*-test, and found no significant differences (**Supplementary Table 3**). Taken together, these results show no clear difference in location or direction between Type 1 and Type 2 sulcal variants. Hence, the effect of sulcal conformation seems limited, at least when analyzed in normalized space.

Probabilistic Maps of the MTL Sulci and Cortices

Probabilistic Maps of MTL Sulci

Because permutation tests conducted in section "Effect of RS-CS Proper Conformation on Sulci Location: Permutation Tests" revealed few significant anatomical differences between Type 1 and Type 2 RS, CS proper and CS post, the probabilistic maps described here were generated by grouping together all subjects regardless of their sulcal type. The coordinates of each sulcus on the rostrocaudal axis (x axis) and on the dorsoventral axis (x-coordinates) are presented in **Table 3**. The probabilistic maps thresholded at 5% are shown in **Figures 4–6**.

Probabilistic Maps of the MTL Structures

The coordinates of each MTL structures on the rostrocaudal axis (x axis) and on the dorsoventral axis (x-coordinates) are presented in **Table 3**. The probabilistic maps thresholded at 5% are shown are shown in **Figures 7–11**.

TABLE 2 | Distance between the minima and maxima of Type 1 and Type 2 for each sulcus, for two different thresholds.

Distance (in mm) between Type 1 and Type 2 minima.				Distance between Type 1 and Type 2 maxima.		
Left hemisphere				**Left hemisphere**		
RS	***x* axis**	***y* axis**	***z* axis**	***x* axis**	***y* axis**	***z* axis**
0.05 threshold	1 [−2, 3]	0 [−4, 14]	−2 [−2, 2]	0 [−3, 1]	0 [−6, 1]	0 [−4, 2]
0.25 threshold	−2 [−3, 2]	−3 [−8, 8]	−3 [−5, 2]	0 [−4, 3]	−1 [−7, 9]	−1 [−3, 2]
CS proper	*x* axis	*y* axis	*z* axis	*x* axis	*y* axis	*z* axis
0.05 threshold	2 [−2, 5]	1 [−3, 5]	8 [−8, 11]	0 [−4, 1]	1 [−6, 3]	0 [−2, 0]
0.25 threshold	−2 [−6, 4]	4 [−7, 8]	−1 [−6, 5]	−3 [−7, 5]	4 [−10, 8]	−2 [−5, 7]
CS post	*x* axis	*y* axis	*z* axis	*x* axis	*y* axis	*z* axis
0.05 threshold	14 [−14, 15]	10 [−10, 14]	7 [−7, 8]	0 [−7, 1]	0 [−4, 3]	0 [−10, 5]
0.25 threshold	3 [−6, 6]	0 [−10, 11]	0 [−5, 4]	18 [−13, 19]	1 [−26, 12]	7 [−5, 9]
Right hemisphere				**Right hemisphere**		
RS	***x* axis**	***y* axis**	***z* axis**	***x* axis**	***y* axis**	***z* axis**
0.05 threshold	1 [−3, 2]	−6 [−9, 4]	3 [−5, 4]	−5 [−2, 3]*	−3 [−3, 6]	7 [−3, 8]
0.25 threshold	2 [−2, 3]	0 [−6, 9]	2 [−6, 3]	7 [−4, 5]*	−3 [−5, 5]	−2 [−6, 5]
CS proper	*x* axis	*y* axis	*z* axis	*x* axis	*y* axis	*z* axis
0.05 threshold	−3 [−4, 2]	−1 [−3, 2]	−2 [−4, 3]	1 [0, 3]	4 [−3, 7]	−1 [−3, 2]
0.25 threshold	1 [−2, 3]	0 [−4, 3]	0 [−3, 5]	1 [−2, 2]	2 [−5, 3]	1 [−3, 3]
CS post	*x* axis	*y* axis	*z* axis	*x* axis	*y* axis	*z* axis
0.05 threshold	2 [−2, 6]	−1 [−9, 8]	1 [−4, 4]	−1 [−2, 3]	−1 [−1, 3]	0 [−8, 7]
0.25 threshold	1 [−2, 2]	2 [−5, 3]	1 [−3, 3]	1 [−10, 8]	−9 [−17, 12]	−1 [−5, 5]

*Permutation tests were used to compare the distance (in mm) between the minimum (i.e., minima) coordinates of the Rhinal Sulcus, Collateral Sulcus Proper, and Collateral Sulcus Posterior for the x, y, and z axis (i.e., the 'x,' 'y,' and 'z' lines of the table). The value outside of the brackets is the observed distance between the minima and maxima of Type 1 and Type 2 sulci, for each sulcus, separately for each axis. The values inside the brackets are the confidence interval of distance values, as computed with 1000 permutation tests. If the observed distance is included in the confidence interval, then it is not significantly different between Type 1 and Type 2 sulci. *Significant at $p < 0.05$. Two different thresholds were used: 0.05 (i.e., voxels present in at least 5% of the population) and 0.25 (voxels present in at least 25% of the population).*

TABLE 3 | Coordinates of the MTL sulci in the MNI space.

MTL structure	RS	CS proper	CS post	ERC	PRC	TPC	PHC	HH	HB	HT
y coordinates	11; −31	−7; −54	−38; −92	6; −31	12; −38	29; 0	−22; −49	−4; −27	−19; −37	−29; −45
z coordinates	−18; −53	−3; −47	7; −22	−19; −49	−11; −54	−9; −53	−2; −35	−8; −33	−1; −26	9; −13

The minimum and maximum coordinates of each sulcus are indicated for the rostrocaudal and dorsoventral axes.

DISCUSSION

We characterized the spatial variability of MTL sulci and cortices in a child and adolescent population using probabilistic maps that constitute a MTL atlas. Such an atlas provides the expected location of each structure in a 3-dimensional stereotaxic space according to validated segmentation rules.

MTL Sulcal Conformation in Children and Adolescents

Comparison With Adult Data

To date, no study had described the morphological characteristics of the RS, CS proper and CS post in a children and adolescents population. As explained in section "RS-CS Proper Conformation," the description provided here uses the same morphotypes (connection vs. separation of the RS and CS proper) as previous studies. The Type 1 vs. Type 2 found in our study are comparable to previous adult studies (**Table 4**), as shown by proportion *z*-test (section "RS-CS Proper Conformation").

Overall, the absence of differences between our results and previous adult studies regarding proportions of Types 1 and 2 suggests that one of the main effects of sulcation in this region, i.e., determining sulcal conformation, was achieved way before the age range studied here (7 to 17 years old). Interestingly, imaging studies of early development showed that most sulci appear during the 3rd gestational semester (Dubois et al., 2008); since CS and RS are visible as early as the 23th to the 25th gestational weeks on (Kier et al., 1997; Garel et al., 2003; Bajic et al., 2010), their sulcation may be achieved particularly early; here, we confirm that the morphogenesis of MTL sulcal conformations does not evolve after middle childhood.

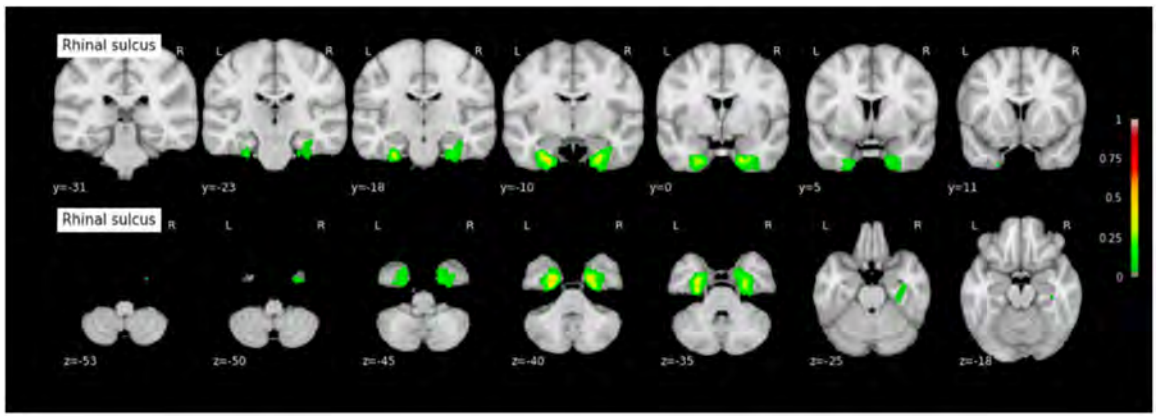

FIGURE 4 | Probabilistic map of the rhinal sulcus (RS). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice. Color bars indicate the probability of presence of the structure, ranging from 0 (voxel absent in subjects) to 1 (voxel present in subjects). A 0.05 threshold was used for visualization purposes in order to get rid of potential outlier voxels and to limit the extension of the maps caused by the 3 mm Gaussian kernel smoothing.

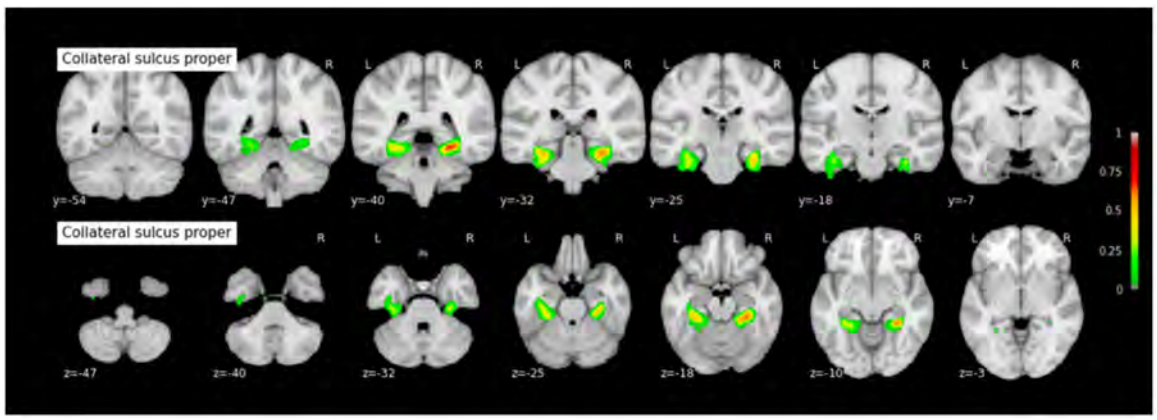

FIGURE 5 | Probabilistic map of the collateral sulcus proper (CS proper). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

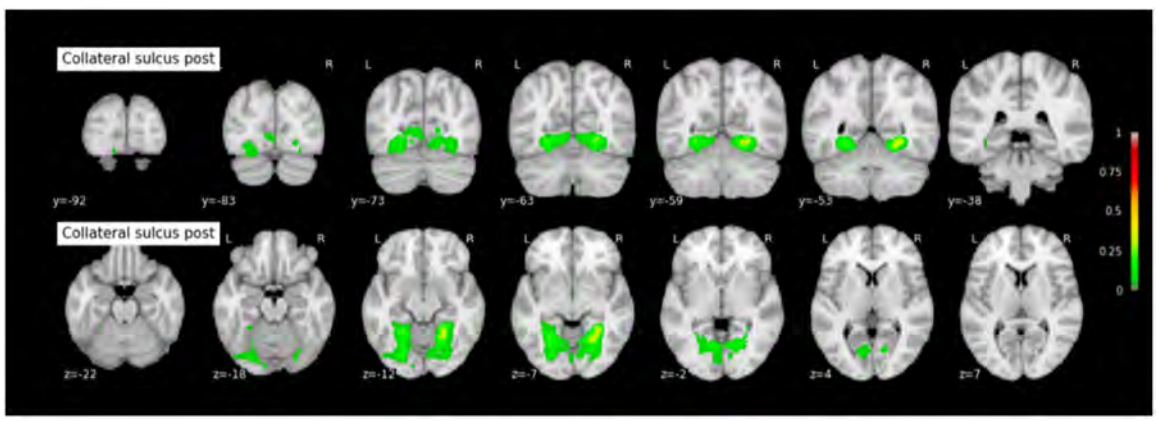

FIGURE 6 | Probabilistic map of the collateral sulcus post (CS post). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

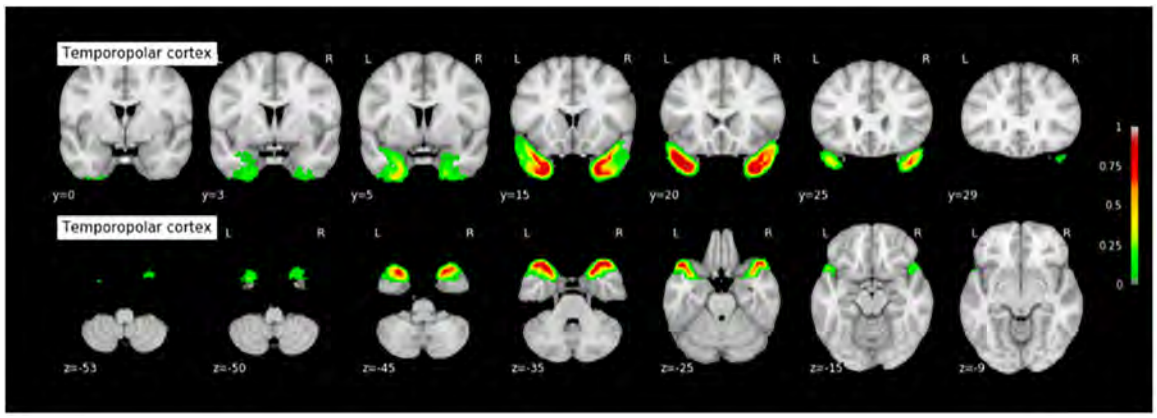

FIGURE 7 | Probabilistic map of the temporopolar cortex (TPC). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

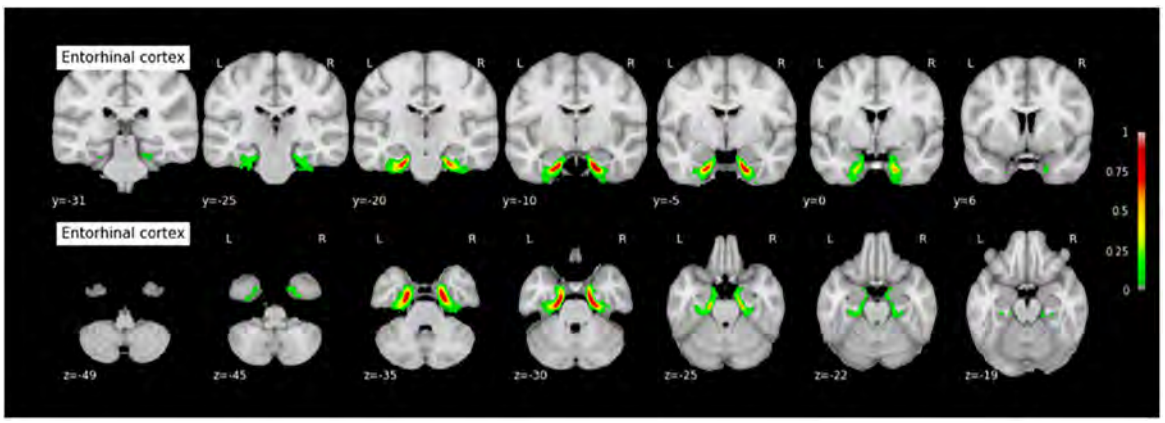

FIGURE 8 | Probabilistic map of the entorhinal cortex (ERC). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

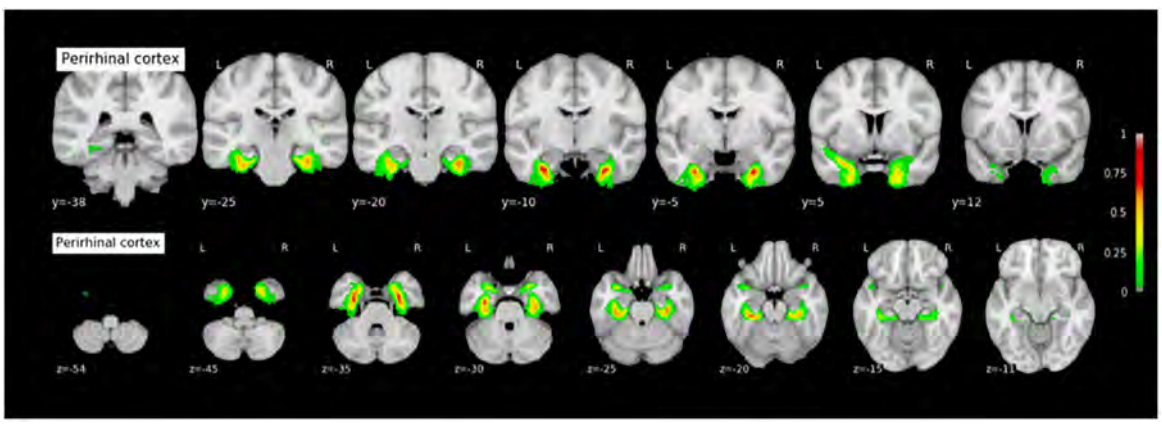

FIGURE 9 | Probabilistic map of the perirhinal cortex (PRC). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

Effect of Age, Sex, and Brain Volume on Morphometric Features

We found no effect of hemispheric volume on sulcal conformation. This may be surprising since Type 1 has been associated with deeper sulci (Feczko et al., 2009), a finding that we replicated in our population (see section "Morphometrical Measurements of the RS and CS According to RS-CS Proper Conformation"). Since larger brains are twistier because of the

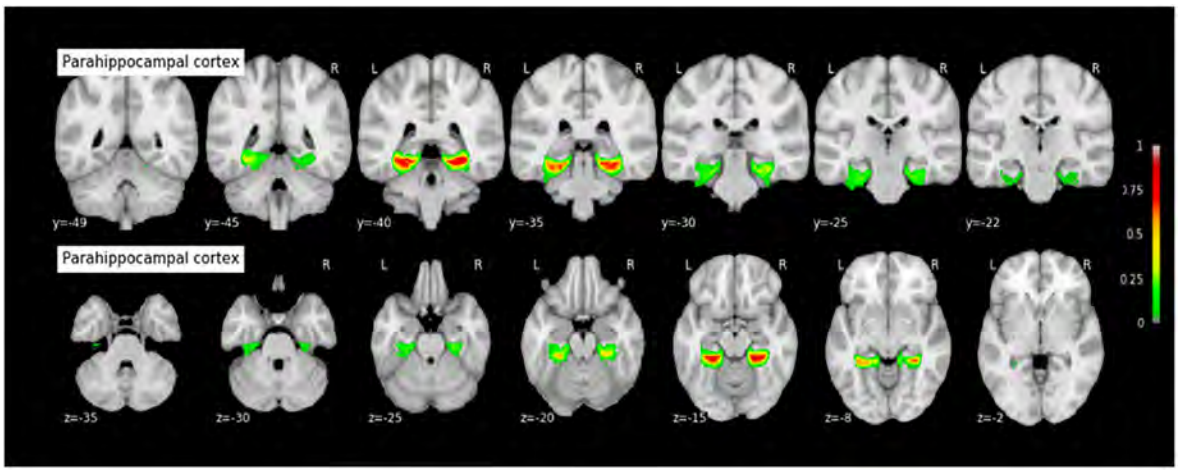

FIGURE 10 | Probabilistic map of the parahippocampal cortex (PHC). The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

ramifications to accommodate the allometric increase of cortical surface (Germanaud et al., 2012), one could have expected hemispheric volume and surface to be positively associated to sulcal confluence and deepening, and therefore to Type 1. A recent study on the heritability of sulcal pits (Le Guen et al., 2017), i.e., locally deepest points in cortical sulci with little inter-subject variability, found that the Rhinal and Collateral sulci were amongst the most heritable brain sulci. These findings together suggest that the morphological variability of the Rhinal and the Collateral sulci could primarily be explained by specific genetic factors, independently of age, sex and brain size. Combined with the absence of effect of age on the proportion of sulcal variants, these findings suggest that the local variability of the MTL sulci is likely explained by specific genetic factors with very early influence.

Effect of Sulcal Conformation on the Variability of Sulcal Location

We did not observe any significant differences in location between Type 1 and Type 2 probabilistic maps, although both types are clearly distinguishable at the subject level, and some morphometric features, such as mean and maximum depth, show significant differences between these two types (as measured in the native space). One first explanation could be that the normalization process may have minimized variability due to sulcal conformation, blurring both the differences in morphometric features measured in the native space and the difference in relative spatial location. Conversely, it could rather relate to the remaining variability after normalization due to a poor alignment of sulci since we used a normalization process not optimized for that purpose. Overall, the normalization process remains a key or even limiting step when it comes to group analysis of sulcal morphology and surface location (Lancaster et al., 2010; Lerch et al., 2017), and some teams try to avoid it (Mangin et al., 2016). We selected a very classical group normalization process as a first attempt to measure the impact of RS-CS proper morphotype on MLT cortices localization to stay close to the routine functional MRI procedure. Further work is needed to investigate whether the two sulcal conformations can be distinguished in terms of spatial location or have a significant impact on MLT cortices location by using other normalization procedures meant to preserve sulcal characteristics, such as a DARTEL normalization, or HIP-HOP model-driven harmonic parametrization of the cortical surface: (Auzias et al., 2013; Mangin et al., 2016). Machine learning could also be used to investigate whether sulcal conformation can be predicted from extrema location and other morphometric features. Nevertheless, it remains likely that the sulcal variation described here (Type 1 vs. Type 2) is not associated with localization differences large enough to cause significant differences at the group level in the normalized space, whatever the normalization process. The methodology used in the present work innovatively investigates the effect of sulcal variants on the anatomical location of said variants, using rigorous permutation testing. This method could be used or expanded in further work interested in investigating the relationships between anatomical variants of a given structure and the anatomical location of these variants, or the anatomical location of a given structure between different groups (e.g., groups based on age or condition).

Relevance of the Probabilistic Maps: A MTL Atlas in Children and Adolescents

Probabilistic maps of MTL cortices have been generated in adults for PRC, ERC, and HC (Amunts et al., 2005; Augustinack et al., 2013a,b; Yushkevich et al., 2015). Comparison of these maps (implemented in SPM8's toolbox 'Anatomy'; see Eickhoff et al., 2005; or in FreeSurfer; Augustinack et al., 2013a) with the maps presented here shows similar locations and similar patterns of spatial variability. However, in the absence of systematic statistical comparison in location with probabilistic maps designed in adults to confirm a clear absence of changes

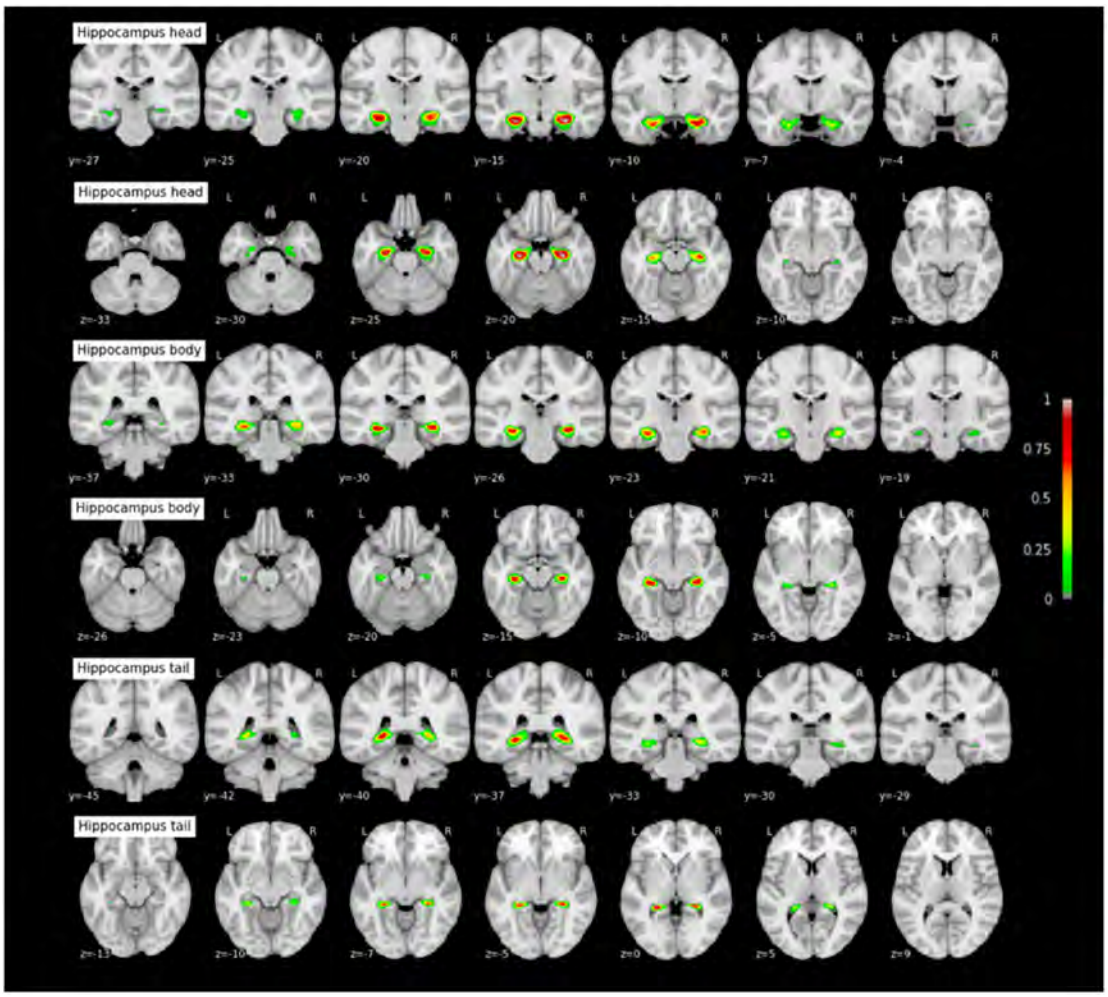

FIGURE 11 | Probabilistic maps of the hippocampal subparts. The maps are normalized into the MNI stereotaxic space. Coordinates are indicated on each slice.

TABLE 4 | Sulcal morphology in children and teenagers compared with adults.

Study	Type 1 (%)	Type 2 (%)	Number of subjects
Present study (Bouyeure et al.)	38.15	61.85	38
Ono et al., 1990	28	72	25
Novak et al., 2002	36	64	50
Kim et al., 2008	45	55	51
Huntgeburth and Petrides, 2012	36.25	63.75	40
Chau et al., 2014	50	50	30 Formalin-fixed hemispheres
Cikla et al., 2016	42.9	57.1	35

The proportions of three major morphological markers are compared between the present study and previous studies conducted in adults.

in location during development, what we provide here is first-hand data regarding the location of TPC and PHC (for which no probabilistic map were available), plus PRC, ERC, and HC subparts, in a children and adolescents population. These maps, that are freely available for download, could be used by the community to easily generate mean masks of said structures when necessary, e.g., to verify the location of activation peaks during task-fMRI study, or to be used as ROIs for resting-state or DTI studies. For the HC, we provide here maps for each of HC subparts using the tripartite head/body/tail division, allowing to test for specific hypotheses regarding the anatomical and functional specialization of the hippocampus on its long-axis during development (e.g., Riggins et al., 2016; Blankenship et al., 2017). This point is particularly important, as several studies have shown that the hippocampus undergoes a protracted maturational process on its long-axis until early adulthood (Gogtay et al., 2006), while the anterior and posterior parts of the hippocampus are involved into different memory processes (Poppenk et al., 2013; Strange et al., 2014), with specific maturational dynamics for each HC subpart (Ghetti and Bunge, 2012; Riggins et al., 2015, 2016; Blankenship et al., 2017). Moreover, the tripartite head/body/tail division used here allows to test more fine-grained hypotheses of HC specialization than the anterior/posterior division that is also used by some studies.

Our study has several limitations. First, the wide age range (7–17 years old) of our sample and our sample size (38 subjects) limits us from performing analyses for distinct age groups because of the small sample size that such groups would have. Therefore, a more comprehensive database of structural scans in the MTL would be beneficial in the future to assess more precisely the anatomical variation of this region during development. In particular, the structural maturation of the MTL region during early childhood is poorly known (except regarding the hippocampus: for example see Ngo et al., 2017; Canada et al., 2018; Riggins et al., 2018, for recent findings), while the first years of life see stark improvements of MTL-based mnemonic competences. It might interesting to apply similar methods to the ones outlined here (probabilistic mapping of anatomical variability, morphometry) to study MTL maturation in young children. A second limitation is that the SPM preprocessing procedure is less optimal than other co-registration and normalization methods. Our measure of the impact of RS-CS proper morphotype on MLT cortices localization aimed at staying close to the routine functional MRI procedure since it is in this context that functional studies, for instance, use MTL sulci as anatomical landmarks to identify cortical regions where activation peaks are located (see Huntgeburth and Petrides, 2016; Weiner et al., 2018 for discussions regarding the relation between the CS proper and PHC function). However, because we kept the same protocol throughout the study, the probabilistic maps were preprocessed using SPM as well. A systematic comparison of available registration methods to devise the most suited procedure for generating a probabilistic atlas in a pediatric population (e.g., choice of registration method, creation of a group template) would be beneficial to future work. Finally, the reader should bear in mind that the present findings stem from a segmentation method of MTL structures based on scarce adult histological data extrapolated to children and adolescents, possibly limiting the accuracy of the present segmentations. This limitation could be overcome if histological data of MTL structures in children and adolescents become available for future work, or ultrahigh resolution MRI as a proxy. Nevertheless, the present findings will be beneficial to studies interested in MTL structures, e.g., that use seed-based functional connectivity techniques that need a precise definition of anatomical regions of interest. Thus, this probabilistic 7–17 year-old MTL atlas should reduce potential errors or approximations in neuroimaging pediatric studies. This may apply for instance in temporal lobe epilepsy studies, in which the lesion and the epileptogenic focus frequently involve the parahippocampal gyrus with significantly more frequent Type 1 than Type 2 patterns (Kim et al., 2008). The MTL is also involved in several major neurodevelopmental conditions, such as autism (Bachevalier, 1994) or schizophrenia (Falkai et al., 1988; Arnold et al., 1997; Penttilä et al., 2008).

CONCLUSION

This work provides the first probabilistic atlas of MTL sulci and cortices in a population of children and adolescents, and shows that the variation in sulcal conformation (connection or separation between the RS and the CS proper) is not explained by age, gender or brain size. This finding suggests that the local variability of the structures is likely primarily explained by genetic factors, with very early influence and further stability over late childhood and adolescence. The probabilistic atlas have been made available online in open access (See text footnote[1]).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the French "Comité de Protection des Personnes" regarding research with minors, and of the "Agence Nationale du Médicament et des Produits de Santé," with written informed consent from all subjects and of the persons legally in charge of the subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Comité de Protection des Personnes (CPP number 11-008).

AUTHOR CONTRIBUTIONS

DG, MN, and CP acquired the neuroimaging data. AB performed sulcal segmentation and analyses with the assistance of CF and MN. MN and AB performed the cortical segmentation and analyses. DB, VD, DR, MN, and AB did the probabilistic maps. JL, DB, DG, AB, and MN did the statistical analyses. AB, DG, and MN wrote the article with the assistance of DR, J-FM, CC, and LH-P.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnana.2018.00098/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Chapter 3. Results

Organization of the chapter

The results chapter is organized in 3 parts, which contain 5 studies in total.

The **first part** examines the developmental trajectories of the components of episodic memory and their relationships, presented in Study 1.

The **second part** examines the relation between the components of episodic memory and the hippocampus. Study 2 examines the transversal organization of the hippocampus (medio-lateral axis; hippocampal subfields). Study 3 examines the longitudinal organization of the hippocampus (anterior-posterior axis).

The **third part** examines the relation between the components of episodic memory and connectivity between cerebral regions. Study 4 examines structural connectivity, and Study 5 functional connectivity.

Figures and tables within each study follow the numbering system specific to the study.

Chapter 3, Part 1:

Behavioral results

Study 1

Development and relationships of episodic memory components during childhood

Presentation

The aim of this study was to introduce our experimental contributions by providing a global picture of the behavioral data. To avoid repetition, further details relative to the context of the study can be found in the Introduction section. Further methodological details and analyses of episodic memory components can be found in the following studies of the Results chapter (pattern separation/memory discrimination: Study 2; episodic recall: study 4; autobiographical memory: study 5).

Context

The relationships between several episodic memory components, such as pattern separation (*via* memory discrimination), episodic autobiographical memory, recognition memory, and episodic recall, are unknown during development. Comparing their developmental trajectories and examining if they are behaviorally correlated or independent would provide new insights on episodic memory function during childhood.

Methods

Several types of regressions models were fitted to describe the associations between episodic memory components and age. Models were compared with the Aikake Information Criterion (AIC). Steiger z-test were used to examine whether the correlation coefficients between age and memory performance were significantly different between components. Relationships between components were assessed by examining the between-components correlations and by performing a dimensionality reduction analysis.

Results

All episodic memory components were positively correlated with age except recognition memory for single items. Components with significant age-related differences were best described by linear models. Their correlation coefficients with age were not significantly different from each other. Memory discrimination (measuring pattern separation) was not correlated with other components (controlling for age), and dimensionality reduction further showed that it shared little variance with other components.

Conclusion

The development of pattern separation could be more protracted than previously thought and we show its behavioral independence from other components of episodic memory.

Article title: Development and relationships of episodic memory components in the developing brain

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Development and relationships of episodic memory components in the developing brain

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1. Introduction

The objective of this study was to describe the developmental trajectories of distinct episodic memory components (episodic recall, episodic autobiographical recall, pattern separation, recognition memory) and to examine their relationships. More specifically, the following questions were addressed:

Are there differences between the developmental trajectories of these components of episodic memory? The existing literature provides some indications regarding this matter (e.g. Ngo et al., 2019), but few studies have assessed simultaneously distinct components on a same dataset. Our approach allows the straightforward comparison of age-related differences of episodic memory components.

Are these components of episodic memory behaviorally separable? Data from the existing literature shows that performance at recognition memory (measured with the item memory index) and pattern separation (measured with memory discrimination) (Ngo et al., 2018), or pattern separation and relational memory (Ngo et al., 2019), were not correlated in children. However, most of the relations between the components studied here (e.g., between memory discrimination and episodic autobiographical memory) are unknown.

For the first question, we expected to show that pattern separation (as assessed with memory discrimination) is subject to important age-related differences during the childhood amnesia period (suggesting rapid improvements during early childhood), and fewer age-related differences in older children (suggesting that maturation is reached during middle or late childhood). This hypothesis was based on the fact that two prior studies showed no age-related differences of pattern separation for single items (which was assessed here) after age 6 (Ngo et al., 2018, 2019). However, as a study showed age-related differences of pattern separation during middle childhood (Rollins & Cloude, 2018), age-related differences could well be observed. For episodic autobiographical memory, its development is known to be protracted (e.g., Piolino et

al., 2007), but comparatively more important age-related difference could be found during early childhood given the phenomenon of childhood amnesia.

For the second question, we expected to show a correlation between episodic recall and episodic autobiographical recall. We also expected that memory discrimination would be moderately correlated with recall components, or not correlated to them. These hypotheses were based on the idea that components depending on overlapping neural correlates are more likely to be behaviorally correlated given that shared variance at the cerebral level is likely to reflect shared variance at the behavioral level. Even if hippocampal subfields are involved in recall (given the general role of the hippocampus in recall memory), pattern separation specifically depends on specific neural correlates (specific subfields: e.g., Berron et al., 2016) and less on other brain areas, and is thus more likely to be behaviorally independent.

2. Methods

We focused our analyses on a limited number of behavioral tests based on their importance for our hypotheses. To study episodic recall, we used the CVLT-c, the children version of a widely used test of episodic memory (see Study 4 for details). The selected tests for the CVLT-c were the following: 1) Short-Delay Free Recall; 2) Long-Delay Free Recall; 3) Long-Delay Cued Recall. Besides episodic recall, these scores could partly tap on source memory processes (the ability to recall the context in which information was learned) as recall depends on the capacity to recall items from a given source (list A) while inhibiting words learned from another source (list B). For pattern separation, we used the Memory Discrimination Index from the Mnemonic Similarity Task (MST) (Ngo et al., 2018; see Methods and Study 2), which is a behavioral proxy for pattern separation. Recognition memory was assessed with the Item Memory Index obtained from the MST, which measures old/new discrimination (see Study 2). Autobiographical memory was assessed with the Child Autobiographical Interview (CAI) (Willoughby et al., 2012), which provides several scores measuring distinct aspects of autobiographical memory (see Study 5 for a detailed description). Here, we

only focused on the total number of episodic event details recalled across all memories, as well as the total number of episodic context details recalled across all memories. These two scores measure children's ability to recall different types of episodic autobiographical information, which could follow distinct developmental trajectories.

Developmental trajectories of episodic memory components were examined by analyzing age-related differences of episodic memory performance. These were assessed with linear regression models in which episodic memory scores were the dependent variables. Sex was added as a covariate of non-interest. Raw p-values were corrected for multiple comparisons with a False Discovery Rate (FDR) procedure (Benjamini & Hochberg, 1995). We fitted several models to see how age-related differences could be best explained models: these models included either a simple age term, a logarithmic transformation of age, a quadratic polynomial of age, or a cubic polynomial of age. Model selection was performed with the Akaike Information Criterion (AIC) which is a widely used criterion for evaluating the balance between goodness of fit and model simplicity; a lower AIC value represents a better balance between explanatory power and complexity. A given model was considered a better explanation of age-related differences of a given memory score if it had 2 AIC units lower than the model of reference, which was the model with the non-transformed age term since it is the simplest.

The relationships between episodic memory components were examined by generating a correlation matrix between all studied scores, which was corrected for multiple comparisons with FDR. To further describe the relationships between episodic memory components, we performed a dimensionality reduction analysis through Principal Component Analysis (PCA), to describe the latent structure of our behavioral data.

3. Results

3.1 Age-related differences of episodic memory components

We examined which model best explained the age-related differences of tests taping on distinct episodic memory components. AIC values for each test are shown Table 1. The linear models were the best fit for all tests since the other models did not have AIC values that were two units below the AIC value of the linear models. Age-related differences were thus best described by linear models in our sample. Analysis of the Bayesian Information Criterion (BIC), which is similar to AIC, yielded the same conclusion.

Model type	SDFR	LDFR	LDCR	Memory Discrimination	Item Memory	Event Details	Context Details
Linear	118.62	119.35	120.76	9.30	-34.80	190.97	172.13
Logarithmic	118.71	118.75	120.32	9.38	-34.81	191.05	170.84
Quadratic	120.62	120.66	120.66	11.30	-32.80	192.94	170.83
Cubic	122.41	122.65	124.29	12.67	-32.64	194.44	171.10

Table 1. AIC values for linear (age), logarithmic (log(age)), quadratic (age+age2) and cubic (age+age2+age3) models predicting episodic memory components**.** The linear model is the default one, as it has the less terms and has no transformation (e.g. log-transformation). If a model has 2 AIC units lower than the default linear model, it can be considered as a better fit of the relationship between age and the tested episodic memory kind. SDFR = Short-Delay Free Recall. LDFR = Long-Delay Free Recall. LDCR = Long-Delay Cued Recall.

To illustrate these linear relationships, we plotted the linear regressions between each episodic memory kind and age (Figure 1).

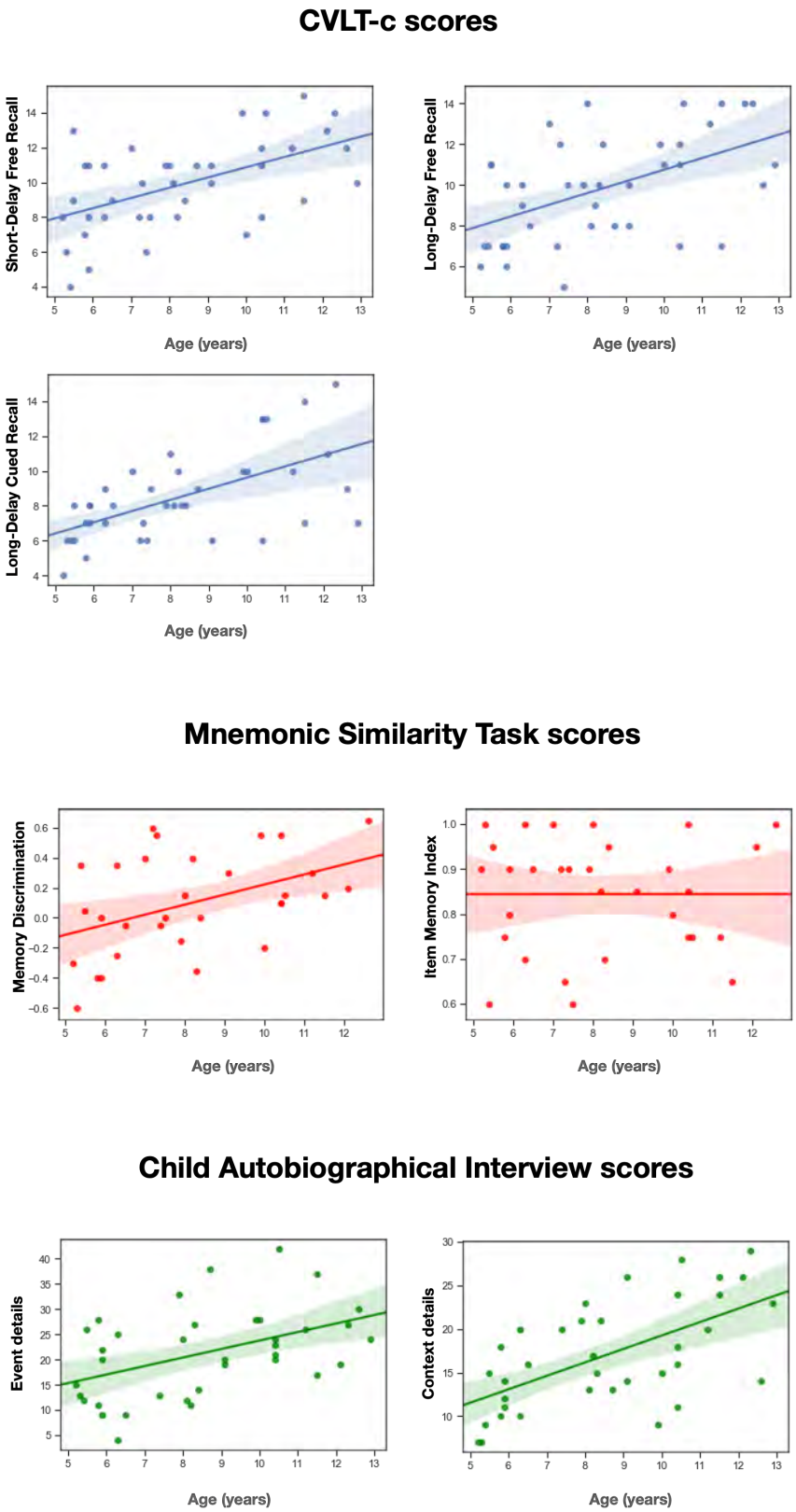


Figure 1. Plots of the relationship between age and episodic memory components. Are represented tests from the CVLT-c (top, blue), the MST (middle, red), and the CAI (bottom, green).

CVLT-c

All of the CVLT-c scores were significantly associated with age in linear regression models. Short-Delay Free Recall was associated with age ($F=15.066$, $p<0.001$, $R2=0.279$, $\beta=0.584$) as well as Long-Delay Free recall ($F=15$, $p<0.001$, $R2=0.273$, $\beta=0.579$), and Long-Delay Cued Recall ($F=19.734$, $p<0.001$, $R2=0.336$, $\beta=0.631$). Sex was not significant when added as a covariate in all models (all p-values>0.15).

MST

Memory discrimination was significantly associated with age ($F=7.205$, $p<0.05$, $R2=0.199$, $\beta=0.067$). However, the Item Memory Index was almost perfectly age-invariant ($F=0.0$, $p=0.9969$, $R2=0.0$, $\beta=0.0$). Sex was not a significant predictor of memory discrimination or item memory when added in the models (all p-values > 0.46).

CAI

Both scores were significantly predicted by age (event details: $F=6.827$, $p<0.05$, $R2=0.159$, $\beta=1.51$; context details: $F=14.987$, $p<0.001$, $R2=0.294$, $\beta=1.423$). Sex was not a significant predictor of recalled event or context details when added in the models (all p-values > 0.23).

To summarize these age-related differences, the Pearson correlation coefficients between age and each memory score are shown in Table 2.

Episodic memory kind	**Correlation coefficient with age**	**95% confidence interval**
SDFR	0.53***	[0.26, 0.72]
LDFR	0.52***	[0.26, 0.71]
LDCR	0.58***	[0.33, 0.75]
Memory Discrimination	0.40*	[0.07, 0.65]
Item Memory Index	0.01	[-0.33, 0.35]
Event details	0.40*	[0.09, 0.64]
Context details	0.54***	[0.27, 0.73]

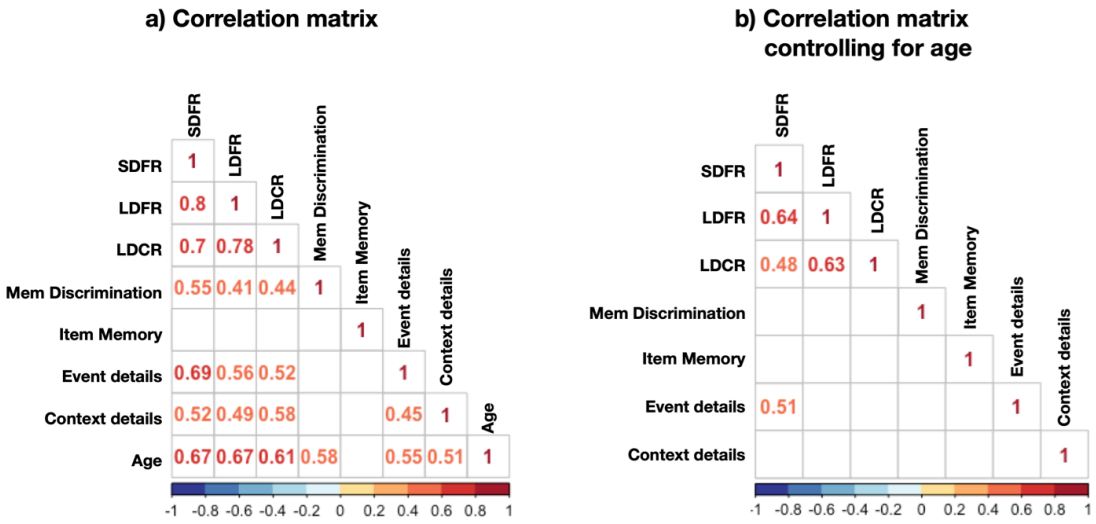
Table 2. Pearson correlation coefficients and 95% confidence intervals for the correlations between age and each episodic memory kind. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Cued Recall. *:p<0.05. ***:p<0.001.

Qualitative examination of the correlation coefficients showed 3 main categories of age-related differences: tests not correlated with age (item memory index); moderately correlated with age (memory discrimination, event details); tests strongly correlated with age (CVLT-c scores and context details). To examine whether the differences between the age-related differences were statistically significant among tests significantly correlated with age, we used Steiger paired z-tests between pairs of correlation coefficients. Given that some subjects did not have scores for all measurements of episodic memory, we used the set of subjects with data for the pair of compared tests (CAI/CVLT-c comparison: N=38; MST/CVLT-c comparison: N=35; CAI/MST comparison: N=28). None of the Steiger z-tests were statistically significant.

3.2 Relationships between episodic memory components

We examined the relationships between components of episodic memory to determine whether episodic memory components are behaviorally independent or correlated. We only used subjects with usable data across all episodic memory scores of our protocol (N=28).

We calculated the correlation matrix of the episodic memory components (Figure 2a), adjusting the p-values of the correlation coefficients with FDR. Most of the scores were significantly correlated with each other, with the exception of the Item Memory Index. However, because most of the scores were correlated with age, these correlations could be caused by the shared variance with age. Therefore, we calculated the correlation matrix between the residuals of the episodic memory tests once the variance explained by age was removed (Figure 2b). Adjusting the p-values of the age-controlled correlations with FDR, the resulting matrix is sparser, with only significant correlations between CVLT-c scores and CAI event details.



Only significant r-values after adjustment with FDR are shown

Figure 2. Correlation matrix showing the correlation coefficients (r-values) between all episodic memory tests. A). Correlation matrix of episodic memory tests. B) Correlation matrix of episodic memory tests controlling for age (the residuals of episodic memory tests once the variance explained by age is removed are correlated together). Only significant correlation coefficients after adjustment with FDR are shown. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Cued Recall. Mem Discrimination: Memory Discrimination Index.

We reduced the dimensionality of our behavioral data to further describe the relationships between memory tests with a PCA analysis with varimax rotation on the age-controlled data. Analysis of the scree plot with the Kaiser rule (Figure 3a) suggested a 3-dimensions solution. The 3 dimensions cumulatively explained 69.70% of the variance (Table 3)

PCA Dimension	**Dim1**	**Dim2**	**Dim3**
Variance	2.753	1.112	1.015
% of variance	39.324	15.879	14.501
Cumulative % of variance	39.324	55.203	69.704

Table 3. Variance explained by the 3 dimensions obtained from PCA analysis. Dim=Dimension (latent variable of the PCA).

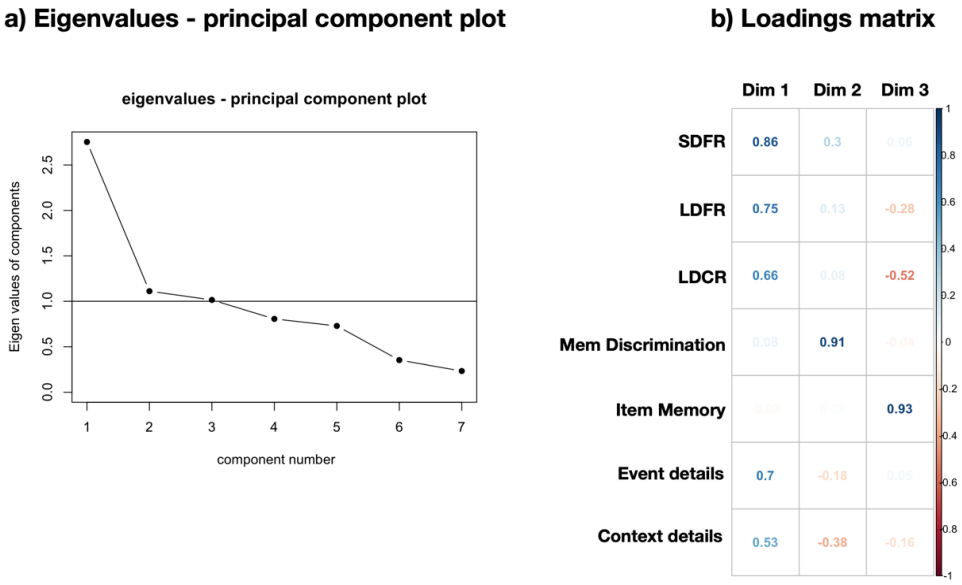


Figure 3. Scree plot and loadings matrix of the PCA. a) Scree plot of the eigenvalues of the PCA analysis. The Kaiser rule suggests a 3-dimensions solution to the PCA. b) Loadings matrix of each episodic memory variable on the 3 PCA dimensions. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Cued Recall. Mem Discrimination: Memory Discrimination.

The loadings of each variables on the PCA dimensions is shown Figure 3b. CVLT-c tests and CAI tests all loaded mainly on the first dimension, which explained 39.2% of the variance. Memory discrimination mainly loaded on the second dimension, which explained 15.8% of the variance. Item memory mainly loaded on the third dimension, which explained 14.5% of the variance.

Since memory discrimination and the Item Memory Index both specifically loaded on their own dimensions, we repeated the PCA analysis with only two dimensions. With only 2 dimensions (explaining 55.2% of the variance), memory discrimination was the only variable to load individually on a given dimension (loading on dimension 2: 0.88). All other variables were mainly loaded on the first dimension (loadings ranging from 0.40 to 0.81 in absolute values). Item memory was negatively loaded on Dimension 1 (loading: -0.4) and its contribution to Dimension 1 (4.64) was low compared to that of the other variables (9.6 for context details, and between 21-23 for CVLT-c scores). This suggests that Item memory performance tends to covary slightly negatively with other tests, which was also by partial correlations between the Item Memory Index and

other tests while controlling for age : most partial correlation coefficients were negative, although not they were significant.

4. Discussion

These behavioral results are briefly discussed here. Each episodic memory component is discussed more thoroughly in its corresponding study (pattern separation: study 2; episodic recall: study 4; episodic autobiographical recall: study 5) as well as in the General Discussion (Chapter 4.1).

4.1 Age-related differences of episodic memory component

The relationships between age and all episodic memory tests were best explained by linear models than by logarithmic, or polynomial quadratic or cubic models. This suggests that there is not specific developmental period (i.e. during childhood amnesia) where age-related differences are significantly different from other developmental periods, contrarily to what we hypothesized for memory discrimination. Moreover, the correlation coefficients between age and episodic memory tests among the tests significantly correlated to age were not significantly different. Thus age-related differences are overall comparable between episodic memory tests, except for the Item Memory Index, which was age-invariant. The Item Memory Index taps on recognition memory by assessing old/new discrimination on a set of previously presented pictures. Given the number of pictures presented (see Study 2 for details), this is a relatively simple recognition task. Performance of children at similar simple recognition tasks have been shown to reach adult-like levels during early childhood (Lloyd et al., 2009; Sluzenski et al., 2006). The absence of correlation between Item memory Index and age is thus not surprising. By contrast, memory discrimination as assessed with the MST was correlated with age, contrarily to some previous findings (Ngo et al., 2018, 2019), but in agreement with Rollins & Cloude (2018) (see Study 2 for discussion).

Tests from the CVLT-c and from the CAI, measuring various aspects of episodic recall and episodic autobiographical memory respectively, were correlated with age. The CVLT-c tests were the most correlated with age among all tests. Even if difference between the correlation coefficients of tests with age were not significant, this could be caused to limited statistical power because of the small sample size. The Steiger z- puts an important penalty on small sample size to determine the significance of the comparisons. Thus, future studies with larger samples should further assess compare the age-related differences of episodic recall and episodic autobiographical recall on the one hand, and pattern separation on the other hand.

4.2 Relationships between episodic memory components

Without controlling for age, most tests were significantly correlated, with the exception of the Item Memory Index (Figure 2a). However, when controlling for age, most of these correlations became not significant (Figure 2b), hence many of these correlations were explained by the shared variance with age. Without the effect of age, the only significant correlations were between subtests of the CVLT-c, on the one hand, and between the recall of Event Details from the CAI and Short-Delay Free Recall from the CVLT-c, on the other hand. The fact that episodic autobiographical recall correlates with (non-autobiographical) episodic recall is unsurprising, since both tap on recall processes, although differently. These two components also share common neural correlates, such as areas of the prefrontal and parietal cortices (see Study 4 5). The PCA analysis also showed that CVLT-c and CAI scores loaded on the same dimension. By contrast, memory discrimination and item memory were not correlated with other tests and both contributed to distinct dimensions of the PCA in a three-dimensions solution. A two-dimensions PCA showed that memory discrimination was the only test to be individually loaded on a single dimension. Item Memory Index loaded negatively on the first dimension, although its contribution to this dimension was small, suggesting that it covaries slightly negatively with other tests. Therefore, pattern separation (measured with memory discrimination) and recognition memory (measured with Item Memory Index) are behaviorally independent from measures of recall. As we show in study 2 and in the complimentary analyses on Study 4 and 5, pattern separation depends specifically on hippocampal subfields and not on other

brain areas: this could explain its behavioral independence from other components of episodic memory. In the case of the Item Memory Index, it taps on recognition memory. The behavioral independence could be explained by the hypothesis that recognition was mediated, in some trials, by familiarity, which has distinct correlates from recollection and recall. However, as we did not included a measure of the recognition process (such as a Remember/Know procedure), we cannot test this hypothesis.

5. Conclusion

Episodic autobiographical recall and episodic recall were strongly correlated with age and were correlated to each other even when controlling for age. Memory discrimination and recognition memory were behaviorally independent from other components of episodic memory. The following studies offer a more detailed description of the age-related differences and neural correlates of each test.

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Chapter 3, Part 2:

Hippocampal organization and memory development

Part 2.1:

Hippocampal organization: transversal axis

Study 2

Memory discrimination predicts hippocampal subfields volume in the developing brain

Presentation

This study was published in the journal *Hippocampus.* We present the published paper which is followed by complementary analyses and a short updated discussion.

Context

The objective of this study was to examine the relationship between the transversal organization of the hippocampus (i.e., hippocampal subfields) and episodic memory in the developing brain. In this order, we focused our analyses on memory discrimination, the behavioral outcome of pattern separation. Indeed, pattern separation has been shown to be depend specifically on hippocampal subfields, namely the dentate gyrus (DG) and CA3, in animal models and human adults. Moreover, there is also evidence of a more general relation between subfields structure and pattern separation, as shown by a study in children that reported an association between a multivariate representation of hippocampal subfields volumes and memory discrimination (Keresztes et al., 2018). Given the important development of pattern separation during early childhood (Ngo et al., 2018), this relationship needs to be further described in the context of development. Indeed, no study to this date examined separately the contribution of DG and CA3 to memory discrimination and it is unknown whether other subfields than DG and CA3 could contribute to memory discrimination in children.

Methods

We manually segmented hippocampal subfields, which we correlated with memory discrimination scores using a hierarchical linear regression approach.

Results

Memory discrimination performance was positively associated with age. Hippocampal subfields' volumes were differentially associated with age, suggesting distinct developmental trajectories: the volumes of CA1 and subiculum were linearly correlated with age, but not CA2/3 and DG. Hippocampal subfields volumes were significantly associated with memory discrimination, but not with recognition memory (assessed with the Item Memory Index). Subfields significantly associated with memory discrimination were CA3, subiculum, and the interaction between age and the subiculum.

Discussion

We further confirm the potential role of CA3 in memory discrimination as suggested by some studies in adults and we provide evidence regarding a relationship between memory discrimination and the subiculum, which has been sparsely reported by some studies. Moreover, the relationship between subiculum volume and memory discrimination was moderated by age. Thus, the transversal organization of the hippocampus could be related to pattern separation in other ways than a specific association with the DG or CA3. This was also suggested by a study relating a multivariate representation of hippocampal subfields volumes with memory discrimination (Keresztes et al., 2018). We provide evidence of the specificity of the subfields-memory discrimination relationship by showing an absence of correlation of subfields volumes with recognition memory and fluid intelligence. We further analyzed this specificity by providing complementary analyses reported after the paper.

Article title: Hippocampus subfield volumes and memory discrimination in the developping brain
Authors: Antoine Bouyeure, Sandesh Patil, Frank Mauconduit, Clément Poiret, Damien Isai, Marion Noulhiane
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Complementary analyses

To further examine the specificity of the relationship between the transversal organization of the hippocampus and memory discrimination, we also examined the statistical relation between hippocampal subfields and episodic verbal recall (measured with the CVLT-c), as such associations have been reported in adults and aging populations (e.g., Stark et al., 2013). However, contrarily to pattern separation, there is no theoretical and empirical framework relating *specific* subfields to episodic verbal recall. Our approach was thus exploratory and we did not have specific hypotheses regarding this relationship. We restricted our analyses on Long-Delay Free Recall as it is the most likely to be related to hippocampal structure. The relation between subfields volumes and episodic autobiographical recall was not assessed because of a lack of evidence in the literature for this relationship. Indeed, EAM relies on the hippocampus and thus on hippocampal subfields, but is also importantly supported by a large-scale cerebral network (see Study 5); therefore, subfields volumes are less likely to correlate with episodic autobiographical recall because of all other possible sources of variance – at least in the healthy developing brain.

Methods

The same hierarchical linear regression framework as the one described in the study above was used.

Results

We found no relationships between subfields volumes and episodic recall (all p-values >0.14), even when adding interaction terms with age (all p-values >0.17).

Conclusion

These complimentary exploratory analyses further confirm the specificity of the relationship between memory discrimination and hippocampal subfields in the developing brain. The transversal organization of the hippocampus was thus related to memory discrimination in our studied sample, and not to recognition memory, episodic recall, and fluid intelligence.

Part 2.2:

Hippocampal organization: longitudinal axis

Study 3

Functional organization of the hippocampus on its longitudinal axis is associated with episodic recall in the developing brain

Presentation

This study was based on research performed during a 3-months visit at the Donders Institute, Radboud University, Nijmegen (The Netherlands). It was done in collaboration with Roselyne Chauvin, Koen Haak and Christian Beckmann from the Statistical Imaging Neurosciences group of the Donders Institute. This study is in preparation and considered for submission in *eNeuro*. We present here the current version manuscript, which was slightly modified for the needs of this dissertation (e.g., references to other studies of the dissertation).

Context

The longitudinal organization of the hippocampus reflects the integration of the hippocampus with cortical regions (Poppenk et al., 2013). The large majority of previous studies on the longitudinal organization of the hippocampus have used an approach contrasting the structure (e.g., volume) or function (e.g., functional connectivity) of segregated anterior and posterior parcels, in a bipartite division view, or of the hippocampal head, body, and tail, in a tripartite division view. These views rely on the assumption that the longitudinal organization of the hippocampus is that of segregated subregions along the longitudinal axis, which are separated by sharp boundaries. However, this view is inexact for some aspects of the longitudinal organization: for example, tracer studies have shown that entorhinal projections to the hippocampus change gradually along the longitudinal axis (Strange et al., 2014).

Therefore, the “segregated parcels” view can be considered a coarse-grained approximation of the true underlying longitudinal organization of the hippocampus. Recent data-driven methods have enabled to use fMRI data to describe the topography of connectivity within a region (“connectopy”). They showed that cortico-hippocampal connectivity changed gradually along the longitudinal axis of the hippocampus.

Whether the longitudinal axis of the hippocampus is organized in terms of a gradient in young children is unknown.

We aimed to examine whether the longitudinal organization of the hippocampus, examined with its functional connectivity, followed a gradient in children. Moreover, as the longitudinal axis reflects differences in the integration of the hippocampus to the rest of the brain (external connectivity) (see Introduction section, 1.5), we hypothesized that differences in these gradients might be associated with differences of episodic recall performance, which is known to engage hippocampo-cortical interactions (e.g., between the hippocampus and the PFC). We also reasoned that they might not be associated with memory discrimination, which is typically associated with specific subfields (see Study 2) rather than with the longitudinal organization (as defined with the topography of its connectivity).

Methods

We used a connectopic mapping approach, a data analysis technique using fMRI data to describe the gradual functional organization of the hippocampus as estimated by its connectivity with the cortex. This arguably provides a more fine-grained description of the organization of the hippocampus on its longitudinal axis compared to traditional approaches. Individual connectivity gradients were estimated from resting-state fMRI data and parameters describing their spatial organization were correlated with age and memory scores.

Results

We showed that the connectivity of the hippocampus is progressively organized along its longitudinal axis in children. This means that there is a topographic organization of connections in the hippocampus that gradually changes in an anterior-posterior direction. The organization of hippocampal gradients was not subject to age-related differences. However, individual differences in hippocampal gradients were associated with individual differences of episodic memory recall, but not of memory discrimination.

Discussion

Connectopic maping methods are efficient tools to describe the functional organization of the hippocampus on its longitudinal axis in children. Connectivity gradients are functionally meaningful as inter-individual differences in the functional organization of hippocampal gradients reflected inter-individual differences of episodic memory recall. Interestingly, the organization of gradients was not associated with memory discrimination. Thus, the two axes of hippocampal organization are related with distinct episodic memory components.

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Functional organization of the hippocampus on its longitudinal axisis associated with episodic recall in the developing brain

(in preparation)

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Abstract

Converging evidence suggests that some aspects of hippocampal organization along its longitudinal axis follow gradual changes rather than abrupt transitions. In particular, the connectivity of the hippocampus with the rest of the brain has been shown to change gradually along the longitudinal axis of the hippocampus. Recent data analysis techniques have enabled to describe functional gradients in the hippocampus *in vivo* based on the analysis of fMRI data. However, it is currently unknown whether such a gradient functional organization is also present in children. Here, we applied a connectopic mapping approach on fMRI data acquired from children aged 4-12 years to describe functional connectivity gradients in the hippocampus in a fully data-driven manner. We found that the functional organization of the hippocampus along its longitudinal axis was gradual. The organization of hippocampal gradients did not change with age. However, we found that interindividual differences in the organization of hippocampal gradients were associated with a measure of episodic recall, but not with memory discrimination. Connectivity gradients thus convey meaningful information related to memory function. These results underline the relevance, for studies interested in memory development, to use methods enabling the description of longitudinal hippocampal gradients.

Keywords: hippocampus, connectivity gradient, resting-state fMRI, episodic memory, episodic memory development

1. Introduction

The hippocampus is organized on its longitudinal axis: genetic, electrophysiological, and neuroimaging studies have shown differences of gene expression, electrophysiological response, and functional activity along the longitudinal axis of the hippocampus in mammals, which corresponds to the anterior-posterior axis in humans (Strange et al., 2014). This longitudinal organization has been historically understood and studied as that of a segregation between discrete parcels with functionally distinct roles. Genetic studies have demonstrated the existence of three distinct gene expression domains along the long-axis, which are demarcated by sharp boundaries (Fanselow & Dong, 2010; Strange et al., 2014; Thompson et al., 2008). The subregions delineated by these gene expression (e.g. the head, body and tail of the hippocampus) domains have been associated to distinct aspects of hippocampal function (Fanselow & Dong, 2010). Alternatively, the hippocampus is often described with a bipartite division, distinguishing an anterior and a posterior parcel (the intermediate parcel of the tripartite division is, in this case, generally merged with the posterior parcel). This 'anterior one-third' bipartition is commonly used by neuroimaging studies that have demonstrated differences of anatomical or functional properties between the anterior and posterior parts of the hippocampus. Overall, numerous evidence showed a functional specialization of the hippocampus on its longitudinal axis (e.g., DeMaster et al., 2014; Grady, 2020; Greicius et al., 2003; Nadel et al., 2013; Persson et al., 2018; Poppenk & Moscovitch, 2011; Strange et al., 2014).

The view that the longitudinal organization of the hippocampus is underpinned by sharply delineated parcels is challenged, however, by evidence for gradual patterns of functional change along this axis. For example, hippocampal place cell field size increases progressively in the dorsal-ventral direction in rodents (posterior-anterior direction in humans) (Kjelstrup et al., 2008), underlying functional differences along the longitudinal axis. Tracer connectivity studies have demonstrated a continuous rather than discrete changes in the projections of the entorhinal cortex on the longitudinal axis (Witter et al., 2000). Thus, some aspects of hippocampal longitudinal organization follow gradual changes rather than being separated into discrete, functionally distinct

parcels. However, the "discrete parcels" and "gradient" approaches to hippocampal longitudinal axis organization are not necessarily mutually exclusive: for example, discrete genetic domains could be overlaid on gradient-like patterns defined by connectivity changes (see Strange et al., 2014, for in-depth discussion).

As mentioned, hippocampal connectivity could follow gradual changes along the longitudinal axis (Witter et al., 2000; Strange et al., 2014). In humans, studies using in-vivo neuroimaging methods have almost exclusively used a discrete parcels approach to investigate differences in hippocampal longitudinal axis connectivity. This is partly due to methodological convenience: describing progressive changes in connectivity requires both higher data resolution and more complex data analysis techniques than comparing segregated ROIs. However, if connectivity changes along the longitudinal axis are gradual, such approaches can only approximate the "true" organization of connectivity.

Recent data analysis techniques have enabled to describe gradual changes in connectivity within a ROI using structural or functional MRI connectivity data and have been successfully applied to describe hippocampal connectivity gradients in adults (Przeździk et al., 2019; Wael et al., 2018). Thus, these methods provide a more refined picture of hippocampal organization compared to approaches that segregate the hippocampus into discrete parcels. Because these methods have never been applied in a developmental context, this leaves open the question of whether hippocampal organization is also gradual in children, and whether it is subject to age-related differences.

Developmental studies to date have used a "discrete parcels" approach, showing distinct patterns of age-related differences between anterior and posterior hippocampal subregions (Blankenship et al., 2017; DeMaster et al., 2014; Riggins et al., 2015, 2016, 2018). Hippocampal subregions have also been shown to contribute differentially to the development of episodic memory abilities (DeMaster et al., 2014; Riggins et al., 2015, 2016, 2018). However, some of these reported anterior-posterior differences could ultimately reflect an underlying gradual organization.

A recent study in adult subjects demonstrated that interindividual differences in hippocampus connectivity gradients were associated with interindividual differences in episodic memory abilities (Przeździk et al., 2019). Therefore, the gradual organization of the hippocampus along its longitudinal axis is related to memory function. Thus, describing this gradual organization in the developmental context would importantly contribute to our understanding of the factors affecting memory development.

Here, we sought to describe the progressive organization of hippocampal connectivity during childhood using resting-state fMRI data. Connectivity gradients were described using a connectopic mapping approach. Connectopy is a concept referring to the fact that within certain brain areas, the connectivity of that area with the rest of the brain is not uniform but changes progressively according to a certain topographic organization pattern (Haak et al., 2018). Thus, connectopic mapping is a data analysis technique representing the topography of the connectivity of a given region with the rest of the brain without making an a priori assumption of a given form of organization. In other words, if the organization of hippocampal connectivity is gradual, then connectopic mapping methods should be able to describe this gradual organization without making the assumption of a specific mode of organization, be it gradual, discrete or otherwise.

We described connectivity gradients using connectopic mapping on fMRI data acquired from children aged 4-12 years, and examined the association between these connectivity gradients and memory performance. Episodic memory was assessed using a measure of episodic recall as well as with memory discrimination, a behavioral proxy of pattern separation, which is typically associated with specific hippocampal subfields.

Our hypotheses were the following: 1) the connectopy of the hippocampus in children should be gradual, as it has been demonstrated in adults. 2) This gradual organization could be subject to age-related differences, translating a progressive maturation of the organization of the hippocampus on its longitudinal axis, echoing the known protracted maturation of hippocampal subfields. 3) The gradual organization could be related to

episodic memory performance in children, similarly to what has previously been shown in adults (Przeździk et al., 2019).

2. Methods

2.1 Population

We studied 50 children aged from 4 to 12 years old (mean 8.27 years, standard deviation 2.3 years). 55% of the participants were males and 45% females. Among our 50 participants, 3 were not included because of a history of learning disorders or of structural anomalies detected on the MRI images; 2 refused to participate to the scanning session; 4 aborted the scanning session. This resulted in a total of 41 participants with complete MRI data.

2.2 MRI acquisitions

Neuroimaging data was collected at the NeuroSpin research center, CEA, Gif-sur-Yvette, France. Children first followed an MRI training session on a mock scanner set in a children-friendly environment. They were told a compelling story, making them astronauts on a mission to understand the brain, taking aboard a spaceship (the scanner), and wearing a space helmet (the head coil). For the mission to succeed, children were told to try staying still as much as possible, for the scanner to take accurate pictures of their brains. Once the children were familiarized with the sonic and visual environment of the scanner, the acquisition begun. Images were acquired on a Siemens PRISMA 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil.

We first acquired a T1-weighted MPRAGE volume (TR=300ms, TE=2.98ms, 0.9mm isotropic resolution, 175 slices, acceleration factor GRAPPA2). We then acquired 4 sessions of resting-state fMRI data of 3’10’’ each (TR=1.81, TE=30.4, 2mm isotropic resolution, 69 slices, FOV 192mm, Multi-Band 3). The 4 sessions were organized in two separate blocs of two sessions each. Inside each bloc, the two sessions were acquired without interruption. The two blocs were separated by the acquisition of other

imaging sequences. Additionally, we acquired two spin-echo EPI volumes for each session, one with same phase-encoding direction (posterior-anterior) and the other in the opposite phase-encoding direction (anterior-posterior), to correct for susceptibility off-resonance field distortions.

During the resting-state scanning acquisitions, children were shown a short movie movie, *Inscapes*, which display abstract shapes and is deprived of narration or structure. This movie was specifically conceived to improve compliance by allowing subjects to focus their attention while minimizing cognitive load during functional acquisitions (Vanderwal et al., 2015). Viewing of this movie has been shown to not significantly alter intrinsic functional activity (except for the somatomotor, visual and ventral attention networks) compared to classical resting-state while improving compliance and reducing head motion. Given that resting-scan sessions can be particularly difficult to bear for young children, we reasoned that viewing of the movie would considerably help to reduce data attrition. Furthermore, movie watching paradigms have been shown to outperform classical task-free rest for functional connectivity prediction of behavior (Finn & Bandettini, 2020). During the first rest acquisition bloc, children watched the standard version of the movie; during the second bloc, they watched a backward version, in order to avoid a presentation of the identical content between acquisition blocs. Moreover, during the T1 acquisition and the rest of the scanning session (i.e., not resting-state sequences), excerpts of the animation movie *Wall-E* (Pixar Animation Studios) were presented.

2.3 MRI preprocessing

T1-weighted images were segmented into Grey Matter (GM), White Matter (WM), Cortico-Spinal Fluid (CSF) tissues types, and skull-stripped, while being corrected for spatial intensity variations (b1 bias field). Both operations were performed with FMRIB's Automated Segmentation Tool (FAST) (Smith et al., 2004).

Resting-state fMRI images were preprocessed as follows. Scans were realigned and corrected for motion with FSL mcFLIRT (Jenkinson et al., 2002) and corrected for slice-timing (FSL slicetimer). Images were then corrected for susceptibility-induced off-

resonance field distortions (FSL *topup*) (Levine et al., 2002) using the spin-echo EPI volumes acquired after each resting-state session. Then, scans were cropped to remove the neck and skull (FSL robustfov) and skull-stripped (FSL Brain Extraction Tool, Smith, 2002). The skull-stripped fMRI scans were then co-registered to their skull-stripped T1-weigted image (6 degrees of freedom) using Advanced Normalization Tools (ANTs) (http://stnava.github.io/ANTs/) (Avants et al., 2011). Normalization of data was done by using non-linear normalization (ANTs SyN algorithm, Avants et al., 2008; Klein et al., 2009) to register the T1 images to the NIHPD pediatric template (http://www.bic.mni.mcgill.ca/ServicesAtlases/NIHPD-obj1). We then applied the normalization fields estimated on the T1 on the fMRI data to transform fMRI scans in template space. Normalized fMRI scans were then concatenated. This resulted in 12'40'' of fMRI data for each subject. Normalized and concatenated images were smoothed with FWHM=4.

Once normalized, fMRI images were further preprocessed in order to mitigate the spurious effect of motion on data analysis. Images were corrected for motion using ICA-AROMA (Pruim et al., 2015) which is an Independent Component Analysis (ICA)-based strategy for the removal of motion artifacts from fMRI data. ICA-AROMA has been shown to remove spurious noise from fMRI data to a larger extent than other motion correction approaches while preserving statistical power (Parkes et al., 2018). We further mitigated the effect of motion by computing volume-to-volume head motion (i.e. framewise displacement, FD) for each raw fMRI scan, using the method described in Power et al. (2012) (FSL's Motion Outliers tool). FD was used to determine the number of outlier volumes within each resting-state scan. A volume was considered an outlier if its FD exceeded 0.25. Subjects were excluded if more than 25% of the volumes across all of their resting-state scans were considered outliers. Moreover, subjects were excluded if their mean FD across all volumes exceeded 0.25, which is consistent with standards of the literature on adult populations (Parkes et al., 2018; Power et al., 2014, 2015). This led us to exclude only two subjects; we believe that this is mainly reflective of the positive effect of movie watching during resting state (Vanderwal et al., 2015).

After motion correction and exclusion of outliers, we further corrected the fMRI images by regressing out of the mean signal of white matter and CSF while orthogonally applying band pass-filtering (high pass=0.001, low pass=0.01) (Lindquist et al., 2019).

2.4 Segmentation of the hippocampus

We manually segmented the left and right hippocampus on the NIHPD pediatric T1w template, following the protocol described in Bouyeure et al. (2018). The segmentations were fairly conservative way in order to avoid the presence of voxels conveying non-hippocampal signal, which would bias the estimation of hippocampal connectopy.

2.5 Connectopic mapping

The connectopy of the hippocampus was estimated at the individual level from resting-state fMRI data with the ConGrads (Connectivity Gradients) method (Haak et al., 2018), which is available for download here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/OtherSoftware. In brief, the aim of the ConGrads method is to represent hippocampal connectopy by estimating the dominant mode of change of the connectivity fingerprints (connectivity patterns specific to each voxel) of hippocampal voxels in an entirely data-driven fashion. In other words, if the connectivity fingerprints of hippocampal voxels change gradually on the longitudinal axis, showing that hippocampo-cortical connectivity is organized in a gradient-like manner, then the dominant mode of connectivity change obtained by the ConGrads method will describe a longitudinal connectivity gradient. No specific scheme of organization is hypothesized by the method, whether it is a discrete organization, or any form of gradient organization. This method has been applied in other brain areas known or supposed to have a connectopic organization, such as the visual cortex (area V1), the motor cortex (area M1), or the hippocampus (in adults) (Haak et al., 2018; Przeździk et al., 2019).

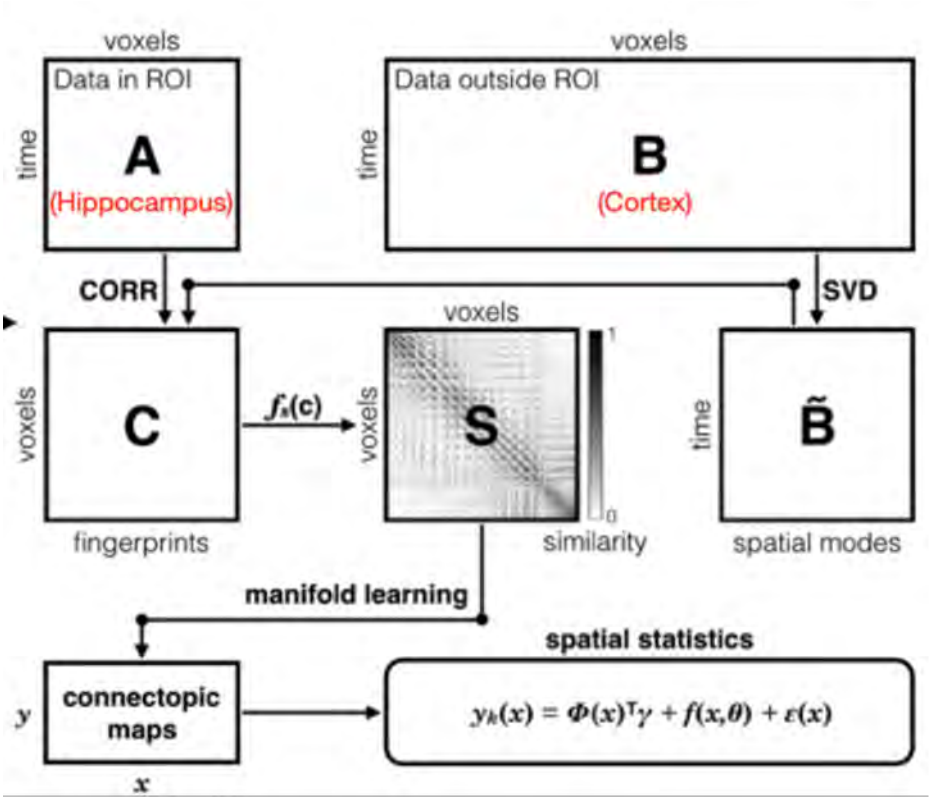

Figure 1. ConGrads method. A time-series-by-voxel matrix B for cortical voxels is decomposed by SVD. The resulting decomposed matrix is correlated with a time-series-by-voxel matrix A of hippocampal voxels. This results in matrix C which conveys the connectivity fingerprints of each hippocampal voxel. The similarity between connectivity fingerprints is computed producing matrix S. S is then decomposed with a manifold learning approach to produce a connectopic map. The connectopic map is then modeled with spatial statistics to produce spatial parameters that can be correlated with behavioral variables. Modified from Haak et al. (2018).

In this aim, the ConGrads method estimates the connectivity fingerprints of hippocampal voxels by correlating the matrix of the time series of each hippocampal voxel with the matrix of the time series of each cortical voxels previously decomposed with SVD (Figure 1). Connectivity fingerprints thus consists in correlation matrices showing, for each hippocampal voxels, the correlation of its time series with the time series of each SVD dimensions representing cortical signal. A similarity function is then applied to each of the connectivity fingerprint matrices to estimate the similarity between the connectivity fingerprints of all hippocampal voxels. A spectral clustering approach (manifold learning approach based on a Laplacian eigeinmap algorithm) is then used to find the main spatial mode of organization of the similarity matrix. This decomposition method computes the major spatial orientations (eigenvectors) of each matrix. A connectopic map of the hippocampus is thus obtained, in which voxels code

a similarity value representing the similarity of hippocampal connectivity fingerprints. Voxels with a close similarity value have a similar connectivity fingerprint. If the connectopy of the studied structure follows an anterior-posterior gradient, then the connectopic map should describe a connectivity gradient in which similarity values of connectivity fingerprints change gradually on the anterior-posterior axis. Moreover, the two extremas of the distribution of similarity values should be located at the most anterior or posterior point of the long-axis of the hippocampus.

The ConGrads method was applied separately for the left and right hippocampus: 1) At the group level by concatenating the functional data of all subjects. This allowed us to visualize the average connectopy of the hippocampus across all subjects. 2) At the individual level using the functional images of each subject. This allowed us to study inter-individual differences on the gradients' organization. Hippocampal signal was extracted with the left and right hippocampal masks segmented from the NIHPD template. Cortical signal was extracted with a mask of grey matter obtained from the NIHPD template.

2.6 Description of individual gradients: spatial statistics

To understand the relationship between inter-individual differences in the organization of hippocampal gradients and behavioral variables such as age and memory performance, we used a Trend Surface Modeling approach (TSM; Haak et al., 2018) to describe the overall spatial organization of each gradient with a small number of parameters. For a given map whose points have a property P of location i, defined in space by a triplet of coordinates (x(i), y(i), z(i)), TSM estimates the spatial distribution of properties P using polynomial regression. The coefficients of the regression are direction parameters estimating the location of each property (here the similarity values of hippocampal gradients) of the points of the surface in the three directions of space. A first order polynomial thus estimates the location of a set of points P(i) by a line approximating the location of the set of points; adding quadratic and cubic coefficients by increasing the order of the polynomials allows to estimate more complex spatial distributions. Each gradient was modeled with the following equation: $\boldsymbol{y}\mathrm{k}(\boldsymbol{x}) = \boldsymbol{\phi}(\boldsymbol{x})\mathrm{T}\boldsymbol{\gamma} + f(\boldsymbol{x}, \boldsymbol{\theta}) + \epsilon(\boldsymbol{x})$, where $\boldsymbol{x}$ is a point to be estimated, $\boldsymbol{y}$k is a connectopy, $\boldsymbol{\phi}(\boldsymbol{x})$ is a spatial

function with its direction parameters $\boldsymbol{\gamma}$, $f(\boldsymbol{x}, \boldsymbol{\theta})$ a Gaussian function to describe finer variations due to smoothing, and where ϵ corresponds to the residuals of the regression. Each polynomial model yields parameters of direction $\boldsymbol{\gamma}$, the number of which is equal to the 3 directions in space (one per direction x, y, z) multiplied by the order of the polynomial (2nd model order: 6 parameters; 3rd order model: 9 parameters). The parameters describe the spatial trends in the distribution of similarity values of each connectopy at the individual level. The aim is therefore to produce a parsimonious estimation of the spatial organization of connectopies with a limited number of coefficients.

We used the Bayesian Information Criterion (BIC) to choose the adequate polynomial model orders to model each individual gradient with TSM. The best model is considered to be the model with the smallest BIC as it represents the best balance between explanatory power of the model and model complexity (i.e., the number of parameters used to model the gradients). The BIC was calculated for each polynomial model order across all subjects. The model with the smallest BIC across all subjects was then selected.

Data quality assessment was performed in two steps. First, we visually inspected each gradients and their TSM reconstructions. We found that for some subjects, connectopies were not gradients but had a functionally unlikely distribution of similarity values (e.g., 95% of voxels have very close similarity values). Therefore, this likely results from errors in the estimation of the connectopy (e.g., caused by outlier voxels) rather than reflecting the “true” functional organization of the hippocampus. Second, we observed that connectopies whose variance was weakly explained by TSM were also connectopies that did not have a gradual aspect. This is likely due to the fact that failed gradient estimations are not modeled with the same order of polynomials as the majority of correctly estimated gradients. To eliminate most of the erroneous connectopies and to match quality standards reported by previous studies (Przeździk et al., 2019), we excluded from our analyses subjects for which the variance of their gradient explained by TSM was below 90%.

2.7 Assessment of episodic memory

To estimate the relationship between the organization of hippocampal connectopy and episodic memory, we used two measurements of episodic memory. The gradual organization of the hippocampus was previously associated to recollection derived from an old/new recognition test followed by a Remember/Know paradigm (Przeździk et al., 2019). Here, we investigated the relationship between hippocampal connectopy with a measure of recall, i.e. the Long-Delay Free Recall score from the CVLT-c (see Study 1 and 3 for details), as it is likely to engage hippocampo-cortical function and thus be associated with differences of the organization of hippocampal connectivity. Moreover, memory discrimination (a measurement of pattern completion) has been regularly associated to the integrity of hippocampal subfields which span on the transversal (medial-lateral) axis of the hippocampus (e.g., Canada et al., 2018; Yassa & Stark, 2011). To verify whether such an association was also found for the longitudinal axis, we included a measurement of memory discrimination obtained with the Mnemonic Similarity Task (Ngo et al., 2018; Stark et al., 2019). Behavioral data was collected out of the scanner.

2.7 Relation between gradients, age, and episodic memory

We estimated the relationship between subject-specific parameters describing the left and right hemisphere connectopies for each subject, and our behavioral variables of interest (age and memory performance) with a hierarchical linear regression approach. For age, we modelized in a first step its variance explained by mean FD. In a second step, we estimated with an ANOVA test if adding TSM parameters (describing individual connectopies) to the model explained the variance of age over and above the variance explained by mean FD. This allowed us to control for the impact of motion. We report the difference of R^2 obtained through the addition of TSM parameters to the model, and the associated F and p-values. A similar approach was used to estimate the relationship between memory performance and TSM parameters. For each measure of episodic memory, we modeled its variance explained by mean FD and age, before estimating the effect of adding TSM parameters.

3. Results

3.1 Group-level connectopy

We first estimated the connectopy of the hippocampus at the group level by concatenating the fMRI sequences of all subjects. This provides an illustration of the average connectopic organization of the hippocampus. The dominant mode of connectivity change of hippocampal connectopy at the group-level was a gradient spanning its anteroposterior (longitudinal) axis, as expected (Figure 2). The connectopy of the hippocampus is thus a gradient spanning its longitudinal axis.

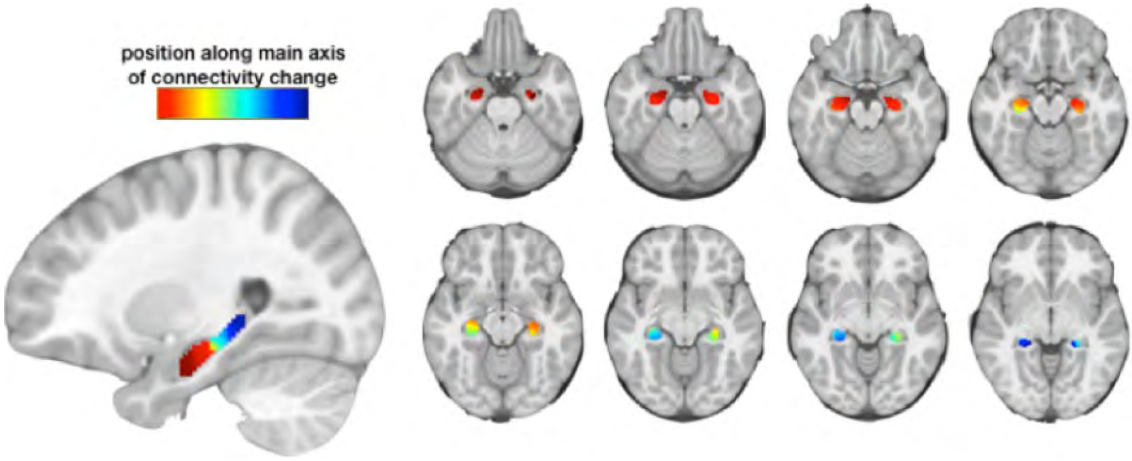

Figure 2. The connectopy of the hippocampus is a gradient along the longitudinal axis. The similarity between the connectivity fingerprints of hippocampal voxels is topographically organized on the longitudinal axis. Similar colors indicate similar connectivity fingerprints. These connectivity fingerprints change gradually on the longitudinal axis. Color values are on an arbitrary scale. Left: group-level gradient shown on a sagittal slice. Right: group-level gradients shown on axial slices.

We verified that the gradual organization of hippocampal connectopy reflected known differences of connectivity on the longitudinal axis of the hippocampus. In this order, we generated the projection map of the group gradient, which shows which brain voxels are preferentially connected to hippocampal gradient voxels. For example, if the temporal pole is preferentially connected to the hippocampal voxels situated in the anterior tip of the gradient (compared to all other voxels of the hippocampus), then the temporal pole on the projection map will have the same similarity value than the value of the hippocampal voxels preferentially connected with the temporal pole.

Visual inspection of the projection map showed that the gradient organization of the longitudinal axis reflected known anterior-posterior differences of hippocampal functional connectivity. Voxels in the anterior part of the gradient were preferentially connected to anterior brain areas, and voxels in the posterior part of the gradient were preferentially connected to posterior brain areas. Hence, the longitudinal connectivity gradient of the hippocampus reflected progressive changes of hippocampo-cortical connectivity that have been previously approximated by studies using a segregated parcel approach. Figure 3 shows the projection map for the right hemisphere group gradient.

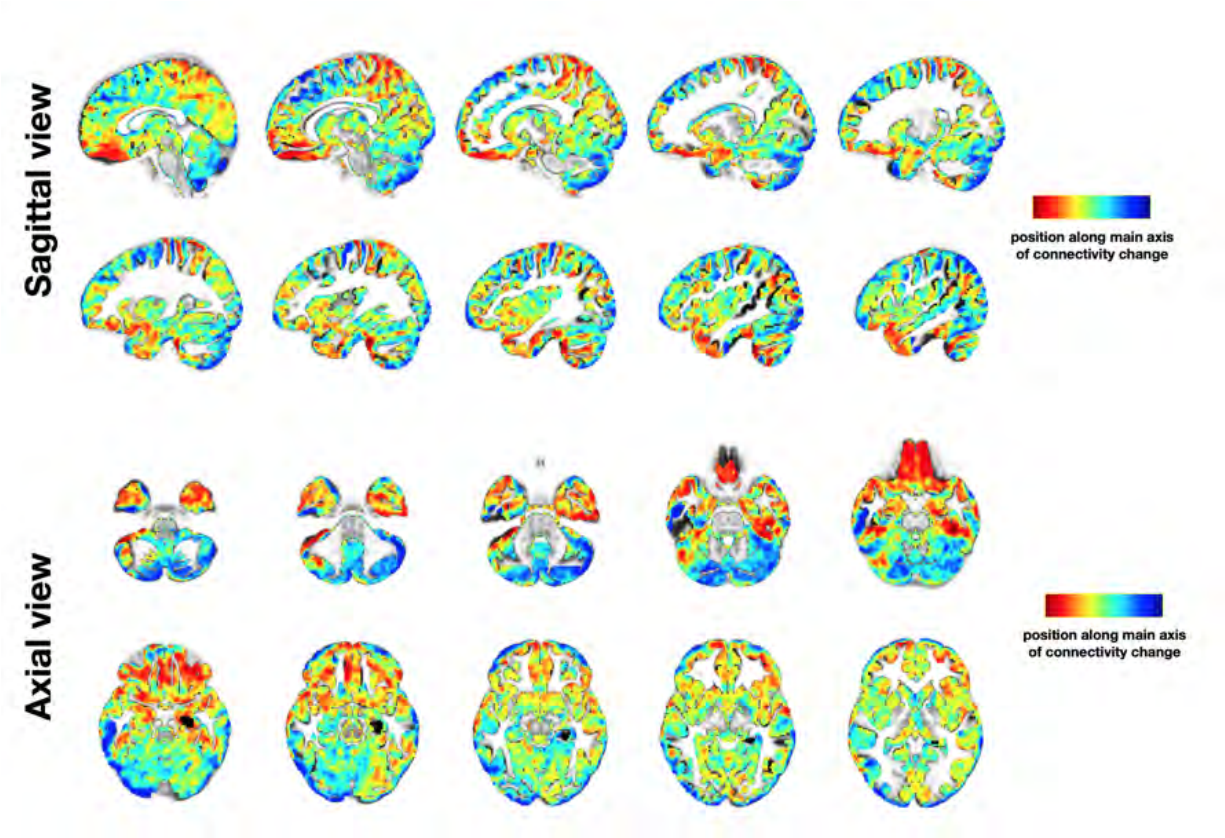

Figure 3. Projection map of the group gradient. The projection map shows the projection of the gradient on the cortex (up: sagittal slices, 5mm slice increment: bottom: axial slices, 5mm slice increment). Voxels with a given color (i.e., similarity value of connectivity fingerprints) on the projection map are voxels preferentially connected to the voxels of the same color in the hippocampus connectopy map of Figure 2.

3.2 Individual-level connectopy

3.2.1 Trend surface modeling

While we found a gradient organization along the longitudinal axis at the group level, a crucial question is whether gradual connectopies could also be described for each individual subject. We therefore estimated individual-level connectopies for the left and right hippocampus, and used TSM to describe each individual gradient with a small number of spatial parameters. Models from 2nd (6 spatial parameters) to 5th (15 parameters) order (see Przeździk et al., 2019) were compared. The 3rd order model (9 parameters) had the lowest average BIC for all subjects (Figure 4) and was therefore selected for both hemispheres. This result is similar to that of Przeździk et al. (2019). The average explained variance of all individual gradients by the third-order model was 93.16% for the left hemisphere, and 92.39% for the right hemisphere. Figure 4 shows the distribution of explained variance of all individual TSM reconstructions. We excluded gradients which explained variance by TSM was less than 90% from the following analyses. This ensured that we only analyzed correctly modeled connectopies and matched quality standards reported by previous studies. This gave us a final sample of 27 gradients for the left hemisphere and 31 for the right hemisphere.

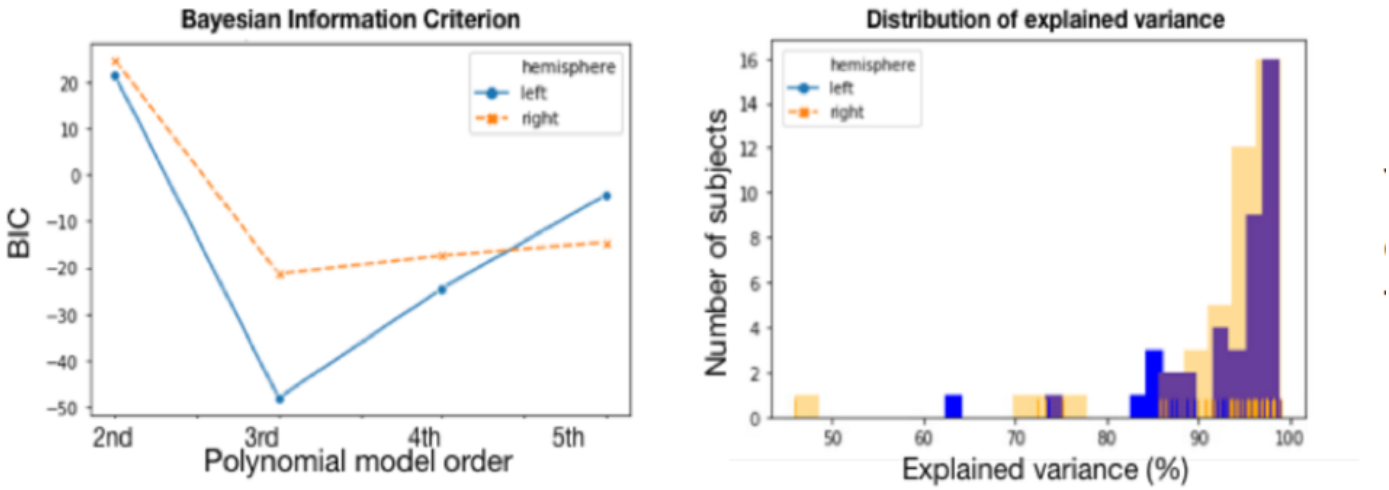

Figure 4. BIC and explained variance of trend surface modeling gradients. Up : BIC values for 2nd to 5th polynomial model orders for both hemispheres. Down: Distribution of explained variance for the 3rd polynomial model order. Blue: left hemisphere gradients. Orange: right hemisphere gradients.

3.2.2 Relationship between connectopies and variables of interest

3.2.2.1 Age

To describe age-related differences in the organization of hippocampal gradients, we used hierarchical linear regression to estimate the relation between age and the 9 TSM parameters (since we selected the 3rd order model) describing each individual gradient for both hemispheres. TSM parameters did not explain the variance of age over and above the variance explained by mean FD (left hemisphere: F=1.34, p=0.39; right hemisphere: F=1.06, p=0.44). This suggest that there are no age-related differences of the parameters describing individual gradients. However, in the left hemisphere model, the 7th parameter (corresponding to x^3) was significant (t=-2.33, p=0.03).

3.2.2.2 Episodic memory

We used the same hierarchical linear regression to estimate the relation between the organization of hippocampal gradients and two measures of episodic memory. TSM parameters in the left hemisphere explained the variance of Long-Delay Free Recall over and above the variance explained by age and mean FD (F=2.97, p=0.03). The full model with TSM parameters and the covariates explained 53% (adjusted R^2) of the variance of Long-Delay Free Recall (F=3.73, p=0.01). The 1st, 5th, 6th and 7th parameters were significant. These parameters describe spatial organization in the x, y^2, z^2, and x^3 directions, respectively. This suggest that individual differences across the three directions of space in the gradual organization of the hippocampus are related to individual differences in recall performance, and particularly differences on the x-axis of the hippocampus (which was represented by two parameters). TSM parameters in the right hemisphere did not explain the variance of Long-Delay Free Recall over and above the covariates (F=1.30, p=0.30). (Figure 5).

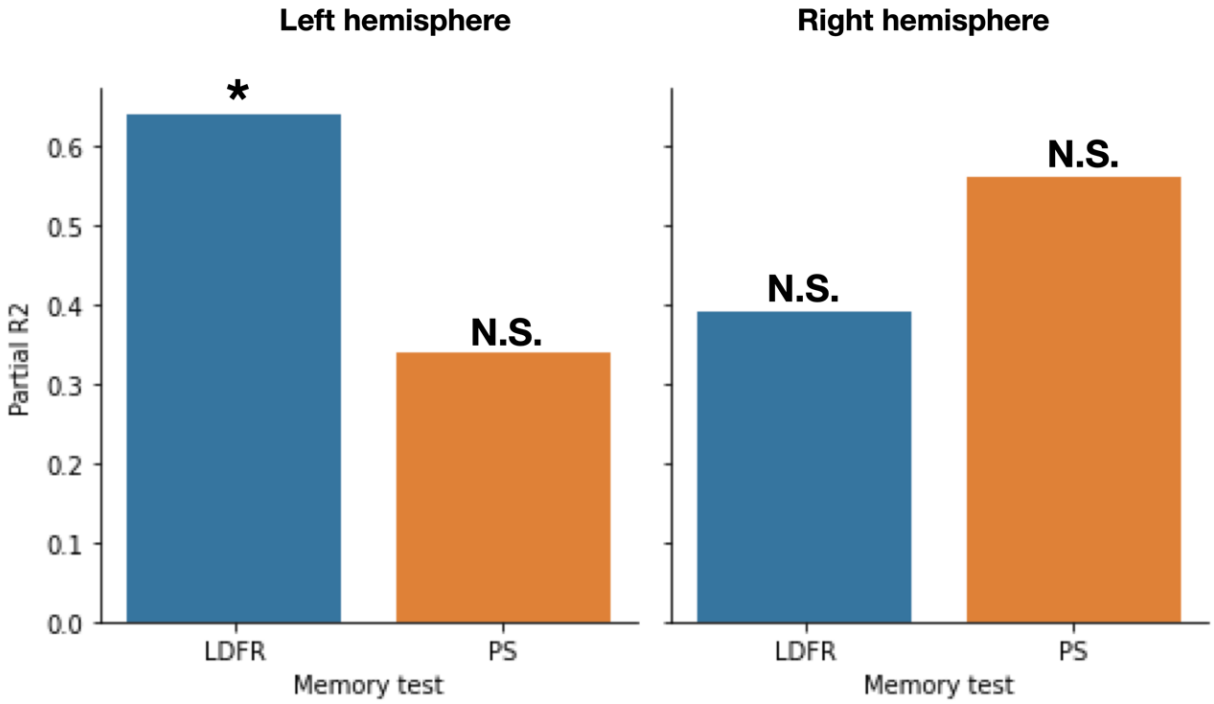

Figure 5. Partial R2 values obtained from hierarchical linear regression. This shows how much of the variance of memory tests (LDFR=Long-Delay Free Recall; PS=Patter separation/memory discrimination) is explained by TSM parameters over and above the variance explained by covariates. *:p<0.05. N.S.: not significant.

TSM parameters did not explain the variance of Memory Discrimination over and above the variance explained by mean FD and age in the left hemisphere (F=0.46: p=0.86). Right hemisphere TSM parameters also did not explain the variance of Memory Discrimination (F=1.56, 0.23).

To visualize the relationship between connectopy and Long-Delay Free Recall performance, we visually compared the left hemisphere gradients of 4 subjects with the lowest scores (controlling for age and mean FD), with the gradients of 4 subjects with the highest scores (controlling for age and mean FD) (Figure 6). Visual comparison did not reveal a clear way in which individual differences in memory performance could be related to visually identifiable differences in gradient organization for these subjects. The visual comparison of the gradients of all subjects based on their memory performance did not revealed either a clear pattern of differences. Indeed, differences in connectopic organization expressed by differences in TSM parameters might be too subtle and/or multifactorial to be truly detected by a simple visual comparison procedure. Our small sample size also entails that it is harder

for subtle patterns of differences to be sufficiently represented by an important number of subjects to facilitate visual detection.

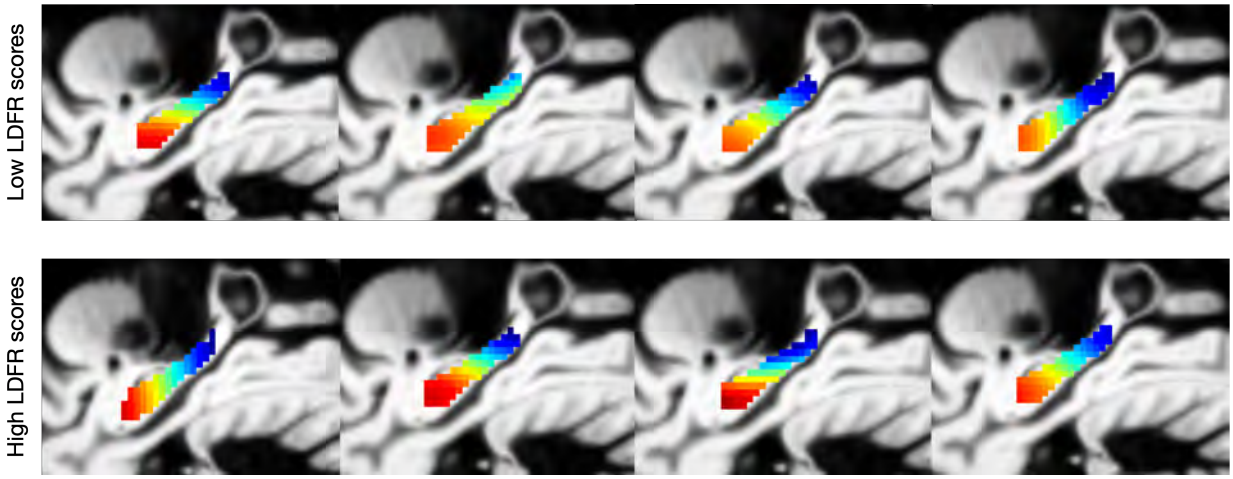

Figure 6. Gradients of subjects with low and high memory scores. Left-hemisphere gradients of subjects with low Long-Delay Free Recall (LDFR) scores (top) and high LDFR scores (bottom). Low and high scores are estimated while controlling for age and mean FD.

4. **Discussion**

We examined whether the longitudinal axis of the hippocampus in the developing brain followed a gradual functional organization with a connectopic mapping approach. We found that the longitudinal axis was functionally organized in a graded manner, as previously shown in adults. There were no age-related differences in this organization. However, inter-individual differences in recall were associated with inter-individual differences in the organization of gradients.

4.1 Gradual organization of the longitudinal axis in children

Connectopies reflect the topographic organization of connectivity within a region. Our results show that the connectopy of the hippocampus in children is a gradient along the longitudinal axis. Thus, the functional connectivity of hippocampal neurons with cortical regions changes progressively along the longitudinal axis.

The projection of the connectopy onto the cortex mirrored known differences in functional connectivity between the anterior and posterior areas of the hippocampus (Figure 3). Therefore, previous functional connectivity studies that compared the connectivity of distinct anterior/posterior areas of the hippocampus averaged into segregated parcels underlying graded changes of connectivity. This underscores the relevance of using techniques enabling the description of graded patterns of changes to study the organization of the hippocampus during development. Our results are a first step in this direction.

4.2 Hippocampal longitudinal gradients were not associated with age

We did not find a relationship between TSM parameters describing the organization of individual gradients and age. Previous studies have reported that the functional connectivity of the anterior and posterior hippocampus (studied with segregated parcels) matured during childhood (Blankenship et al., 2017). Our results suggest that the overall organization of connectivity differences along the longitudinal axis is however invariant with age. This could be caused, for example, by equally similar age-related connectivity changes in the anterior and posterior parts of the hippocampus. This could lead to a conservation of the general arrangement of connectivity differences along the long axis. Therefore, while the connectivity of the anterior and posterior hippocampus with the cortex are subject to age-related differences during childhood, the organization of these anterior-posterior differences on the longitudinal axis would not.

However, our study was statistically underpowered and we may not have been able to detect subtle age-related differences. For approximately 20% of our subjects, connectopic estimation was unsuccessful. This can be caused by outlier voxels or other factors affecting data quality. While 20% of data attrition is reasonable, this is detrimental for studies with an initial small sample size such as ours. Because the 7th parameter describing the left individual gradients was significantly associated with age, age-related changes of hippocampal connectopies during childhood could be found by future studies. A functional connectivity study in infants reported a lack of functional specialization of the hippocampus on its longitudinal axis (Howell et al., 2020). Thus,

it remains to be further described whether the organization of the longitudinal axis develops in the very early years of life or whether developmental changes extends into childhood or beyond.

4.3 Association between hippocampal longitudinal gradients and episodic recall

Interindividual differences in the organization of hippocampal longitudinal gradients were related to interindividual differences in episodic verbal recall. Thus, we report an association in children similar to what has been described in adults (Przeździk et al., 2019). Long-Delay Free Recall was associated with left hemisphere gradients but not right hemisphere gradients, consistent with known hemispheric asymmetries in verbal information processing (e.g., Nagel et al., 2013). The mechanistic reasons underlying how interindividual differences in gradient organization relate to interindividual differences in memory performance remain to be fully understood (discussed in Przeździk et al., 2019). One possibility is that differences in gradient organization reflect differences in the amount of neural resources dedicated to a particular task. Neurons in the hippocampus that are dedicated to the same task are likely to have a similar connectivity fingerprint with the cortex and thus have close similarity values in the spatial organization of the gradient (Przeździk et al., 2019). The different patterns of gradient organization could reflect the fact that for some individuals, fewer neural resources are allowed to the task being measured.

However, visual comparison of the gradients as illustrated in Figure 6 for a few subjects did not reveal clear differences in the gradient topography of subjects with low and high Long-Delay Free Recall scores. It is possible that these differences are too subtle and/or multifactorial to be effectively detected by simple visual comparison, although they were statistically detected by the significant association between Long-Delay Free Recall scores and TSM parameters. This association could be caused by interleaved patterns of spatial differences that could not be translated into easily detected differences visually. Other methods, such as voxel-based morphometry methods applied to connectopies, or fine-grained analysis of the spatial distribution of similarity values within gradients, could more accurately describe how differences in the topography of hippocampal gradients are associated with behavior.

Memory discrimination was not related with the organization of hippocampal longitudinal connectivity gradients. We reported in a previous study (Bouyeure et al., In press; supplementary analyses of the Study 2 of this dissertation) that the transversal organization of the hippocampus (hippocampal subfields) was associated with memory discrimination, but not with verbal episodic recall, which is the opposite of what we report here. Therefore, distinct aspects of hippocampal organization might be associated with distinct components of episodic memory. An important avenue of research is to integrate the longitudinal and transversal axes of hippocampal organization to understand hippocampal function (see Vos de Wael et al., 2018) and how it unfolds during development.

5. Conclusion

We described a gradual organization of hippocampal connectivity on its longitudinal axis during development. While the topography of hippocampal gradients were not subject to age-related difference, they were associated with episodic recall but not with memory discrimination. These results stress the need to further use data-driven techniques enabling the description of graded patterns of changes to study hippocampal organization in children.

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Chapter 3, Part 3:

Connectivity within brain networks and episodic memory development

Part 3.1:

Structural connectivity

Study 4

Maturity of white matter tracts is associated with episodic memory recall during development

Presentation

This study was, at the time of writing, under revision in *Cerebral Cortex Communications.* We provide here the current state of the manuscript. The final manuscript will likely contain modifications following the completion of the review process. The manuscript is followed by complementary analyses and a short updated discussion.

Context

It is unclear how white matter maturation contributes to the development of episodic memory in children, particularly during early childhood. Our goal was to examine the relationship between white matter maturation and episodic memory development. Previous studies in adults and adolescents have shown an association between episodic memory performance and the integrity of the prefrontal-limbic tracts. There is no evidence of such relationships in young children, which may be due to the prolonged maturation of the prefrontal area. To address this question, we studied several tracts connecting the prefrontal cortex to the MTL area: the Uncinate Fasciculus (UF), the Cingulate Bundle (CB), and the Fornix. We focused our analyses on episodic recall, because recall engages hippocampal-prefrontal interactions, and also verified the specificity of our findings by studying memory discrimination.

Methods

White matter tracts were reconstructed with state-of-the art DWI methods and used to sample diffusion parameters values (Fractional Anisotropy, Radial Diffusivity, Axial Diffusivity) to describe the microstructure of each tract. We used a multivariate statistical method (Partial Least Square Correlation) to extract, for each tract, latent variables representing the shared information between age and diffusion parameters.

These ‘tract maturity scores’ thus represent age-related differences in tract microstructure in a multivariate fashion. To determine the relation between tract maturity and memory performance, we correlated these tract maturity scores with scores of episodic recall.

Results

The microstructural maturity of the UF was associated with Long-Delay Free Recall and Long-Delay Cued Recall performance. Moreover, the microstructural maturity of the dorsal CB was associated with Short-Delay Free Recall. These associations were not moderated by age. The Fornix and the ventral CB were not associated with measures of recall. Memory discrimination was not associated with the microstructure of white matter tracts.

Discussion.

Our results show that the microstructural maturity of prefrontal white matter tracts, as assessed by a multivariate statistical representation, was associated with episodic memory performance in children. We found distinct relationships between episodic recall scores and white matter tracts, suggesting specialization of white matter tracts for distinct aspects of episodic recall. Furthermore, because the relationship between tract maturity and recall performance was not moderated by age, this means that the microstructural maturity of tracts known to have prolonged development contributes to memory function in a similar manner in younger and older children. Thus, our results provide new insights into the role of white matter tracts connecting neocortical regions in the development of episodic memory.

Article title: Maturity of white matter tracts is associated with episodic memory recall during development.
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Maturity of white matter tracts is associated with episodic memory recall during development

(under revision)

Running title: Episodic memory and white matter in children

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

Ethics approval statement

Ethical agreements were obtained from the appropriate ethical board and written consent of the children and their parents was collected (ethical agreement number CPP 2011-A00058-33).

Abstract

The structure-function relationship between white matter microstructure and episodic memory (EM) performance has been little studied in the developing brain, particularly during early childhood. This is detrimental as the first years of life are a period of rapid development of EM abilities. In adolescents and adults, EM recall has been associated to the microstructure of prefrontal-limbic white matter tracts. Whether this association is observed during early ontogeny as well as during further development is unknown. We studied the association between the microstructure of prefrontal-limbic tracts and EM performance in a cross-sectional sample of children aged from 4 to 12 years old. To estimate the relation between differences of white matter microstructure with differences of EM performance, we used a multivariate Partial Least Square Correlation (PLSC) approach. We extracted tract-specific latent variables representing shared information between age and diffusion parameters describing tract microstructure. Individual projections on these latent variables describe patterns of inter-individual differences of tract maturation, which can be interpreted as microstructural maturity scores of white matter tracts (see Keresztes et al., 2017). Tract maturity scores of the Uncinate Fasciculus and the dorsal Cingulum Bundle were correlated with distinct, non-overlapping measures of EM recall. The association between tract maturity scores and EM recall was comparable between younger and older children. Our results provide evidence on the relation between the microstructural maturity of white matter tracts and EM performance. They also suggest that late-maturing tracts connecting the prefrontal cortex could be associated to EM performance during early childhood as much as during further development.

Keywords: episodic memory; white matter; diffusion weighted imaging; memory development.

1. Introduction

The maturation of the microstructural properties of white matter pathways is pivotal to cognitive development. Many cognitive functions, such as working memory, language, or theory of mind, have been shown to be associated to the integrity of white matter tracts in the adult and developing brains (Krogsrud et al., 2018; Mürner-Lavanchy et al., 2018; Nagy et al., 2004; Short et al., 2019; Walton et al., 2018). This is also the case for episodic memory (EM), the ability to remember verbal information learned in a given spatiotemporal context over long-term delays. Several studies demonstrated a structural-functional relationship between white matter integrity and EM performance during development (Mabbott et al., 2009; Samara et al., 2018; Schaeffer et al., 2014). However, because this association has mainly been examined in preadolescents or adolescents, the contribution of white matter maturation to the ontogeny of EM during early childhood is poorly known.

This paucity of data is damageable because the first 7 years of life are a period during which EM abilities increase greatly. This period also corresponds to infantile and childhood amnesia, which are defined by an absence, at adult age, of episodic memories from early childhood (Bauer, 2015; Bouyeure & Noulhiane, 2020, 2021; Guillery-Girard et al., 2013; Lavenex & Banta Lavenex, 2013; Newcombe et al., 2007; Olson & Newcombe, 2013; Picard et al., 2012). Development of EM during childhood has been related to the structural and functional maturation of the hippocampus (e.g., Lavenex & Banta Lavenex, 2013; Newcombe et al., 2007; Olson & Newcombe, 2013). How the maturation of white matter tracts contribute to the development of EM abilities in young children and during subsequent development remains to be further described. We studied the relationships between white matter maturity and EM recall in a cross-sectional sample of children aged from 4 to 12 years. We estimated white matter maturity using multivariate associations between measurements of white matter microstructure and age. We used these statistical approximations of white matter maturity to describe their associations with EM performance during development.

1.1 Development of episodic memory

The development of EM is protracted and extends from early infancy to adolescence. The first two to three years of life are a period of rapid development of EM abilities which has been associated to the structural and functional maturation of its cerebral substrates. Infants in their first year of life display rudimentary conscious long-term memory abilities (explicit memory), as deferred imitation paradigms showed that 6 months old infants can reproduce a learned sequence of actions over delays up to a month (Bauer et al., 2011; Bouyeure & Noulhiane, 2020; Carver et al., 2000; Carver & Bauer, 2001). These explicit memories have been shown to be mainly supported by cerebral activity in the medial temporal lobe region (Alberini & Travaglia, 2017; Gómez & Edgin, 2016; Lavenex & Banta Lavenex, 2013; Mullally & Maguire, 2014; Olson & Newcombe, 2013), e.g., of the hippocampus and the parahippocampal cortices. Indeed, the hippocampus participates actively in the formation of early memories in infants (e.g., see Alberini & Travaglia, 2017; Li et al., 2014; Travaglia et al., 2016), but is still largely immature in terms of structural and functional features. The size of the hippocampus nearly doubles during the first two years of life, reaching adult size around age 3 (Olson & Newcombe, 2013; Utsunomiya et al., 1999).

From age 3 to 7, consequential albeit less dramatic structural and functional changes are observed in the hippocampus. While its overall size stays relatively stable, distinct patterns of volumetric changes are observed in the hippocampal subfields (Canada et al., 2018; Daugherty et al., 2016; Krogsrud et al., 2014; Riggins et al., 2018). These have been associated to the rapid increase of EM abilities during early childhood (Canada et al., 2018; Ngo et al., 2017; Olson & Newcombe, 2013; Riggins, 2014; Riggins et al., 2015, 2016, 2018). While the maturation of the hippocampus continues at a slower rate afterwards (Olson & Newcombe, 2013), age-related increases of EM competence after age 7 have also been related to the development of neocortical regions. For example, increase of prefrontal activity and increase of prefrontal-hippocampal connectivity with age have been shown to correlate with EM performance (Chiu et al., 2006; Ghetti & Bunge, 2012; Maril et al., 2010; McAuley et al., 2007; Menon et al., 2005; Ofen et al., 2007; Qin et al., 2014). Neocortical regions such as the prefrontal cortex thus seem to have an increasingly more important role in EM with

developmental time, which could be related to an increasing demands on recall strategies and mnemonic control (for a discussion see Ghetti & Bunge, 2012). The maturation of white matter pathways connecting the limbic region (comprising the hippocampus) with the prefrontal cortex should therefore play a key role in the development of EM. It is however unknown if this contribution is to be found early during development or only emerges progressively.

1.2 White matter correlates of episodic memory

The integrity of prefrontal-limbic pathways has been consistently associated to EM performance in adolescents and adults (Ghetti & Bunge, 2012; Mabbott et al., 2009; Ngo et al., 2017; Samara et al., 2018). Major prefrontal-limbic tracts are the Uncinate Fasciculus (UF), the Cingulum Bundle (CB), and the Fornix (Bubb et al., 2018; Daitz & Powell, 1954; Douet & Chang, 2015b; Olson et al., 2015). The UF connects the prefrontal cortex and the anterior temporal lobe and is involved in episodic recall and mnemonic control (Olson et al., 2015; Wendelken et al., 2015). The CB connects the prefrontal cortex to the posterior medial temporal lobe by running along the cingulate gyrus, connecting the prefrontal cortex and subcortical nuclei and is associated with mnemonic control and EM recall and recognition (Bubb et al., 2018; Ezzati et al., 2016; Zhuang et al., 2012). It is often subdivided in functionally distinct segments (Bubb et al., 2018). The dorsal CB connects the prefrontal and parietal cortices and is associated with cognitive control, and the ventral CB runs along the medial temporal lobe and continues dorsally until the retrosplenial cortex and the parietal cortex and is associated with EM. Finally, the Fornix connects the bilateral hippocampi to subcortical nuclei and the orbitofrontal cortex. Fornix microstructure has been shown to be critical to EM function in normal and pathological populations (Douet & Chang, 2015; Gaffan, 1992; Hodgetts et al., 2017; Zhuang et al., 2012).

The UF and the CB have a protracted maturation, lasting until early adulthood (Lebel et al., 2012; Lebel & Deoni, 2018; Reynolds et al., 2019). By contrast, the Fornix is an early-maturing tract, showing adult-like microstructural properties during early childhood (Dubois et al., 2012; Lebel et al., 2012; Reynolds et al., 2019). Prefrontal-limbic tracts could have distinct contributions to EM function during development

because of their different developmental trajectories. Previous studies have shown an association between prefrontal-limbic tracts microstructure and EM in school-age children and adolescents (Mabbott et al., 2009; Samara et al., 2018; Schaeffer et al., 2014). The only study that examined white matter correlates of EM in young children (Ngo et al., 2017: 4-6yo) found no relation between prefrontal-limbic tracts and EM, indicating that the contribution of prefrontal-limbic connectivity (mediated by the UF) to EM might appear during later development. However, an examination of the relationship between the maturation of the prefrontal-limbic tracts and the development of EM covering different developmental periods still lacks to this date.

1.3 The current study: a multivariate assessment of white matter-EM relations

Our aim was to examine the relation between white matter integrity and the development of EM during childhood. EM was assessed with the children version of the California Verbal Learning Tool (CVLT-c) (Delis, 1994), which is widely in both clinical and research contexts as it allows to measure distinct aspects of EM retrieval. We studied prefrontal-limbic tracts that have previously been associated with EM, namely the UF, the CB (ventral CB and dorsal CB), and the Fornix.

The microstructure of white matter tracts is often examined with diffusion tensor imaging (DTI) parameters such as Fractional Anisotropy (FA), Axial Diffusivity (AD) and Radial Diffusivity (RD). The interpretation of these parameters provide distinct microstructural information about a structure (i.e. a given white matter tract). When they describe the same structure, they can be colinear to each other. For example, changes of FA value of a tract can derive from change of its AD, RD, or both (Wheeler-Kingshott & Cercignani, 2009; Winklewski et al., 2018). Developmental studies typically assess the age-related differences and relationships with cognitive functioning of each diffusion parameter individually; for example, associations of EM with FA and mean diffusivity (a linear combination of AD and RD) have been reported (Mabbott et al., 2009). This type of approach has several advantages (e.g., relative straightforwardness of interpretation) but neglects the fact that individual differences of a cognitive function can be related to a pattern of differences within distinct properties of a given white matter tracts. Age-related differences of white matter

microstructure are likely to be related in distinct but related ways on age-related differences of cognitive function. Moreover, another inconvenient of the classical approach is that the bivariate exploration of structure-function relationships for several diffusion parameters of several white matter tracts can lead to an inflation of the number of statistical tests required.

An interesting alternative is to use a multivariate statistical perspective. Specifically, Partial Least Square Correlation (PLSC) is a dimensionality reduction technique which has gained popularity in the field of neuroimaging in the recent years to study structure-function relationships (Abdi & Williams, 2013; Chen et al., 2019; Garthwaite, 1994; Keresztes et al., 2017; Krishnan et al., 2011; Roon et al., 2014; Van Roon et al., 2014). PLSC is designed to search for latent variables which represent the shared information between two sets of variables (e.g., brain features and behavior). In particular, this approach was recently used to study the relationship between Memory Discrimination and hippocampal maturity defined as the multivariate representation of the shared information between hippocampal subfields' volumes and age (Keresztes et al., 2017). A similar approach could be fruitfully applied to the question of the relationship between white matter maturity and EM development, which we aimed to do here.

Our aim was threefold: 1) to determine if there was a multivariate pattern associating differences of tract microstructure with differences of EM performance during childhood. We hypothesized that the shared information between tract microstructure and measures of EM recall could be significantly represented by latent variables, demonstrating a multidimensional structure-function relationship. 2) To determine if these multidimensional associations were specifically related to individual differences in tract maturity. We hypothesized that for tracts with a protracted maturation (e.g. the UF and the CB) the multivariate association described in step 1 could be specifically described by the relationship between individual differences in tract microstructural maturity and individual differences in EM abilities. Tract maturity was defined with PLSC by latent variables representing the shared information between tract microstructure and age (see Keresztes et al., 2017). We then correlated these estimations of tract maturity with EM scores. 3) To determine if the relationship

between tract maturity and EM performance was different between younger and older children. We hypothesized that these relations could differ as a function of age: for example, tracts with a protracted maturation could be too immature in younger children for their microstructural maturity to be associated as much with EM performance as in older children (see Ngo et al., 2017).

2. Methods

2.1 Participants

We recruited 50 healthy children (22 females) aged 4 to 12 years old (mean age=8.1, s.d.=2.28). Ethical agreements were obtained from the appropriate ethical board and written consent of the children and their parents was collected. Participants completed a range of cognitive tasks and underwent a 45 minutes MRI protocol as part of a larger study on the maturation of the neural substrates of EM during childhood. Among our 50 participants, 11 had no data, incomplete data, or were excluded because of a history of learning disorders or of structural anomalies detected on the MR images. Moreover, two participants were excluded because of low compliance during behavioral assessments. Therefore, we studied 37 children (15 females).

2.2 Assessment of verbal episodic memory

Memory performance was assessed with the French adaptation of the children's version of the CVLT-c (Delis, 1994). The CVLT-c is widely used in clinical and experimental settings to assess verbal learning and verbal EM. It provides several verbal EM scores, including recall (free and cued) and a recognition test, with and/or without delay. The procedure of the CVLT-c is as follows: first, participants learn a list of 15 words belonging 3 semantic categories through 5 learning trials. In each learning trial, the experimenter reads the list of words to the participant, which tries to recall the most words immediately afterward. A second list of words is then read to the participant followed by the recall of this second list. The participant is then asked to recall the words from the first list (the Short-Delay Free Recall score used in this study). A cued recall is also administered for each semantic category. After a 20 minutes delay, the participant is asked to recall words from the first list (Long-Delay Free Recall score

used in this study). This is followed by another cued recall of the first list (Long-Delay Cued Recall used in this study) and a word recognition task. Given the multiplicity of indices provided by the CVLT-c, we chose to focus on three scores: Short-Delay Free Recall, Long-Delay Free Recall, and Long-Delay Cued Recall. These tests were chosen as they allow us to contrast two types of conditions: free recall (short-delay or long-delay) and delay recall (free or cued). We can thus examine distinct but related aspects of EM recall. This guarantees that the multivariate relationships studied here include conceptually related aspects of EM, which is easier for interpretation.

2.3 MRI data acquisition

Imaging data were collected at the NeuroSpin research center, CEA, Gif-sur-Yvette, France. Children first followed an MRI training session on a mock scanner set in a children-friendly environment. They were told a compelling story, making them astronauts on a mission to understand the brain, taking aboard a spaceship (the scanner), and wearing a space helmet (the head coil). For the mission to succeed, children were told to try staying still as much as possible for the scanner to take accurate pictures of their brains. Once the children were familiarized with the sonic and visual environment of the scanner, the acquisition began. Images were acquired on a Siemens PRISMA 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil. The animation movie *Wall-E* (Pixar Animation Studios) was shown to children during the scanning sessions to bolster engagement and reduce head motion caused by intolerance to noise and the sensation of boredom.

We collected a standard high-resolution T1-weighted MPRAGE sequence of 160 axial slices (TR = 2.3sec, TE=3.05msec, FOV = 256mm, 73° flip angle, 0.9mm isotropic resolution). Multishell high-angular resolution diffusion-weighted data was acquired through two distinct sequences: 1) a sequence with a gradient b-value of 1500sec/mm^2 applied along 64 isotropic directions; 2) a sequence with a gradient b-value of 1000sec/mm^2 applied along 30 anisotropic directions. Both sequences shared the following parameters: TE = 55.2msec; voxel dimensions = 1.8 x 1.8 x 1.8mm^3; field of view = 238mm; 78 contiguous slices acquired along an axial plane with 1.8mm thickness (no gap) in the posterior-anterior direction. For distortion correction, we

collected 5 non-diffusion weighed images with b=0sec/mm^2 at the beginning of each sequence (same phase-encoding direction) and 5 non-diffusion weighed b=0sec/mm^2 images in the opposite phase-encoding directions.

2.3 MRI Preprocessing

Individual T1-weighted images were segmented into Grey Matter (GM), White Matter (WM), Cortico-Spinal Fluid (CSF) tissues types while correcting for spatial intensity variations (b1 bias field) using FMRIB's Automated Segmentation Tool (FAST). The bias-corrected T1 images were further processed with the Freesurfer anatomical pipeline to obtain cortical parcellations (Destrieux et al., 2010). For segmentation of subcortical structures, we chose to use FSL instead of Freesurfer, as the latter is known to produce more 'blocky' segmentations. Subcortical structures (including the hippocampus) were thus segmented with FMRIB's Integrated Registration & Segmentation Tool (FIRST; (Patenaude et al., 2011). We combined the resulting Freesurfer cortical parcellations and FSL's subcortical segmentations to produce individual cortical-subcortical maps. These were registered to the average b0 images of each subject with FSL's Boundary-Based Registration Algorithm (Greve & Fischl, 2009).

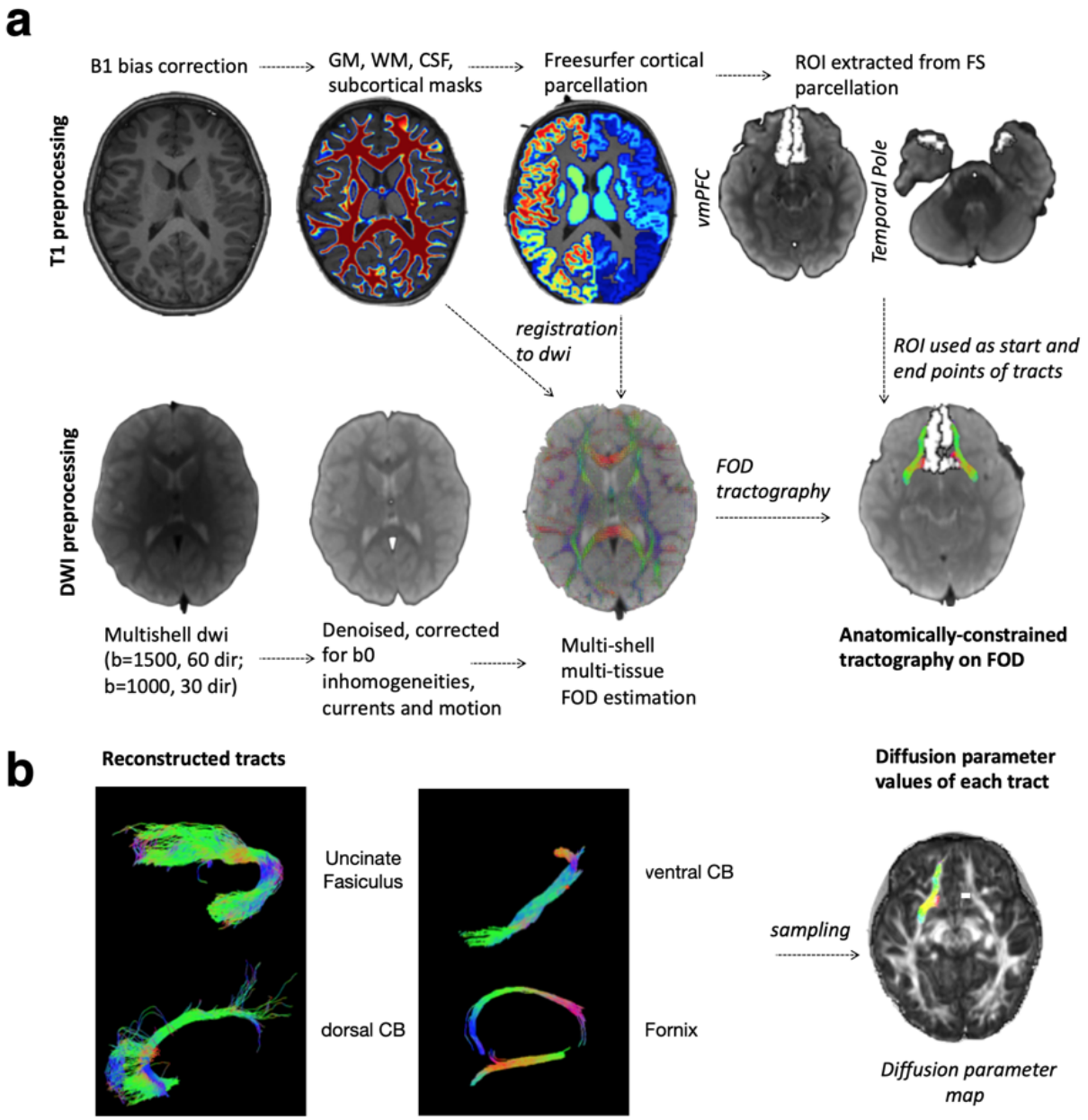

Figure 1. Overall analysis pipeline used in this study. a) Tract reconstruction pipeline. b) Examples of reconstructed tracts and sampling of diffusion parameters. GM = grey matter. WM = white matter. CSF = cortico-spinal fluid. FS = FreeSurfer. dwi = diffusion-weighted imaging. dir = directions. FOD = fiber orientation distribution. CB = Cingulum Bundle.

Diffusion data were preprocessed using a combination of tools from FSL (Jenkinson et al., 2012), version 6.0.0, http://fsl.fmrib.ox.ac.uk, and MRtrix3 RC3 (Tournier et al., 2019), https://www.mrtrix.org. We registered the average image of the b1000 sequence to the average image of the b1500 sequence with the Boundary-Based Registration Algorithm (Greve & Fischl, 2009) as implemented in FSL (*epi_reg*). We concatenated the co-registered DWI sequences, obtaining a single multishell image

including 2 b-values (1500 and 1000) for each subject. We then performed data denoising with MRtrix's *dwidenoise* function, which exploits data redundancy in the PCA domain (Veraart et al., 2016), and removed Gibbs ringing artifacts (MRtrix's *dwidegibbs*) (Kellner et al., 2016). We estimated the susceptibility-induced off-resonance field in the data using FSL *topup* (S. M. Smith et al., 2004). The resulting denoised, unringed, susceptibility-corrected images were corrected for eddy currents and motion with FSL *eddy* (Andersson & Sotiropoulos, 2016). The corrupted slices were re-interpolated using a Gaussian process method implemented in the FSL *eddy* function (Andersson et al., 2016). Finally, we corrected the data for the B1 bias field with MRtrix *dwibiascorrect*. The general outline of our preprocessing pipeline is represented Figure 1.

2.4 Tractography

Probabilistic tractography of the selected tracts of interest was performed at the individual level using constrained spherical deconvolution (CSD) (Tournier et al., 2007) as implemented in MRtrix. Tissue-specific (WM, GM, CSF) response functions were estimated with the multishell multi-tissue algorithm to estimate a 'representative' fiber orientation density function (fODF) for each tissue type. These response functions were used as kernels by a CSD algorithm with default parameters to estimate continuous fODF at the voxel level. Anatomically constrained probabilistic tractography (Smith et al., 2012) was then performed on FOD peaks with anatomical priors (the WM, GM and CSF maps) to constrain tractography within white matter. Cortical or subcortical ROIs were used as seeds and target regions to define specific tracts. The CB was subdivided in ventral and dorsal segments, with the Cingulate isthmus as the demarcation point between the two segments (Bubb et al., 2018). Appropriate ROIs were selected for each tract based on prior works (UF: Olson et al., 2015; CB: Bubb et al., 2018; Fornix: Daitz & Powell, 1954, Douet & Chang, 2015). These tracts were selected based on their association to EM performance in previous studies conducted in children or adults (Mabbott et al., 2009; Ngo et al., 2017; Samara et al., 2019; Schaffer et al., 2014; Windelken et al. 2015). Streamlines were selected if they connected the selected ROIs at the location of their respective GM/WM interface while following a path along with FOD amplitude above 0.1 within the white matter mask.

The seed ROIs were dilated in all directions by a factor of one voxel to allow the intersection between the ROI and the grey matter/white matter interface. Appropriate exclusion ROIs were additionally used to further guide tractography **(Table 1)**. We used the "stop" option to stop the propagation of streamlines once they traversed all inclusion regions. Other parameters were set to default. For the Fornix, we used a modified anatomical masks as priors. The body of the Fornix was not fully included in the original white matter masks because of contamination/partial volume effects resulting from CSF contamination. As a result, attempts to perform tractography of the Fornix with the original tissue types failed. To overcome this limitation we used subject-specific dilated white matter masks in which we constrained the tractography of the Fornix.

Tract	Seed ROI	Target ROI	Exclusion ROIs
Uncinate Fasciculus	Temporal pole	Ventromedial prefrontal cortex	Controlateral ventromedial prefrontal cortex; Temporal pole; Amygdala
dorsal Cingulum Bundle	Cingulate isthmus	Ventromedial prefrontal cortex	Parahippocampal cortex; Lingual gyrus ; Controlateral ventromedial prefrontal cortex and posterior cingulate cortex
ventral Cingulum Bundle	Parahippocampal cortex	Cingulate isthmus	Mask of the ipsilateral uncinate fasciculus; Controlateral posterior cingulate cortex and cingulate isthmus
Fornix	Mammilary bodies	Hippocampus (both hemispheres)	

Table 1. Anatomical ROIs used to define each white matter tract of interest. White matter tracts were defined as the streamlines connecting a seed and a target ROI. Appropriate exclusion ROIs were used to eliminate unwanted streamlines that did not belong to the studied tract.

Quality control of tract reconstructions was performed by visually inspecting each tract, superimposed on the matching T1w and grey and white matter masks. Reconstruction of the UF and the Fornix failed for one subject. Therefore, these tracts were not included in the following analyses.

2.5 Prefrontal-limbic tracts microstructure

Prefrontal-limbic tracts microstructure was assessed with several diffusion parameters: Fractional Anisotropy (FA), Axial Diffusivity (AD), and Radial Diffusivity (RD). Diffusion parameters maps were mapped onto tracts using a sampling scheme of 1000 points location for each streamline contained in the tract. We computed the within-streamlines averages of each diffusion parameter, followed by between-streamlines average of these within-streamline average values. We thus obtained tract-specific diffusion parameters describing tract microstructure.

2.6 Statistical analyses

2.6.1 Age-related differences of memory performance and white matter microstructure

We preliminarily described the age-related differences of 1) EM scores 2) diffusion parameters describing white matter microstructure. This allowed us to verify if EM scores and diffusion parameters were indeed associated to age in order to further describe maturity profiles of each tract and their relation to the development of EM abilities. Age-related differences were examined with Pearson correlations between EM scores or diffusion parameters, and age. The p-values were adjusted for multiple comparisons with False Discovery Rate (FDR: Benjamini & Hochberg, 1995).

2.6.2 Multivariate assessment of the relationship between white matter and memory performance

Our first aim was to examine the multivariate relationship between memory performance (Short-Delay Free Recall, Long-Delay Free Recall, Long-Delay Cued Recall) and diffusion parameters. We used PLSC, also known as PLS-SVD (for Singular Value Decomposition), a dimensionality reduction technique commonly used in neuroimaging to examine structure-function relationships (e.g., Chen et al., 2019;

Keresztes et al., 2017; Krishnan et al., 2011, 2011; Roon et al., 2014; Van Roon et al., 2014). PLSC aims at performing dimensionality reduction with SVD by finding the optimal representation of the shared information between two sets of variable (e.g., EM scores and diffusion parameters). It can thus be understood similarly to Principal Component Analysis (PCA). PCA aims to find latent variables maximizing the variance shared by a set of variables X, while PLSC aims at finding latent variables maximizing the shared information (correlation) between two sets of variables X and Y.

We used PLSC to estimate the relationship the diffusion parameters for tract microstructure (X) and EM scores (Y). We used PLSC models for each tract separately. Models included diffusion parameters from both hemispheres of a given tract (X) and the three EM scores (Y). PLSC works by decomposing the correlation matrix: corr(X,Y) with SVD. A latent variable LV is then estimated which represents the optimal statistical association between the singular vectors of X and Y. The significance of the variance of the singular vectors explained by the latent variable was assessed with permutation testing (5000 permutations). Additionally, the reliability of the contributions of the diffusion parameters with the latent variable were assessed with 5000 bootstraps. This yields bootstrap ratios which represent the reliability of the contributions of the diffusion parameters to the multivariate association between diffusion parameters and EM. The weights of the EM scores were defined as the correlation between each EM score and the latent variable.

2.6.3 Multivariate representations of the microstructural maturity of white matter

Our second aim was to understand how the multivariate association between white matter microstructure and EM performance was related to age. In this order, we used PLSC to define latent variables representing, for each tract, the optimal statistical association between diffusion parameters and age. The same statistical principles as the ones described above (permutation testing, bootstraps) were used. Because the obtained latent variables maximize the shared information between diffusion parameters and age, the projections of individual subjects on the latent variable can be used to study inter-individual differences on the shared information between tract microstructure and age (Keresztes et al., 2017). These individual projections can thus

be interpreted as a subject-level 'tract maturity score' of a given white matter tract (see Keresztes et al. (2017) for a similar approach on hippocampal maturation). Indeed, if the maturity scores are positively correlated with age, then the higher the value of an individual maturity score, the more it conveys white matter properties represented in older (compared to younger) children, and conversely. We examined the relationship between this statistical approximation of the microstructural maturity of white matter and EM performance by correlated tract-specific maturity scores with EM recall separately for each EM recall score. We verified the specificity of the relationships between EM recall and tract maturity by correlating tract maturity with a measurement of Memory Discrimination which was also acquired in our behavioral assessment protocol (see Study 2 for details). Raw p-values of EM scores/tract maturity scores were adjusted for multiple comparisons with FDR.

2.6.3 Effect of age on tract maturity-EM performance associations

Our third aim was to verify whether the associations between tract maturity and EM performance of aim 2 differed as a function of age. In this aim, we plotted tract maturity scores-EM performance relationships separately for younger and older children. We used the age of 7 as a cutoff to define age groups because it roughly corresponds to the offset of childhood amnesia, and because it allowed an equivalent distribution of subjects into groups. We statistically verified the influence of age groups by using linear regression models predicting EM scores with the tract maturity score of a given tract, age group, and the age group*tract maturity score interaction.

3. Results

3.1 Age-related differences of memory performance and white matter microstructure

We first described age-related differences of verbal EM scores. Immediate Free recall was associated to age ($F=11.71$, $R2=0.251$, $\beta=0.52$, $p<0.01$), as well as Delayed Free Recall ($F=11.02$, $R2=0.239$, $\beta=0.52$, $p<0.01$), and Delayed Cued Recall ($F=18.98$, $R2=0.35$, $\beta=0.626$, $p<0.001$), showing, in all cases, linear increases of verbal EM performance with respect to age. Figure 2 shows the relationships between EM scores

and age. Adding sex as a covariate in these models did not change the significance of age and no significant sex differences were found for all EM scores.

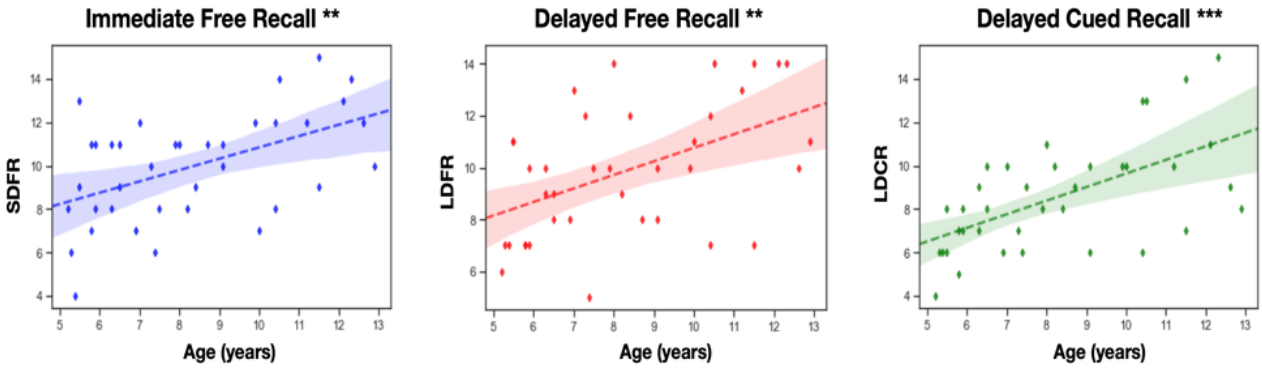

Figure 2. Plots of the regressions between memory scores and age. The shades represent the 95% confidence intervals. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Free Recall. **: p<0.01; ***: p<0.001 (corrected).

We examined age-related differences of diffusion parameters with linear models in which diffusion parameters were the dependent variable and age the predictor variable. Figure 3 shows the plots of the linear regressions between age and diffusion parameters. The correlation coefficients and p-values are reported Table 2. Among all diffusion parameters, the RD was the most correlated with age, showing a negative correlation. AD was never significantly correlated with age. The UF and the dorsal CB had RD and FA (for the right UF) significantly correlated with age. The FA of the left Fornix was also significantly correlated with age (p-values are corrected with FDR).

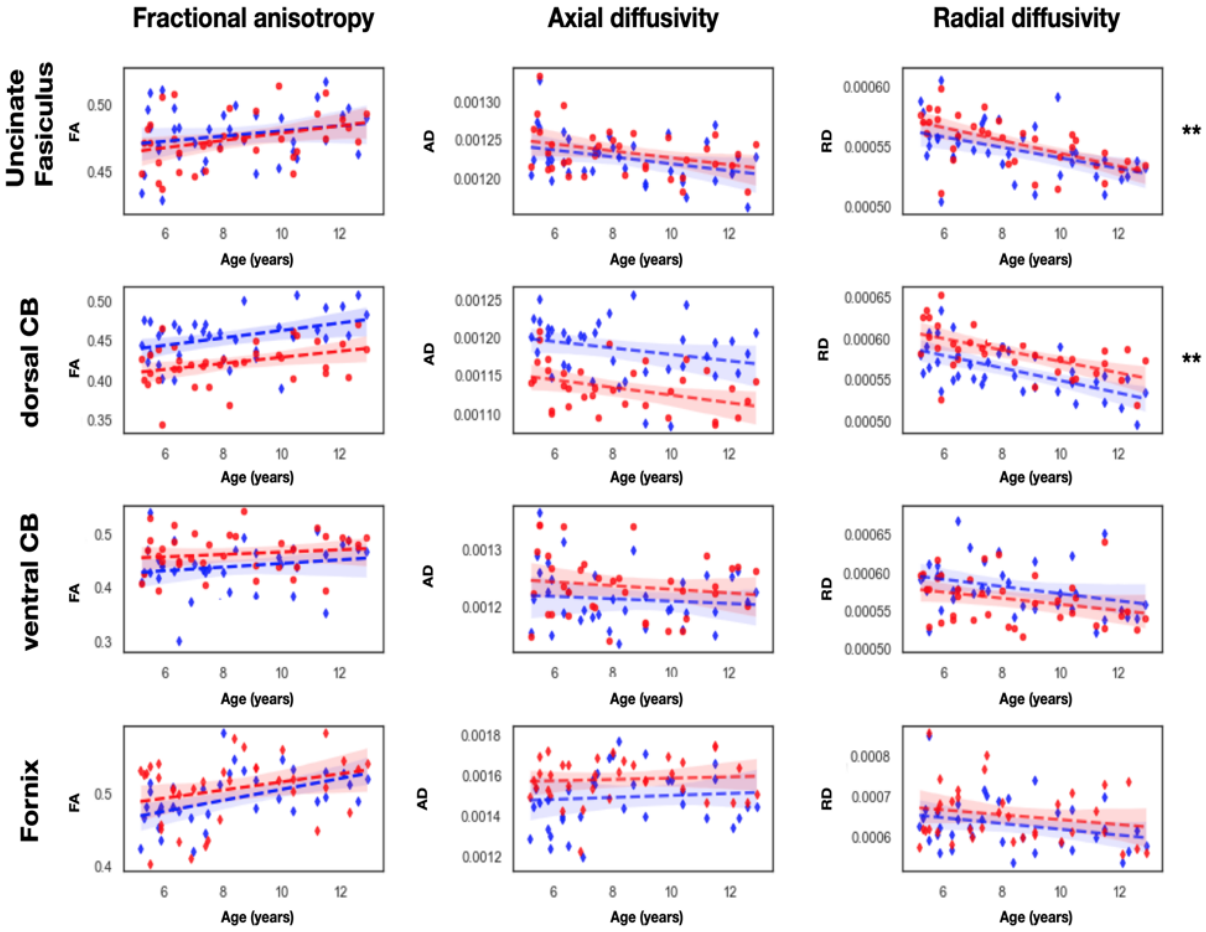

Figure 3. Plots of the regressions between diffusion parameters and age. The relation between diffusion parameters and age is represented for each tract. Red : left hemisphere. Blue: right hemisphere. The shades represent the 95% confidence intervals. CB = Cingulum Bundle. FA = Fractional Anisotropy. RD = Radial diffusivity. AD = Axial diffusivity. **: p<0.01 (corrected).

Tract	*Hemisphere*	*Diffusion parameter*	*r value*
Uncinate Fasiculus	Left	FA	0.24
		RD	**-0.46****
		AD	-0.32
	Right	FA	**0.35***
		RD	**-0.61****
		AD	-0.34
dorsal CB	Left	FA	0.36
		RD	**-0.61****
		AD	-0.30
	Right	FA	0.33
		RD	**-0.56****
		AD	-0.38
ventral CB	Left	FA	0.16
		RD	-0.31
		AD	-0.09
	Right	FA	0.14
		RD	-0.29
		AD	-0.11
Fornix	Left	FA	**0.44***
		RD	-0.27
		AD	0.06
	Right	FA	0.28
		RD	-0.21
		AD	0.02

Table 2. Pearson correlation values between age and diffusion parameters for each white matter tract. CB = Cingulum Bundle. FA = Fractional Anisotropy. RD = Radial diffusivity. AD = Axial diffusivity *:p<0.05; **:p<0.01; ***:p<0.005 (corrected).

3.2 Multivariate associations between episodic memory and white matter microstructure

Our first aim was to explore the multivariate relationship between EM scores (Short-Delay Free Recall, Long-Delay Free Recall, Long-Delay Cued Recall) on the one hand, and the diffusion parameters of each tract (from both hemispheres) on the other hand. We used PLSC to extract latent variables representing the shared information between

EM scores and diffusion parameters. The significance of the variance explained by the latent variable was assessed with 5000 permutations of the data.

Uncinate Fasciculus: A latent variable significantly represented the multivariate association between EM scores and diffusion parameters of the left and right UF (p=0.001). Bootstrap ratios indicated that FA and RD diffusion parameters (both hemispheres) were reliable components contributing to the latent variable (values above +1.96 or below -1.96), but not left or right AD. Bootstrap ratios of FA and RD were of opposite signs given that they respectively correlate positively and negatively with cognitive function. In this case, RD bootstrap ratios were positive and FA bootstrap ratios were negative, but these signs only show that diffusion parameters contribute to the latent variable in opposite direction and could be arbitrarily inverted. Still, the weights of the EM scores on the latent variable were negative correlations given that RD was positively loaded on the latent variable and FA negatively. Long-Delay Free Recall was the variable with the most important weight on the latent variable (r=-0.60, p=0.0001), followed by Long-Delay Cued Recall (r=-0.49, p=0.002) and Short-Delay Free Recall (r=-0.38, p=0.02). Bootstrap ratios of diffusion parameters and weights of EM scores on the latent variable are shown Figure 4.

Dorsal Cingulum Bundle: A latent variable significantly represented the multivariate association between EM scores and diffusion parameters of the left and right dorsal CB (p=0.03). All diffusion parameters except right hemisphere FA were reliable components contributing to the latent variable. Left and right RD were the most reliable contributors. The weights of EM scores showed that Short-Delay Free Recall was significantly represented in the latent variable (r=-0.45, p=0.006) as well as Long-Delay Cued Recall (r=-0.35, p=0.03). Long-Delay Free Recall was not significantly loaded on the latent variable (r=-0.28, p=0.09) (Figure 4).

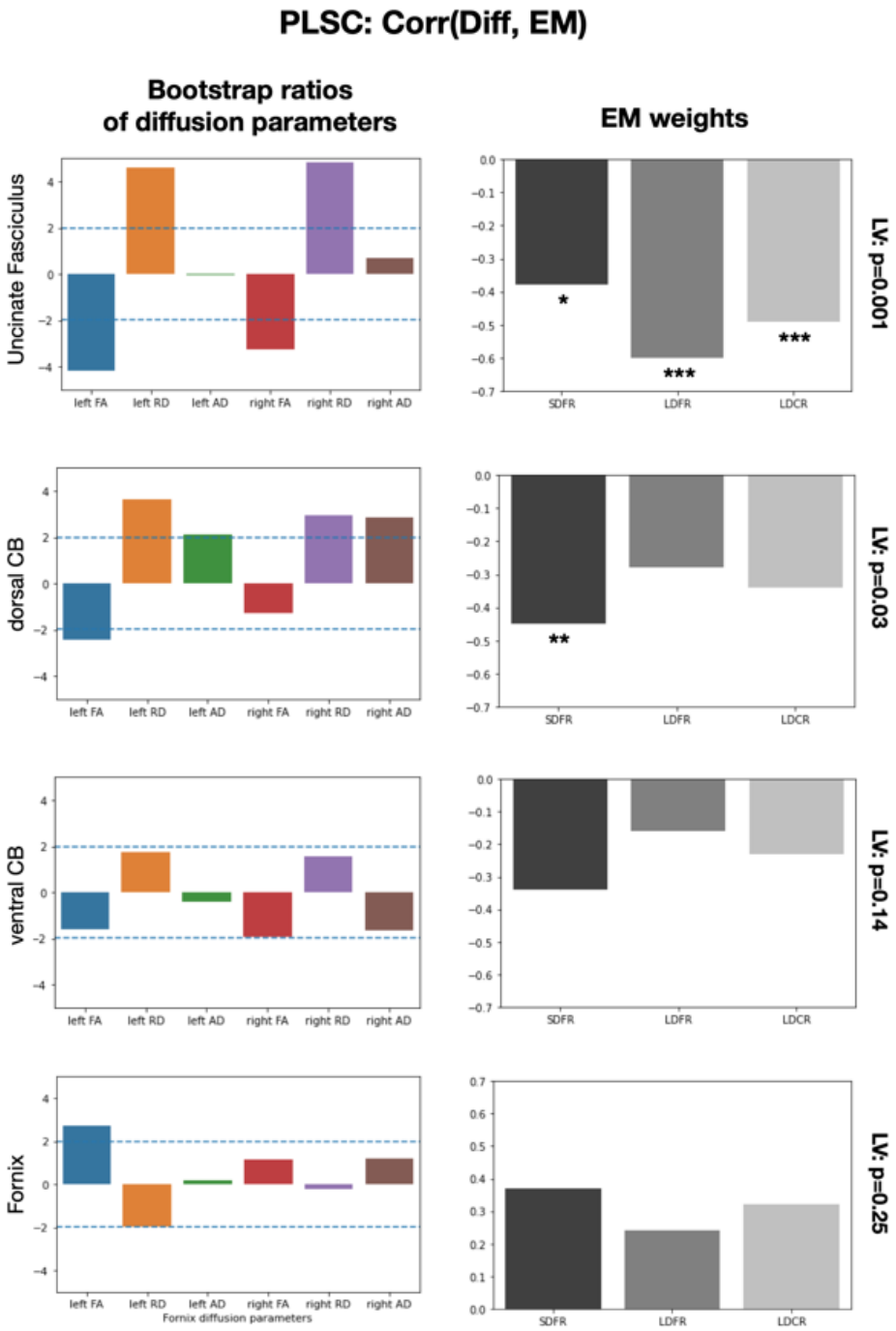

Figure 4. PLSC results extracting latent variables representing the shared information between diffusion parameters and EM scores. Left column: bootstrap ratios of diffusion parameters showing the reliability of the contribution of each diffusion parameter to age. A ratio +/- 1.96 (blue dotted line) show that the contribution of the diffusion parameter to the latent variable is reliable. Right column: weights (correlation values) of EM scores on the obtained latent variable. The significance of each LV is shown on the top right. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Free Recall. *:p<0.05; **:p<0.01; ***:p<0.005.

Ventral Cingulum Bundle: We did not find a latent variable significantly representing the association between EM scores and the diffusion parameters of left and right ventral CB (p=0.14). This suggests that the microstructure of left and right ventral CB is not associated to measures of EM recall in a multivariate fashion.

Fornix: We did not find a latent variable significantly representing the association between EM scores and the diffusion parameters of left and right ventral CB (p=0.25).

Thus, there were latent variables significantly representing the relationship between the microstructure of the UF and the dorsal CB with measures of EM recall in children, but no multivariate relationships were found for the ventral CB and the Fornix.

3.3 Multivariate associations between white matter microstructure and age: tract maturity scores

Our second aim was to examine if the multivariate associations reported in the previous sections could also be described in terms of a relation between individual differences of tract maturity and individual differences of EM performance. In this aim, we extracted multidimensional representations of the shared information between tract microstructure and age with PLSC ('tract maturity scores'), which we then correlated to EM.

Uncinate Fasciculus : We extracted a single latent variable significantly representing the association between age and the diffusion parameters of left and right UF (p=0.001). The correlation between this maturity profile and age was of -0.61. Bootstrap ratios indicated that all diffusion parameters except left FA were reliable components contributing to the maturity score, with left and right RD being the most reliable. Because RD is the most reliable component of the maturity profile and since RD decreases with age, this explains why the maturity profile is negatively correlated with age. We multiplied the maturity score by -1 in order to have a positive correlation between the maturity score and age (the higher the maturity score, the older the children) rather than the opposite. This was arbitrary and for interpretative purposes.

Figure 5 shows the correlation with age of the (inverted) maturity score as well as the bootstrap ratios of the diffusion parameters.

Dorsal Cingulum Bundle: A single latent variable significantly represented the association between age and the diffusion parameters of the left and right dorsal CB (p=0.0008, 5000 permutation tests). The correlation between this maturity profile and age was of -0.65. We hence also inverted the sign of the maturity scores. Bootstrap ratios indicated that all diffusion parameters were reliable components contributing to the maturity profile, with left and right RD being the most reliable components (Figure 5).

We also examined if the Fornix and the ventral CB were associated to age in a multivariate fashion. We did not find latent variables significantly explaining the variance shared by the diffusion parameters of these tracts and age (Fornix: p=0.07; ventral CB: p=0.25; 5000 permutations). This was expected given the few correlations between the diffusion parameters of these tracts and age (Figure 3).

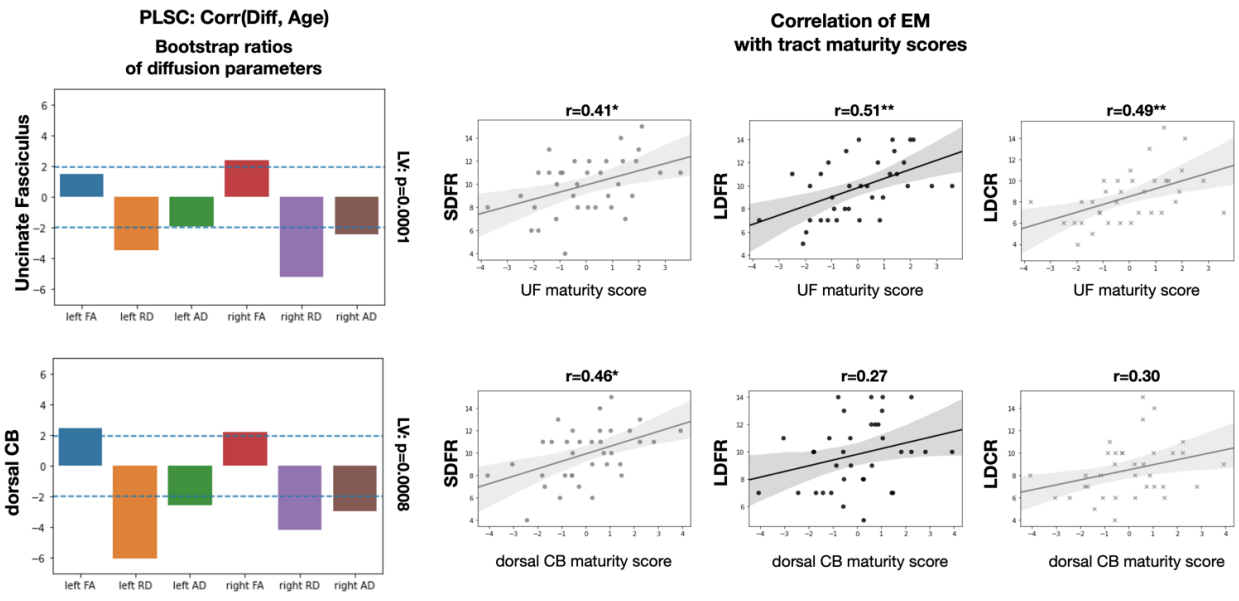

Figure 5. Tract maturity scores for the UF and the dorsal CB obtained from PLSC, and correlation between tract maturity scores and EM. Left: bootstrap ratios of the diffusion parameters showing the reliability of their contribution to the latent variables. Right: regression plots showing the relation between tract maturity scores and EM performance. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Free Recall. ***:p<0.005 (corrected with FDR).

Relation between maturity scores and EM recall: We examined the relationships between tract maturity scores and EM recall scores. The maturity score of the UF was not correlated with Short-Delay Free Recall (r=0.41, corrected p=0.06). It was however correlated with Long-Delay Free Recall (r=0.51 corrected p=0.01) and Long-Delay Cued Recall (r=0.49, corrected p=0.01) (Figure 5). Thus besides a global multivariate association between diffusion parameters of the UF and EM scores we also showed that the maturity of the UF (defined by a latent variable representing shared information between UF diffusion parameters and age) correlated with EM. The maturity score of the dorsal CB was correlated with Short-Delay Free Recall (r=0.46, corrected p=0.03), but not with Long-Delay Free Recall (r=0.27 corrected p=0.20), or with Long-Delay Cued Recall (r=0.30, corrected p=0.20). The specificity of the correlation between the maturity of the dorsal CB and Short-Delay Free Recall is coherent with the fact that this EM score was the main weight on the multivariate association between dorsal CB diffusion parameters and EM scores (Figure 4). The evidential value of the significant correlations was further assessed by estimating Bayes Factors (BF10) from the significant correlations. BF10 indicate the likelihood of the tested hypotheses relatively to the null. BF10 of 8.51 (correlation between CB maturity score and Short-Delay Free Recall), 24.6 (correlation between UF maturity score and Long-Delay Free Recall), and 15.3 (correlation between UF maturity score and Long-Delay Free Recall). This indicates moderate evidential value (3>BF10>10) to decisive evidential value (BF10>10 or BF10>20).

We further examined if the relationship between tract maturity score and EM recall was specific to EM recall by also correlated tract maturity profiles with measurements of Memory Discrimination, a mnemonic process which is often specifically associated with the maturation of hippocampal subfields (Keresztes et al., 2017). Memory Discrimination was not correlated with tract maturity scores of the UF (r=0.22, corrected p=0.24) or of the dorsal CB (r=0.35, corrected p=0.20).

3.4 Influence of age on tract maturity-EM recall relationship

Our third aim was to examine whether tract maturity-EM relationships differed as a function of age. As the dorsal CB and the UF have a protracted maturation, it is possible that the maturity score of these tracts contribute differently to EM performance

in older children compared to younger children. While the correlation between tract maturity and EM was more important in older children in a few comparisons, no interactions terms between tract maturity and age groups were significantly associated to EM scores (Figure 6).

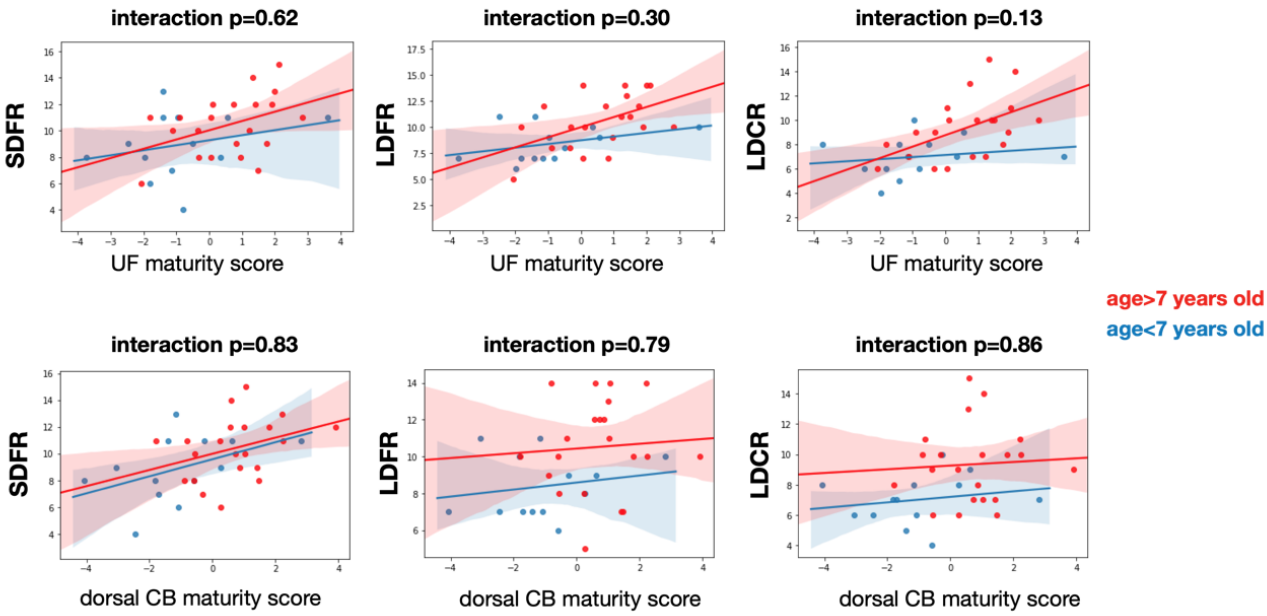

Figure 6. Interaction plots showing the relations between tract maturity scores and EM recall as a function of age groups. Children younger than 7 years old are plotted in blue and children older than 7 years old in red. SDFR=Short-Delay Free Recall. LDFR=Long-Delay Free Recall. LDCR=Long-Delay Free Recall.

4. Discussion

Our aim was to study age-differences in the microstructure of prefrontal-limbic tracts involved in EM recall, as well as the relation between their microstructure and EM recall performance, in children aged from 4 to 12 years old. The main results were: 1) UF and dorsal CB diffusion parameters were associated to EM recall scores in a multivariate perspective. The ventral CB and the Fornix were not associated with EM recall. 2) There was multivariate association between UF and dorsal CB diffusion parameters and age, yielding within-subject tract maturity scores. The tract maturity score of the UF was correlated to Long-Delay conditions of EM recall. Tract maturity

score of the dorsal CB was only correlated to Short-Delay Free Recall. 3) Relationships between tract maturity and EM did not differ as a function of age.

4.1 UF and dorsal CB microstructure are associated with EM recall

Our first aim was to analyze the relationship between tract microstructure and EM performance. We demonstrated that there was a multidimensional pattern relating microstructural differences of UF and dorsal CB microstructure with EM abilities in the developing brain (Figure 4). Therefore, for the UF and the dorsal CB, but not the ventral CB and the Fornix, the relationship between their diffusion parameters and EM scores could be described with a single latent variable representing their shared information.

Because of this multivariate approach, aspects of all diffusion parameters and EM scores were taken into account to extract a significant latent variable picturing a global relationship. With this in mind, analysis of the contributions of diffusion parameters and weights of EM scores showed differences in the structure of these latent variables. For the UF, the diffusion parameters contributing reliably to the latent variable were FA and RD, but not AD. All EM scores significantly correlated with the latent variable. EM scores were negatively correlated to the latent variable. The contributions of diffusion parameters assessed with bootstrap ratios showed that the contribution of RD was positive and the contribution of FA negative. This suggests that aspects of EM performance are positively related to FA values and negatively related to RD values, albeit in a multivariate fashion. For the dorsal CB, FA, AD and RD (with the exception of right FA) were reliable contributors to the multivariate association with EM scores. Short-Delay Free Recall was the only EM score significantly contributed to the latent variable, which is coherent with the fact that the tract maturity profile of the dorsal CB was correlated to Short-Delay Free Recall but not to other EM scores. The UF and the dorsal CB were hence related to EM scores in distinct ways. There was more important contributions of AD for the multivariate association with the dorsal CB compared to with the UF and the association for the dorsal CB was more correlated with Short-Delay Free Recall than other scores.

4.2 Maturity scores of the UF and the dorsal CB are associated to EM recall

Our second aim was to determine if the multivariate relationship between tract microstructure and EM performance could be further described in terms of a relationship between tract maturity and EM.

For the UF and the dorsal CB, we found latent variables significantly representing their relationship with age. This is not surprising given that these two tracts are known to have a particularly protracted maturation compared to other white matter tracts (e.g., (Lebel et al., 2008, 2012; Reynolds et al., 2019; Simmonds et al., 2014). Their extended maturation is likely related to the maturation of some of the cortical regions connected by these tracts, e.g. the prefrontal and posterior parietal areas (Arain et al., 2013; Caballero et al., 2016; Dosenbach et al., 2010; Lebel et al., 2008; Sowell et al., 2004). For the Fornix and ventral CB however, we did not find significant multivariate associations their microstructure and age. These PLSC results are overall in line with diffusion parameters-age bivariate correlations (Figure 3). The Fornix has been described as an early-maturing tract (Dubois et al., 2008; 2012; Lebel, 2008; 2012). The maturation of the ventral CB is poorly known, but the only one developmental study (to our knowledge) that separated dorsal ventral CB segments showed an earlier maturation of the ventral segment (Simmonds et al., 2014). Compared to the dorsal CB, the earlier maturation of the ventral CB could be explained by the fact that it mainly connects limbic regions, which have an earlier maturation than the prefrontal and posterior parietal regions connected by the dorsal segment (Arain et al., 2013; Paus, 2005; Utsunomiya et al., 1999).

The analysis of the weights of EM scores on the latent variables from our initial PLSC analyses showed that EM scores were differently related to the UF and the CB. We thus examined the relationships between tract maturity scores and EM recall scores separately. We found significant correlations between tract maturity scores and EM recall. Specifically, the maturity score of the UF was correlated to Long-Delay conditions of EM recall (Free and Cued). The maturity of the dorsal CB was only correlated to Short-Delay Recall (Figure 5). These results are in line with the EM weights of our initial multivariate analyses, which yielded similar observations (Figure

4). This suggests a specialization of structure-function relationships between white matter tracts and distinct aspects of EM recall in children. More precisely, white matter microstructural differences related to age, thereby expressing tract maturity, were related to EM recall differently for the UF and the dorsal CB. These two tracts could hence contribute to distinct aspects of EM function and development.

The relationship between UF microstructure and EM recall was reported by previous studies on older children and adolescents (Mabbott et al., 2009; Schaffer et al., 2014; Samara et al., 2019). We develop these findings by showing that distinct aspects of delayed EM recall were associated to a multivariate representation of the microstructural maturity of the UF. Some diffusion parameters contributed more to the UF maturity score than others (e.g., RD). However, age-related differences of all diffusion parameters importantly or marginally contributed to the maturity score. Hence age-related differences of microstructural properties typically inferred from diffusion parameters, such as myelination, axonal density, and overall tissue integrity, are likely all related to individual differences of EM performance.

Retrieval of episodic memories following a delay has been shown to elicit activity in the hippocampal and medial temporal lobe regions and in the prefrontal cortex (e.g., Dupont et al., 2001; Hayama et al., 2012; Maril et al., 2010; Rugg et al., 2015). These areas are precisely the ones connected by the UF (Olson et al., 2015). A higher tract maturity score of the UF could thus be associated with microstructural differences causing a quicker and more efficient transmission of information between the prefrontal and medial temporal regions. This could in turn benefit the development of the capacity to recall episodic information following delays.

Contrarily to the UF, the maturity score of the dorsal CB was specifically correlated to Short-Delay Free Recall. To our knowledge, this is the first time that a relationship between dorsal CB microstructure and EM recall is reported in children. In the CVLT-c, Short-Delay Free Recall is administered immediately after learning a distractor list. Success at this task thus likely depends on the ability to efficiently retrieve items that were learned moments ago while inhibiting items of the distractor list. This could

involve mnemonic control and executive functions-related processes. Accordingly, the dorsal CB has been associated with such cognitive functions by previous studies (Bubb et al., 2018; Wendelken et al., 2015). Short-Delay Free Recall performance could be related to the maturity of the dorsal CB which would ensure more efficient information transmission between regions essential for mnemonic control and executive functions, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, and parietal areas.

We provide evidence regarding the specificity of our findings given that tract maturity scores of the UF and the dorsal CB were correlated with distinct, non-overlapping EM scores, and both maturity profiles did not correlate with Memory Discrimination, which has been shown to be associated to a multivariate expression of hippocampal maturity (Keresztes et al., 2017).

4.3 Similar tract maturity score-EM performance in younger and older children

Contrarily to our hypothesis, the relationship between maturity scores and EM performance did not differ as a function of age (Figure 6). A previous study examining the white matter correlates of EM in 4 and 6 years old (Ngo et al., 2017) found no relation between the UF or between hippocampal- prefrontal connectivity and EM recall. The authors speculated that this absence of association could be related to the particularly protracted maturation of prefrontal-hippocampal connectivity, e.g. because the medial prefrontal cortex and/or the UF are not mature enough, during early childhood, to be fully involved in these cognitive processes. Our results rather show that the microstructural maturity of prefrontal tracts with a protracted maturation contributes to EM recall similarly in younger and older children. Methodological differences and the fact that our studied age span (despite including 4-6 years old children) is overall older could account for these differences. The present results nevertheless suggest that the UF and the dorsal CB might play an ealier role in EM function during development than previously thought.

4.4 Limitations and future directions

Our study has several limitations. The main one is that we aimed to characterized tract maturity with a multivariate representation of the association between tract

microstructure and age while using a cross-sectional design. Descriptions of tract 'maturity scores' are hence only statistical approximations which do not directly describe developmental dynamics, contrarily to longitudinal designs (e.g., Giorgio et al., 2010; Krogsrud et al., 2016; Simmonds et al., 2014). Contrasting the contributions of white matter to maturation to EM development would benefit from a longitudinal design that investigates the relation between tract maturation and cognitive competence over developmental time. A related limitation is that this design prevents us from trying to analyze causal relations between tract maturity and EM performance. Therefore, while we show a relationship between a statistical representation of tract maturity and EM performance, other causes could account for this relationship. Such factors could include the maturation of other white matter tracts, cortical maturation, or the development of other aspects of EM or of other cognitive functions. We however provide some evidence of the specificity of the reported associations.

Another limitation is that our sample size was small, particularly compared to the important age range studied (4-12 years of age). The acquisition of neuroimaging data can be particularly challenging in children and sample size is a limitation often faced by developmental studies. Studying larger samples restricted to smaller age groups could lead to more specific investigation of the contribution of white matter maturity to EM development.

Third, we used multishell high resolution with state-of-the-art methods for modeling crossing/kissing fibers. Still, tract microstructure was assessed by diffusion parameters that depend on tensor modeling, a technique known to have a number of methodological limitations. Past years have seen a surge of methodological development that take benefit from multishell data to estimate fiber microstructure in a way that overcomes some of the traditional limitations associated to tensor estimation, such as estimation of neurite orientation dispersion and density imaging (NODDI), or fiber density and cross-section (Raffelt et al., 2012; 2017). To date, no study investigated memory development using these recent diffusion MRI data analysis techniques.

Fourth, we only focused on a narrow aspect of EM function, i.e. recall tasks from the CVLT-c. Studying the white matter correlates of other EM processes, such as relational memory, context memory, or pattern separation/completion, might provide insightful results regarding memory development, especially in younger populations (see, for instance, Ngo et al., 2017, 2018, 2019). Future studies will benefit from investigating the white matter correlates of a variety of EM processes during development, a topic that has little been studied to this day.

Finally, we did not find relations between ventral CB and Fornix microstructure and EM performance, despite the fact that these tracts, particularly the Fornix, have been repeatedly associated to EM function in adults. An interesting avenue of research is thus the further investigation of the role of these tracts in EM development. The microstructure of the Fornix has been associated with relational memory and context memory (Hodgetts et al., 2017; Schwarb et al., 2019) and with verbal EM recall in the context of normal aging and mild cognitive impairments (Metzler-Baddeley et al., 2011). The ventral CB has mainly been associated to object recognition, discrimination and spatial navigation in animal models (Bubb et al., 2018) and to EM performance in pathological contexts in humans adults (Metzler-Baddeley, Hunt, et al., 2012; Metzler-Baddeley, Jones, et al., 2012). The cognitive demands of EM recall tasks used here could hence not rely on the Fornix and the ventral CB in the context of healthy development. This hypothesis is purely speculative given that the relation of these two tracts to EM have been understudied in children.

5. Conclusion

We described multivariate associations between the microstructure of the UF and the dorsal CB and EM recall. These associations could be described in terms of inter-individual differences of tract maturity. The progressive maturity of these two tracts are hence likely contributors to the progressive unfolding of EM function during childhood. Furthermore, these tracts were associated to distinct aspects of EM function. Our results also suggest that these two tracts could be involved in EM function early during

development. This calls for further research to determine more precisely the contribution of white matter microstructure on EM development and function.

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Complementary analyses

Among prefrontal-limbic tracts, the Fornix has been related to episodic autobiographical memory in literature on adults (Hodgetts et al., 2017). We thus conducted a complementary analysis examining a putative relationship between Fornix microstructure and episodic autobiographical recall. We also performed an exploratory analysis examining relations between episodic autobiographical recall and the microstructure of the UF to further assess the specificity of the findings reported in the paper presented above.

Methods

Fornix microstructure was associated with the number of recalled event details and context details from the CAI, as well as memory discrimination assessed with the Mnemonic Similarity Task. We performed an exploratory analysis examining if a latent variable could significantly represent the association between Fornix microstructure and memory scores.

Results

There was no latent variable describing the association between the microstructure of the Fornix and the number of event and context details recalled ($p=0.11$). A similar result was found for the UF ($p=0.22$).

Conclusion

These complimentary exploratory analyses further confirm the specificity of the relationship between episodic recall and prefrontal-limbic tracts microstructure in the developing brain.

Part 3.2

Functional connectivity

Study 5

Functional connectivity correlates of autobiographical memory in the developing brain

Presentation

This study is in preparation and is considered for submission to *Neuroimage*.

Context

Studies in adults showed a particular relationship between the functional organization of the brain at rest and the ability to recall autobiographical memories. For example, damage to the DMN has been shown to impair autobiographical recall. Still, the resting-state functional connectivity correlates of autobiographical memory in children are unstudied.

Methods

Autobiographical memory was assessed with the CAI paradigm. We obtained separate scores for episodic autobiographical memory (EAM) and semantic autobiographical memory (SAM) details. Functional connectivity within a large-scale network of 15 regions covering the main correlates of EAM and SAM as described in adults was computed and correlated with EAM and SAM details.

Results

The recall of EAM, but not SAM, details was positively correlated with age. The recall of EAM details was associated with functional connectivity. We observed different connectivity correlates for recent and remote EAM memories, and event or context information recalled in EAM memories. Associations were not moderated by age. SAM details were not associated with functional connectivity.

Discussion

The functional architecture of the brain at rest is related with the ability to recall EAM details during childhood. Relationships were not moderated by age suggesting that younger and older children use a similar version of the same EAM network. This has potential consequences for our understanding of childhood amnesia.

The manuscript is followed by an updated discussion with complementary analyses.

Article title: Functional connectivity correlates of autobiographical memory during childhood

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Functional connectivity correlates of autobiographical memory during childhood (in preparation)

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

Ethics approval statement

Ethical agreements were obtained from the appropriate ethical board and written consent of the children and their parents was collected (ethical agreement number CPP 2011-A00058-33).

Abstract

Autobiographical memory (AM) is the ability to recall episodic (episodic autobiographical memory; EAM) or semantic (semantic autobiographical memory; SAM) information from one's personal past. Episodic autobiographical memories from early childhood are forgotten during later development, a phenomenon known as childhood amnesia. In adults, several studies have shown a relationship between the functional architecture of the brain at rest and the ability to recall autobiographical memories. This relationship is evidenced, for example, by the overlap between regions recruited during AM recall tasks and the Default Mode Network, a network of strongly connected regions specific to the task-free brain. However, the resting-state functional connectivity correlates of AM have been almost never studied in children. We acquired resting-state fMRI data and assessed AM recall in children aged 4-12 years. Functional connectivity was measured within a network of 15 brain regions corresponding to the functional correlates of AM as described in adults. AM was assessed out of the scanner with the Children's Autobiographical Interview. We found that the episodic richness of recalled autobiographical memories was associated with resting-state functional connectivity between multiple regions. Distinct correlates were found for the recall of event and context episodic details, as well as for episodic details recalled in recent memories and in remote memories. These results provide important evidence that the functional architecture of the brain at rest is related with the episodic richness of recalled autobiographical memories in children, which is important for our understanding of the development of AM and of childhood amnesia.

Keywords : Autobiographical memory, episodic memory, childhood amnesia, functional connectivity, resting-state fMRI

1. Introduction

Few personal memories remain from our early years of life, a phenomenon known as childhood amnesia (Bauer, 2015; Bauer et al., 2011; Bauer & Larkina, 2014; Bouyeure & Noulhiane, 2021). Specifically, what appears missing from our autobiographical memory (AM) are the memories of specific episodes, which are part of episodic autobiographical memory (EAM). By contrast, the self-knowledge of semantic autobiographical memory (SAM) appears to be comparatively relatively spared by early forgetting. This observation highlights two features of the memory system dedicated to personal memories: first, AM is a multifaceted memory system comprised of both episodic and semantic components; second, the development of AM, and particularly of EAM, is a gradual processes that begins in early childhood and that has been shown to continue developing into late childhood and adolescence (Bauer & Larkina, 2014; Ghetti & Bunge, 2012; Picard et al., 2009; Piolino et al., 2007; Willoughby et al., 2012).

Because of its multifaceted nature, AM is supported by a large-scale cortical and sub-cortical network of regions distributed throughout the brain (Addis et al., 2017; Bauer et al., 2017; Cabeza & St Jacques, 2007; Conway et al., 2002; Svoboda et al., 2006). While the details of the functional correlates of AM vary from study to study, core regions of the AM network include the hippocampus and medial temporal lobe regions, the prefrontal cortex (PFC), the anterior and lateral temporal lobes, posterior midline regions, parietal regions, as well as subcortical structures (Addis et al., 2017; Bauer et al., 2017; Cabeza & St Jacques, 2007; Conway et al., 2002; Svoboda et al., 2006). The distributed nature of the AM network suggests that developmental improvements of AM must in part be related to more efficient interactions between regions of this network.

Resting-state functional connectivity is a privileged approach to study the functional organization of the brain. It consists in correlating the spontaneous low-frequencies fluctuations of the BOLD signal observed in different brain regions. Brain regions at

rest are organized in functionally meaningful networks that have strong correspondences with networks of regions co-activated to perform specific cognitive tasks (Smith et al., 2009). Resting-state functional connectivity can thus inform on how brain networks are organized and interact 'by default', and on the relation between this organization and cognitive function. In the case of AM, this relationship can be particularly relevant as shown by the relations between the functional correlates AM and the Default Mode Network (DMN), a network of activated regions in the task-free brain that usually deactivates during cognitive tasks (Buckner et al., 2008; Martin-Subero et al., 2021; Philippi et al., 2015; Shapira-Lichter et al., 2013).

That said, the functional connectivity correlates of AM during childhood have been understudied. While there are more studies on the functional connectivity correlates of episodic memory (e.g., Cho et al., 2012; Geng et al., 2019; Riggins et al., 2016), episodic memory investigated with laboratory material is only partly comparable to the recall of autobiographical memories. The latter process is susceptible to engage a greater number of cognitive functions supported by a wider range of brain regions, e.g. because it required a sense of self and a strong autonoetic consciousness, the ability to travel back in time to re-experience past events (Conway et al., 2002; Fivush, 2011; Ross et al., 2020).

Studying the functional correlates of AM during childhood is important for understanding its ontogeny. The earliest autobiographical memories are generally dated around the age of 2 or 3, and most autobiographical memories prior to age 6 are forgotten during later development, a phenomenon known as childhood amnesia (Bauer & Larkina, 2014; Peterson, 2021). AM has a protracted development: studies reported linear increases throughout childhood and adolescence in the ability to recall rich, detailed autobiographical memories. With developmental time, children recall autobiographical memories that are richer in episodic details, more coherent and more organized (Bauer & Larkina, 2019; Picard et al., 2009; Piolino et al., 2007; Willoughby et al., 2012). Thus, studying the functional correlates of AM in children could contribute to our understanding of its development and of the phenomenon of childhood amnesia.

To date, two studies have investigated the functional correlates of AM during childhood (Bauer et al., 2017; Østby et al., 2012). Bauer et al. (2017) used a cue-word paradigm to elicit the autonoetic re-experience of autobiographical memories in a task-based fMRI paradigm, comparing functional activations in children and adults. They highlighted both similarities and differences of regions recruited in AM recall between children and adults. Adults showed greater activation in the hippocampal, prefrontal and parietal regions compared to children. These results suggest that age-related differences in AM recall could be related to distinct patterns of functional organization in the AM network. Østby et al. (2012) investigated the resting-state functional connectivity correlates of EAM in 9 to 21 years old children and adolescents. The authors showed that average functional connectivity within a cluster of voxels overlapping with the DMN correlated with self-ratings of autonoetic re-experience of autobiographical memories, which were measured out-of-the-scanner. This means that functional connectivity within the DMN is related to the ability to re-experience AM from an autonoetic perspective during late childhood and adolescence. The study from Østby et al. (2012) used subjective self-ratings of autonoetic re-experience as a proxy for the quality of AM retrieval and restricted their analyses to functional connectivity within a subset of the DMN. While seminal in its report of the relation between resting-state functional connectivity and AM, these are two potential limitations, which we tried to circumvent here. In particular, assessing AM recall with an objective assessment procedure (i.e., experimenter-based rather than subject-based) could provide valuable information about the functional correlates of AM.

Our aim was to contribute to the understanding of the functional correlates of AM recall during childhood, and specifically of the relationship between the brain's functional architecture at rest (measured with resting-state functional connectivity) and AM recall.

AM was assessed using the Children's Autobiographical Interview (CAI) (Willoughby et al., 2012), the child-friendly version of the Autobiographical Interview (Levine et al., 2002), a widely used tool for assessing AM recall. The CAI allows for objective (experimenter-based) ratings of AM recall as it consists in counting the number of episodic and semantic details in autobiographical memories reported by children, thus

measuring the EAM and SAM richness of recalled memories. It allows to distinguish between different types of EAM content, namely details related to events and detailed related to the context of these events (see Methods section).

Functional connectivity was assessed using a functional connectivity matrix approach: functional connectivity was calculated between pairs of regions in an atlas providing comprehensive coverage of the neural correlates of AM as described in adults. Because this method systematically explores connectivity between pairs in a given set of regions, it is arguably more comprehensive than other functional connectivity methods (independent component analysis, seed-voxel analyses). We correlated functional connectivity between pairs of regions with our measures of AM recall.

Our hypotheses were the following: 1) richness of recalled autobiographical memories should be positively correlated with age and should show more important age-related differences for EAM content than for SAM content; 2) we expected to find associations between resting-state functional connectivity and richness of AM recall, with distinct associations for the type of details recalled and for memory recency.

2. Methods

2.1 Participants

50 children aged from 4 to 12 years old (mean 8.27 years, and standard deviation 2.3 years) participated in this study as part of a larger study on the neural correlates of episodic memory during development. 55% of the participants were males and 45% females. Among our 50 participants, 8 were excluded because they had no data, incomplete data, our because of a history of past disabilities or the detection of structural anomalies on their MRI images. This resulted in a total of 42 participants with MRI data. Among them, 6 had incomplete or unusable behavioral data because the recordings of their memories was lost, corrupted or of poor audio quality, making them unusable. This resulted in a sample of 36 children with both complete neuroimaging

and behavioral data. Data acquisition was performed under the regulations of an appropriate Ethical Committee board (CPP 2011-A00058-33).

2.2 Autobiographical memory interview

2.2.1 Procedure

AM was assessed out-of-the-scanner with the Children Autobiographical Interview (CAI) (Willoughby et al., 2012). The CAI was chosen over paradigms for the assessment of AM as it comprises several advantages. First, it distinguishes between episodic and semantic content within autobiographical memories. Second, it allows to distinguish between several types of details within the episodic content of the memories (e.g., information related to events, information related to spatial, temporal, perceptual context, and so on). Third, it consists in assessing the richness of autobiographical recall by counting the number of recalled details for distinct categories of details. This is arguably a more fine-grained approach for the evaluation of the quality and richness of autobiographical memories compared to paradigms rating memory richness with fixed scales (see Willoughby et al., 2012, for a discussion).

The CAI consists in asking children to recall personal memories based on cue-words. For example, if given the word ‘toy’, they had to recall a memory related to a toy. Children had to recall 6 memories in total. We modified the standard CAI procedure by providing the same cue-words to all children, which were not able to freely choose cue-words among a pre-determined list. This is because the identity and order of cue-words was used for the needs of a subsequent temporal order memory task which was part of another study (see Supplementary Material S1 for details). We also modified the standard CAI procedure by manipulating memory recency: 3 memories had to be recent (from a day to a week old) and 3 had to be remote (from a month to one year old). This allowed us to contrast the characteristics and functional correlates of autobiographical recall as a function of the temporal distance of the memories. Remoteness was limited to a year at most to ensure that older children (e.g., age 10) and younger children (e.g., age 4) recalled memories of a similar degree of remoteness.

Aside from these differences, the standard CAI procedure was used to elicit autobiographical recall (see Willoughby et al., 2012 for details and Supplementary Material S1 for a detailed description of the procedure). Broadly, recall consists in an initial free recall phase and is then followed by a general probe ("can you tell me more about this memory?") and by specific probes ("where did it happen? When did it happen?") to elicit further recall. Children were first trained to ensure that they understood that they had to recall specific personal memories. Once the interview was complete, we briefly verified the plausibility of the reported memories by asking the participant's parents if they thought that the broad factual core of the memory was plausible to them. Based on these exchanges we did not chose to exclude any memories from our analyses. It should be noted that, as for most studies using autobiographical interviews, we cannot guarantee that each reported memory did not contain factual errors.

2.2.2 Coding of autobiographical memories

The memories of each participant were recorded and transcribed. Recorded data was anonymized and securely stored to guarantee privacy. The transcriptions were used to code autobiographical details in each narrative following the CAI protocol (Levine et al., 2002; Willoughby et al., 2012). In brief, the CAI distinguishes between two main categories of autobiographical details: episodic details, which convey information about episodic details recalled from a first-person point of view, and external details, which convey about details recalled from a third-person point of view (e.g., factual information). Episodic details and external details are further divided into several subcategories which are shown Table 1. An example of a coded memory is presented Figure 1.

General category	***Detail subcategory***	***Description***	***Example***
Episodic	Event	Events, actions, reactions, happenings	“I played with my friend”
	Time	Temporal information about the event (year, month, day, time of day, season…)	“It was last week”
	Place	Spatial information about the event (country, city, street, part of room…)	“I was at home”
	Perceptual	Visual, auditive, olfactory, and other sensory details	“It was very sunny”
	Thought/emotion	Emotional states, thoughts	“I was quite happy”
External	Semantic	General knowledge or facts, extended events or states of being	“He is my best friend”
	Event	Details from other events external to the main event of the narrative	“It reminds me that there was this other time when…”
	Repetition	Repetition of details	“I was at school. It happened at school”.
	Other	Metacognitive statements	“I don’t remember very well“

Table 1. Categories of autobiographical memories details obtained with the CAI.

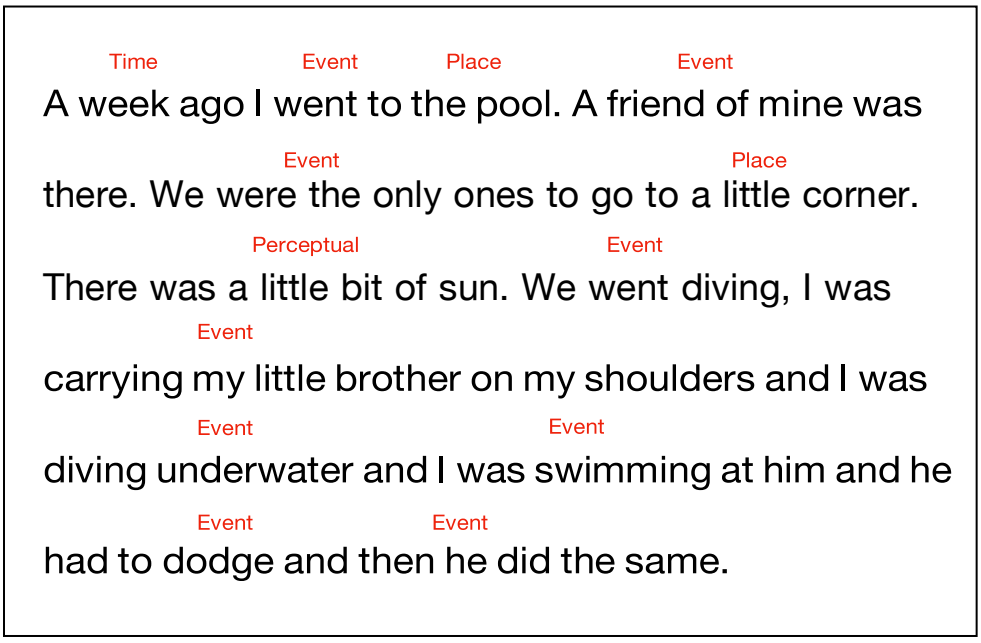

Figure 1. Coding example of an autobiographical memory (theme: ‘family’).

We adapted several aspects of to the CAI coding protocol to better fit the scope of our study:

1) Details in each memory were collapsed across the free recall phase and the general and specific probes phases. Probes have been shown to not significantly alter the characteristics of autobiographical recall compared to details recalled during the initial recall phase (Willoughby et al., 2012, 2014). This was done in order to limit the number of tested conditions.

2) We collapsed place, time, perceptual, emotional and cognitive details into a single 'context' details subcategory. This context subcategory was opposed to the 'event' subcategory within categories of EAM details. This allowed us to contrast the functional correlates of the recall of episodic event information and of episodic context information without performing statistical test for each subcategories of details related to context (place, time, etc.) We hypothesized that the recall of event and context information could have distinct functional correlates. We hypothesized that event details could be in some cases more factual, schematic, and broader than context details. Indeed, the recall of broad, general information has been shown to rely on distinct regions than the recall of sharp, specific information (Diana et al., 2007; Poppenk et al., 2013; Ranganath & Ritchey, 2012; Ritchey et al., 2015).

3) For the external details category, we focused our analyses on semantic details as the other external subcategories are less relevant for the assessment of autobiographical recall.

4) To analyze the effect of recency or remoteness on autobiographical recall, event and context EAM details was assessed across all memories, as well as separately for memories in the recent or remote conditions.

To summarize, we focused our analyzes on the following subcategories of autobiographical details to analyze the effect of information type (event vs context) and of memory recency (recent vs remote): a) event details (in all memories, and

separately for recent and remote memories); b) context details (in all memories, and separately for recent and remote memories); c) semantic detail (in all memories, and separately for recent and remote memories).

The coding of details was performed by two raters (C.C. and A.B.) who followed a training procedure by coding a set of memories obtained from a pilot study. The training allowed the raters to agree on the coding rules and procedures to be used in case of ambiguity. Once the training was completed, the coding of all memories was carried out by C.C. who was blind to the age and sex of the children. Coding reliability was tested by having the other rater (A.B.) code the memories of a randomly selected subset of 10 anonymized subjects. Inter-rater reliability was determined with intra-class correlation, which was of .85, which is satisfactory based on thresholds reported in the literature.

2.2.3 Other cognitive measurements

To test the specificity of our findings, we administered a non-autobiographical episodic memory recall task. We used the children version of the California Verbal Learning Test (CVLT-c; Delis, 1994), a widely used laboratory test of episodic memory recall, to assess episodic memory recall in a non-autobiographical context. We limited our analyses to the Long-Delay Free Recall score since is it involves free recall after a delay, similarly to the recall of autobiographical memories (although the delay is of 20 minutes in the CVLT-c).

A potentially confounding effect for the assessment of autobiographical recall is that part of the richness of recalled memories depends on the language skills of children rather than on their ability to re-experience past memories. The protocol of the current study did not include a measurement of language. However, we performed a pilot study administrating both a measurement of autobiographical memory and an assessment of language skills with the comprehension subtest of the WISC-IV. We found that these two measurements were not correlated with each other (see Supplementary Material, S2). This provides partial evidence of an independence between richness of autobiographical recall and language skills. However, even if language can play a role

on the quality of autobiographical recall (Bauer & Larkina, 2019), it should be noted that it is well-established that the quality of autobiographical recall mainly depends on memory-specific cognitive processes and neural correlates (e.g., Willoughby et al., 2012).

2.3 MRI acquisitions

Neuroimaging data was collected at the NeuroSpin research center, CEA, Gif-sur-Yvette, France. Children first followed an MRI training session on a mock scanner set in a children-friendly environment. Once the children were familiarized with the sonic and visual environment of the scanner, the acquisitions began. Images were acquired on a Siemens PRISMA 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil. We first acquired a T1-weighted MPRAGE volume (TR=300ms, TE=2.98ms, 0.9mm isotropic resolution, 175 slices, acceleration factor GRAPPA2). We then acquired 4 sessions of resting-state fMRI data of 3'10'' each (TR=1.81, TE=30.4, 2mm isotropic resolution, 69 slices, FOV 192mm, Multi-Band 3). The sessions were separated in two distinct blocs. Sessions were acquired successively within a bloc and blocs were separated by the acquisition of other MRI sequences. We also acquired two spin-echo EPI volumes for each session, one with same phase-encoding direction (posterior-anterior) and the other in the opposite phase-encoding direction (anterior-posterior), to correct for susceptibility off-resonance field distortions. During the resting-state scanning acquisitions, children were shown a short movie specifically conceived to improve compliance by allowing subjects to focus their attention while minimizing cognitive load during functional acquisitions (Vanderwal et al., 2015).

2.4 MRI preprocessing

Individual T1-weighted images were segmented into Grey Matter (GM), White Matter (WM), Cortico-Spinal Fluid (CSF) tissues types and skull-stripped while correcting for spatial intensity variations (b1 bias field) using FMRIB's Automated Segmentation Tool (FAST). For function images, volume-to-volume head motion (framewise displacement, FD) was estimated within each fMRI scan with the method described in (Power et al., 2012) implemented in FSL's Motion Outliers tool. Resting-state scans

were realigned and corrected for motion with FSL mcFLIRT (Jenkinson et al., 2002). Realigned scans were corrected for slice-timing (FSL slicetimer). Images were further corrected for susceptibility-induced off-resonance field distortions using FSL *topup* with spin-echo EPI volumes (Levine et al., 2002). Realigned, slice-timing corrected, susceptibility distortion-corrected images were then skull-stripped using FSL Brain Extraction Tool (Smith, 2002) after cropping the remove date from the neck and skull (FSL robustfov). Within each subject, fMRI scans were co-registered to subject's skull-stripped T1 image using rigid body registration with 6 degrees of freedom as implemented in Advanced Normalization Tools (ANTs) (http://stnava.github.io/ANTs/) (Avants et al., 2011). T1 images were non-linearly normalized to the NIHPD pediatric template (http://www.bic.mni.mcgill.ca/ServicesAtlases/NIHPD-obj1) with the ANTs SyN algorithm, which has been demonstrated to be one of the best performing algorithms for non-linear registration (Avants et al., 2008; Klein et al., 2009). Resting-state scans were normalized using the transformations estimated on the T1 data. Once in template space, resting-state scans were concatenated, resulting in 12'40'' of fMRI data for each subject. Normalized and concatenated images were smoothed with FWHM=4. We then verified that the signal intensity of temporal signal-to-noise ratio (tSNR) was above the threshold of 40 (Simmons et al., 2010) for all subjects on our regions of interest.

Motion correction is an important step for the preprocessing of fMRI data. Motion artifacts have been shown to alter correlations in resting-state functional connectivity which could lead to Type I errors in subsequent statistical analyses (Power et al., 2012, 2014, 2015). This risk is particularly important for motion-prone population such as young children. Finding an adequate balance between stringent motion correction procedure to mitigate the risk of false positives, while preserving statistical power, is a delicate task. In this aim, we opted for three-stepped motion correction approach. First, normalized resting-state scans were corrected for head motion using ICA-AROMA (Pruim et al., 2015) with non-aggressive denoising. ICA-AROMA is an Independent Component Analysis (ICA)-based strategy for the removal of motion artifacts from fMRI data. A recent benchmark (Parkes et al., 2018) of motion correction methods demonstrated that ICA-AROMA was among the most efficient method across tested

conditions with the advantage of preserving the autocorrelation structure of time-series and temporal degrees of freedom for ICA-AROMA. Second, we used Framewise Displacement (FD) to count the number of outlier volumes in each resting-state scan. In each session, a volume was considered an outlier if its FD exceeded 0.25. Subjects were excluded if more than 25% of the volumes across all of their resting-state scans were considered outliers. Moreover, subjects were excluded if their mean FD across all volumes exceeded 0.25. These thresholds are within the range of what is deemed reasonable in the adult literature (Parkes et al., 2018; Power et al., 2014, 2015) and are stringent compared to previous works in children (Geng et al., 2019; Riggins et al., 2016). Despite this, the combination of these thresholds led us to exclude only two subjects, for a final sample of 34 subjects (mean age = 8.67, sd = 2.42). We believe that this is mainly reflective of the positive effect of movie watching during resting state (Vanderwal et al., 2015). Third, we demonstrated that mean FD was not correlated to age or to memory measurements (Supplementary material, S3) to ensure that differences in head motion did not account for our results.

Motion-corrected images were further corrected by regressing out of the data the mean white matter and CSF signals while orthogonally applying band pass-filtering (high pass=0.001, low pass=0.01) (Lindquist et al., 2019) using Nilearn's signal_clean function (https://nilearn.github.io/).

2.5 Functional connectivity of the neural correlates of autobiographical memory

We created a custom functional atlas selecting cortical regions involved in AM to study how resting-state functional connectivity was associated with the recall of autobiographical memories. Region selection was performed by examining the literature on the functional neuroanatomy of AM, reviewing meta-analysis, reviews and experimental papers, on children and adult populations (Addis et al., 2017; Bauer et al., 2017; Cabeza & St Jacques, 2007; Conway et al., 2002; St. Jacques, 2012; Svoboda et al., 2006). We selected regions that were robustly identified as cores regions of the AM network in the literature. Specifically, we used results from a meta-analysis (Svoboda et al., 2006) to select regions identified as part of a core autobiographical network comprising the hippocampus, the medial temporal lobe

(parahippocampal gyrus), the medial PFC, the ventrolateral PFC, the lateral temporal gyrus, the temporoparietal junction, the retrosplenial/posterior cingulate cortex, and the cerebellum (Svoboda et al., 2006). We also selected most, but not all of regions identified as being part of a secondary AM nework (Svoboda et al., 2006). Regions of the secondary network were included based on their significance as assessed by other reviews (Addis et al., 2017; Cabeza & St Jacques, 2007; St. Jacques, 2012) and in the task-fMRI developmental study (Bauer et al., 2017). This led us to select the dorsomedial PFC, the anterior cingulate cortex, the amygdala, the thalamus, the temporal pole and the inferior temporal gyrus.

Selected ROIs were extracted from the MIST functional atlas (Urchs et al., 2017), a multi-resolution parcellation of functional brain networks obtained through an implementation of the bootstrap analysis of stable clusters algorithm (Bellec et al., 2010). MIST is available in 9 different resolutions with the number of functional parcels varying from k=7 to k=444, such that higher-resolution parcels fall largely within the boundaries of lower-resolution parcels. This allowed us to choose ROIs with adequate resolution for each region, given that the AM network is typically described as comprising regions of finer-grained (e.g., the hippocampus proper) or coarser-grained (e.g., the lateral temporal lobe) resolutions. Functional parcellations methods such as the BASC algorithm implemented in MIST have been shown to be more efficient to predicting behavioral measurements with rest functional connectivity than structural atlas or clustering methods (Dadi et al., 2019). To cover the regions described above, we created a custom functional atlas of autobiographical memories by extracting ROIs corresponding to the core regions of AM from the MIST functional atlas. Some regions were covered by several ROIs when necessary; see Supplementary Material S4 for a detailed description of the atlas edition procedure. In total, we selected 15 ROIs shown Table 2 and represented projected on a template brain Figure 2.

Region name	Importance in the AM network
Ventromedial Prefrontal Cortex	Core AM network
Dorsomedial Prefrontal Cortex	Seondary AM network
Ventrolateral Prefrontal Cortex	Core AM network
Anterior Cingulate	Secondary AM network
Middle temporal gyrus	Core AM network
Inferior temporal gyrus and temporal pole	Secondary/tertiary AM network
Hippocampus	Core AM network
Amygdala	Secondary AM network
Thalamus	Secondary AM network
Posterior MTL	Core AM network
Anterior MTL	Core AM network
Lateral fusiform Gyrus	Secondary AM network (lateral temporal lobe) / tertiary AM network (fusiform gyrus)
Posterior cingulate cortex	Core AM network
TPJ/angular gyrus	Core AM network (TPJ)
Cerebellum	Core AM network

Table 2. Regions of Interest (ROIs) included in the custom autobiographical memory atlas. We also indicate their importance for AM based on the literature (Svoboda et al., 2006).

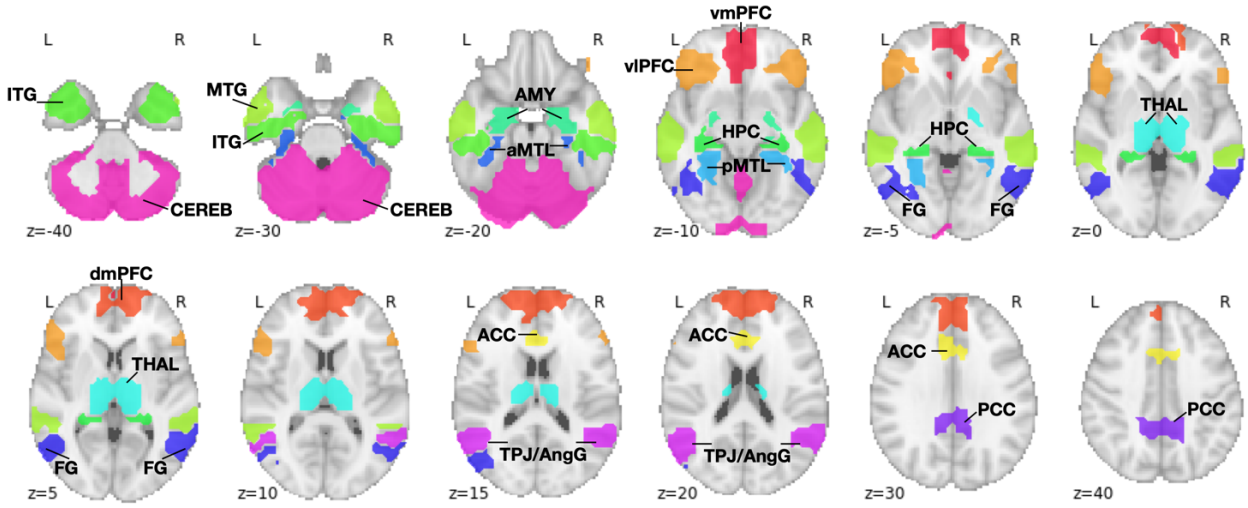

Figure 2. ROIs of the custom autobiographical memory atlas projected on a template brain. ITG=Inferior Temporal Gyrus. MTG=Medial Temporal Gyrus. CEREB=Cerebellum. AMY=Amygdala. aMTL=anterior Medial Temporal Lobe. pMTL=posterior Medial Temporal Lobe. HPC=Hippocampus. vmPFC=ventromedial Prefrontal Cortex. vlPFC=ventrolateral Prefontal Cortex. FG=Fusiform Gyrus. THAL=Thalamus. dmPFC=dorsomedial Prefrontal Cortex. ACC=Anterior Cingulate Cortex. TPJ/AngG=Temporopolar Junction/Angular Gyrus. PCC=Posterior Cingulate Cortex.

This custom atlas was used to compute resting-state functional connectivity between all pairs of region of the atlas. For each subject, we extracted the time series spatially overlapping with each ROI. Functional connectivity between pairs of ROI was defined with two metrics: the correlation between the time series of the ROI, or the partial correlation between the time series while controlling for correlation between all other pairs of ROI. Both metrics were used as their provide distinct and complementary information: correlation shows the global connectivity between ROIs, which can be either direct (A is connected to B) or indirect (A is connected to C, and C is connected to B). Partial correlations is an approximation of direct connectivity between regions (Wang et al., 2016) by representing the connectivity between A and B while controlling for the connectivity of other ROIs. Correlation and partial correlation coefficients were transformed using Fischer r-to-z to normalize the distribution of values. Subject-specific correlation matrices representing the functional connectivity between all ROIs were thus created, using functions from nilearn (https://nilearn.github.io/). Quality control was performed by comparing results on our data using a widely atlas (MSDL atlas, Varoquaux et al., 2011) and with a pre-processed developmental dataset of reference using the same atlas (https://openneuro.org/datasets/ds000228/versions/1.0.0, Richardson et al., 2018). We also verified the presence of systematic outliers in the distribution of the connectivity between pairs of ROI across all subjects (none were identified).

2.6 Statistical analyses

2.6.1 Development of autobiographical memory

Differences in the number of autobiographical details recalled between subcategories of details were examined using either paired t-tests or a two-way ANOVA followed by post-hoc Tukey-HSD tests after verifying for homogeneity of variances. Age-related differences in the number of recalled autobiographical details was assessed with linear regression models with the number of recalled details as the dependent variable, age as the predictor. Steiger z-tests were used to examine differences between age-recalled details correlation coefficients. The p-values of all linear regression models were adjusted for multiple comparisons using False Discovery Rate (FDR) (Benjamini & Hochberg, 1991). An alpha value of 0.05 was used in all analyses.

2.6.2 Association between functional connectivity and autobiographical memory

2.6.2.1 Association with functional connectivity

We studied the association between functional connectivity and AM recall with linear regression models. We used separately functional connectivity matrices estimated functional connectivity with correlation or with partial correlation.

For each subject-level connectivity matrix (connectivity=correlation or connectivity=partial correlation), we defined the AM detail subcategory of interest as the explanatory variable, and the connectivity between a given pair of regions of the matrix as the dependent variable. Age was included as a covariate of non-interest. We defined a 'comparison family' as the set of all associations between: a) a given AM detail subcategory, and b) a given functional connectivity matrix (i.e., estimated with correlation or partial correlation). Thus, each comparison family yielded correlation matrices, in which a given entry indicated the correlation value between: a) the number of recalled details for the subcategory of interest, and b) the functional connectivity between a given pair of ROIs. We corrected for multiple comparisons within each comparison family with FDR. This means that, within each correlation matrix, the p-values were adjusted across all other p-values (N=105) obtained from the linear regression models of that matrix. We report the t-values and corrected p-values of the explanatory variables (AM scores) of the linear regressions. Regressions analyses were performed using an adapted version of a script from ConPagnon, a python module designed to facilitate the analysis of resting-state fMRI data (https://github.com/ConPagnon/conpagnon).

2.6.2.2 Moderating effect of age

We also examined if the relation between functional connectivity and AM was influenced by the children's age. In this order, we used the same regression models described in the previous subsection, but including an interaction term between age and the tested AM score. Models with and without an interaction term were fitted separately to first examine the main effect (described in subsection above) without the influence of the interaction effect.

3. Results

3.1. Autobiographical memory details

3.1.1 Differences between categories of autobiographical details

We analyzed 6*34 memory narratives (6 per subject), for a total of 204 narratives across all subjects. These narratives comprised 1612 details across every detail categories (average number of details per narrative: 7.90). The complete description of the number of details for each category is presented Table 3. Among these 1612 details, there was 1340 episodic details and 272 external details, and this difference was largely significant (paired t-test: t=13.40, p=2.61e-18). The full presentation of recalled details across all subcategories is shown Table 3.

We analyzed EAM details with a two-way ANOVA to examine the effect of information type (event vs context) and memory recency (recent memories vs remote memories) on the number of recalled details. There was an effect of information type (context or event) on the number of details recalled (F=10.01, p=0.001, partial n2=0.07). Pairwise Tukey-HSD test showed that event details (mean: 11.09 per subject) were significantly more recalled than event details (mean: 8.61 per subject) (T= 3.18, p=0.002). The effect of recency (recent or remote memories) on the number of details recalled was not significant (F=3.50, p=0.06, partial n2=0.03). However, the interaction between information type and memory recency was significant (F=4.48, p=0.03). For event details, there was more details in recent memories than in remote memories; while for context details, there was a comparable number of details independently of recency (Table 3).

Category	**Episodic**				**External**			
Number of recalled details	1340				272			
Significant difference?	Yes							
Subcategory	**Episodic Event**		**Episodic Context**		**Semantic**		**Other external details**	
Number of recalled details	750		590		145		127	
Significant difference?	Yes				No			
Subcategory	**Event Recent**	**Event Remote**	**Context Recent**	**Context Remote**	**Semantic recent**	**Semantic remote**	**Other recent**	**Other remote**
Number of recalled details	424	326	292	298	71	74	70	57
Significant difference?	Yes		No		No		No	

Table 3. Number of recalled details for each main subcategory of AM. We also indicate if the differences between each subgroup of a given higher-level category (e.g.: between event and context; between event recent and event remote) are significant. Event, context = EAM event details and context details. Recent, remote = details recalled across recent memories (from a day to a week old) or details recalled across remote memories (from a month to a year old) .

3.1.2 Age-related differences of autobiographical details

We then examined age-related differences among subategories of autobiographical details by correlating the number of details with age in linear regression models, adding sex as a covariate of non-interest (Figure 3). Among EAM details, both event details ($F=7.5$, $R2=0.19$, $\beta=1.55$, corrected $p<0.05$) and context details ($F=17.1$, $R2=0.34$, $\beta=1.52$, corrected $p<0.01$) were significantly positively correlated with age. These age-related trajectories were not significantly different (Steiger's one-tailed z-test: $t=-0.94$, $p=0.17$).

Next, we examined the effect of memory recency on EAM details. The number of episodic details in recent memories and in remote memories were both associated with age (recent: $F=14.87$, $R2=0.31$, $\beta=1.57$, $p=0.005$; remote: $F=14.63$, $R2=0.31$, $\beta=1.50$,

p=0.005). These age-related trajectories were not significantly different (Steiger's one-tailed z-test: t=0, p=0.5).

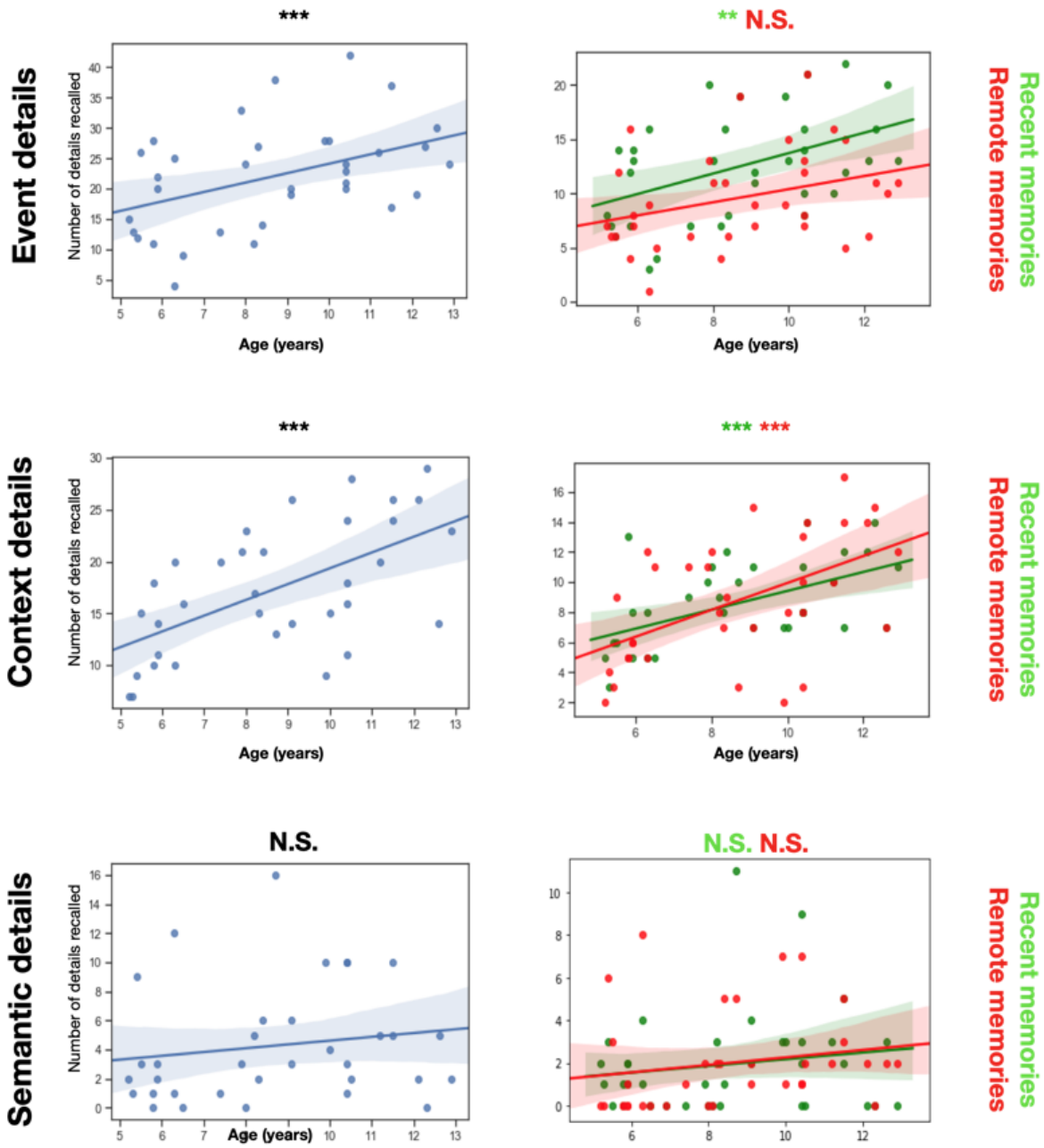

Figure 3. Plots of age-related differences for AM details. The plots of event, context and semantic details are shown on the left (across all memories). These details categories are also plotted separately for recent memories (in green) and remote memories (in red) on the right. **:p<0.01. ***:p<0.001. N.S.: not significant.

Then, analysis of information type (event vs context) as a function of recency (recent vs remote) showed that the number of episodic event details in recent memories was associated with age ($F=8.59$, $R2=0.21$, $\beta=0.22$, $p=0.006$) but not the number of episodic event details in remote memories ($F=3.78$, $R2=0.10$, $\beta=0.17$, $p=0.06$). By contrast, both the number of contextual event details in recent memories ($F=12.93$, $R2=0.28$, $\beta=0.45$, $p=0.001$) and the number of contextual event details in remote memories ($F=11.77$, $R2=0.27$, $\beta=0.30$, $p=0.001$) were associated with age. These age-related trajectories were not significantly different (Steiger's one-tailed z-test: $t=0.18$, $p=0.42$). Sex was not associated to autobiographical details in all models.

The number of semantic details ($F=0.82$, $R2=0.02$, $\beta=0.26$, $p=0.36$) was not associated with age. This was also the case when analyzing semantic details in recent and remote memories separately.

In sum, all episodic details subcategories but one were positively associated with age, while semantic details were not.

3.1.3 Relation between autobiographical details and episodic recall

We examined the relation between AM recall and other cognitive measures to see if inter-subject differences of autobiographical recall performance was related to inter-subject differences of performance at other cognitive tasks. The total number of recalled episodic details was not correlated with Long Delay Free Recall when controlling for age and sex ($t=2.17$, $p<0.05$). Similar results were found for the event/context and recent/remote categories and SAM details.

3.2 Functional connectivity analyses

3.2.1 Group-average functional connectivity

To first illustrate functional connectivity between regions of our custom atlas, we computed the average functional connectivity matrix across subjects. Figure 4 shows the average functional connectivity matrices computed with correlation and partial correlation as connectivity metrics. For the connectivity matrix using correlation as the connectivity metric, functional connectivity between regions consisted mainly in

positive correlations, except for the functional connectivity between the cerebellum and other regions. Applying hierarchical clustering to the matrix (using unweighted pair group method with arithmetic mean as implemented in nilearn), we identified a cluster of several highly connected regions mostly overlapping with the Default Mode Network (Figure 4). For the connectivity matrix obtained with partial correlation as the functional connectivity metric, functional connectivity was evenly distributed between positive and negative partial correlations, which was expected, and no particular structure was observable using hierarchical clustering.

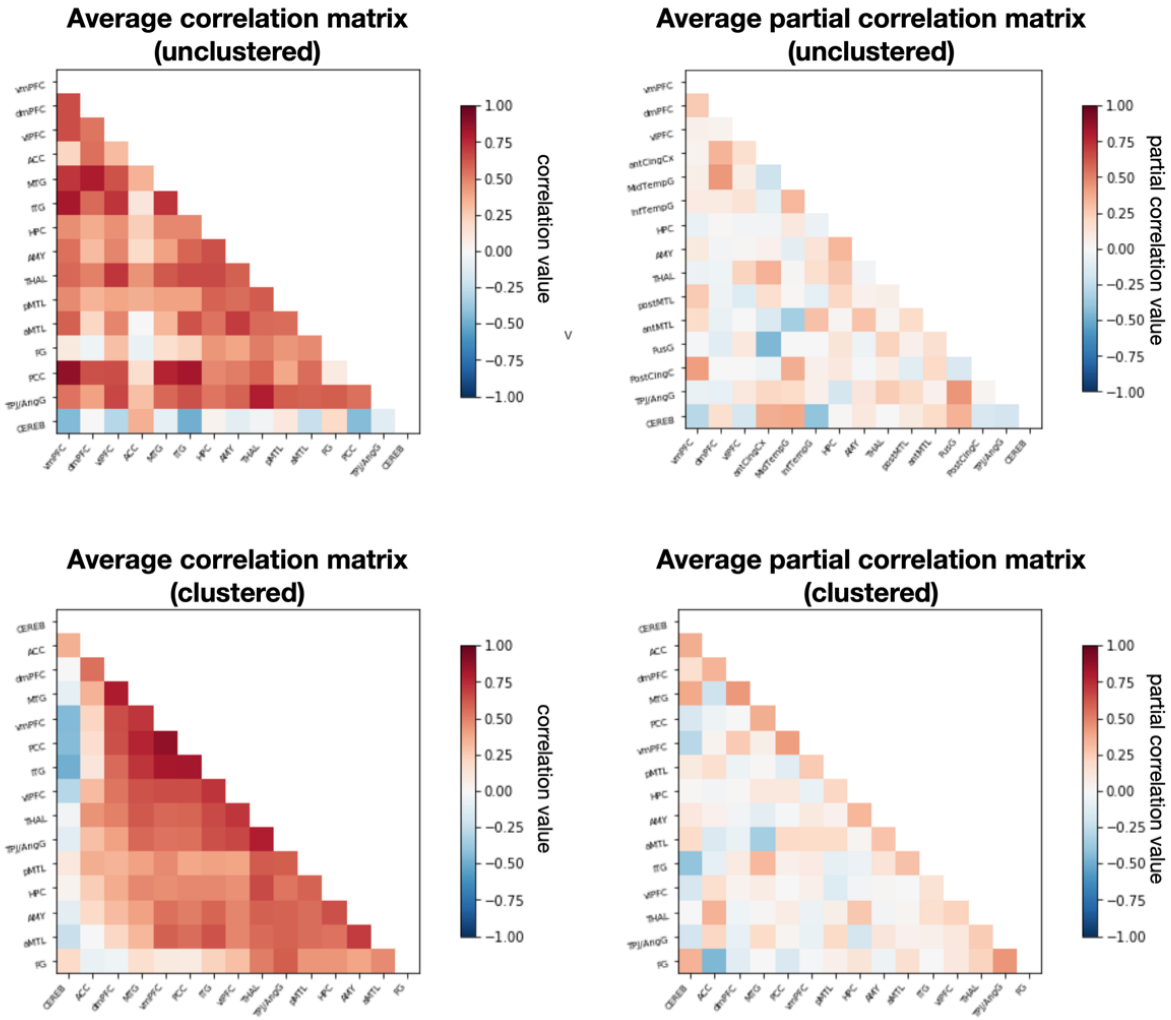

Figure 4. Group-average connectivity matrices. Connectivity matrices are computed with correlation as the functional connectivity metric (left) or partial correlation (right). Top: default, unclustered matrices. Right: matrices reordered with hierarchical clustering.

3.2.2 Association with autobiographical memory

Our main objective was to describe the functional connectivity correlates of AM recall. We correlated subject-level functional connectivity matrices (estimated with correlation, or with partial correlation) with measurements of autobiographical recall. We used regression models that estimated the association between the connectivity of each pair of region of a connectivity matrix (as the explanatory variable) and the number of details recalled for the AM subcategory of interest (as the dependent variable). Age was added as a covariate. We obtained correlation matrices showing, for each pair of regions of our atlas, if their connectivity was associated with the number of recalled AM details. The p-values of all regressions within a given matrix were adjusted for multiple comparisons.

3.2.2.1 Episodic autobiographical details

Event vs context

We first examined the effect of information type (event vs context) within EAM details. The significant connectivity/behavior associations are plotted Figure 5b.

Episodic event details

When using correlation to estimate functional connectivity, the number of recalled event details was significantly associated with the connectivity between the ventrolateral PFC and the inferior temporal gyrus (including the temporal pole) (t=-2.94, corrected p=0.04). It was also associated with the connectivity between the hippocampus and the cerebellum (t=-3.22, corrected p=0.02). When using partial correlation to estimate functional connectivity, no associations were found.

Episodic context details

When using correlation to estimate functional connectivity, no associations with the number of recalled context details was found. However, when using partial correlation, the number of context details was associated with functional connectivity between the cerebellum and the dorsomedial PFC (t=3.53, corrected p=0.04), as well as between the lateral fusiform gyrus and the middle temporal gyrus (t=-3.83, corrected p=0.02).

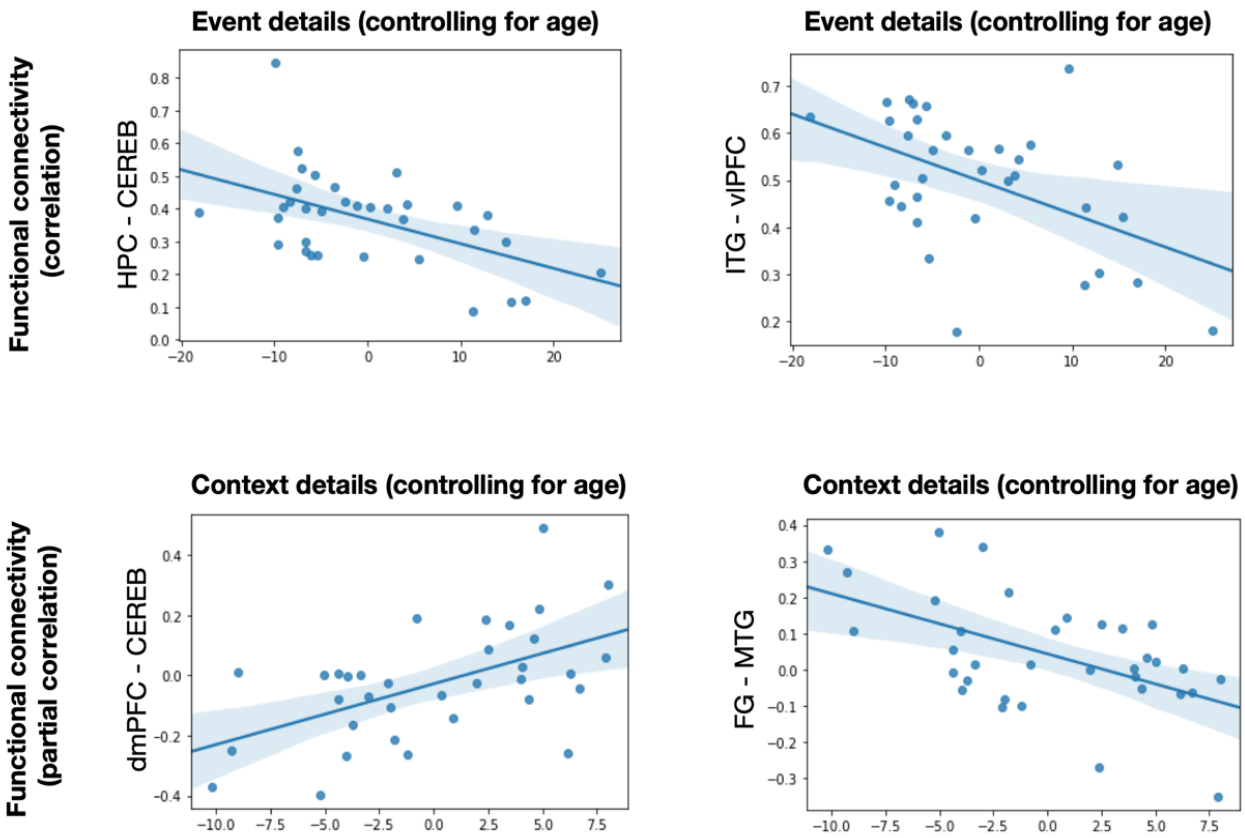

Figure 5. Plots of significant connectivity/behavior association for event details (up) and context details (down). On the x-axis: residuals of the number of recalled AM details controlling for age. On the y-axis: connectivity between a pair of ROIs. Significant associations were found for event details when connectivity=correlation, and for context details when connectivity=partial correlation. HPC=Hippocampus. CEREB=Cerebellum. ITG=Inferior Temporal Gyrus. vlPFC=ventrolateral Prefrontal Cortex. dmPFC=dorsomedial Prefrontal Cortex. FG=Fusiform Gyrus. MTG=Middle/Lateral Temporal Gyrus.

Recent vs remote

Then, we estimated the effect of recency (recent vs remote memories) on the associations with functional connectivity. The significant associations are plotted Figure 6.

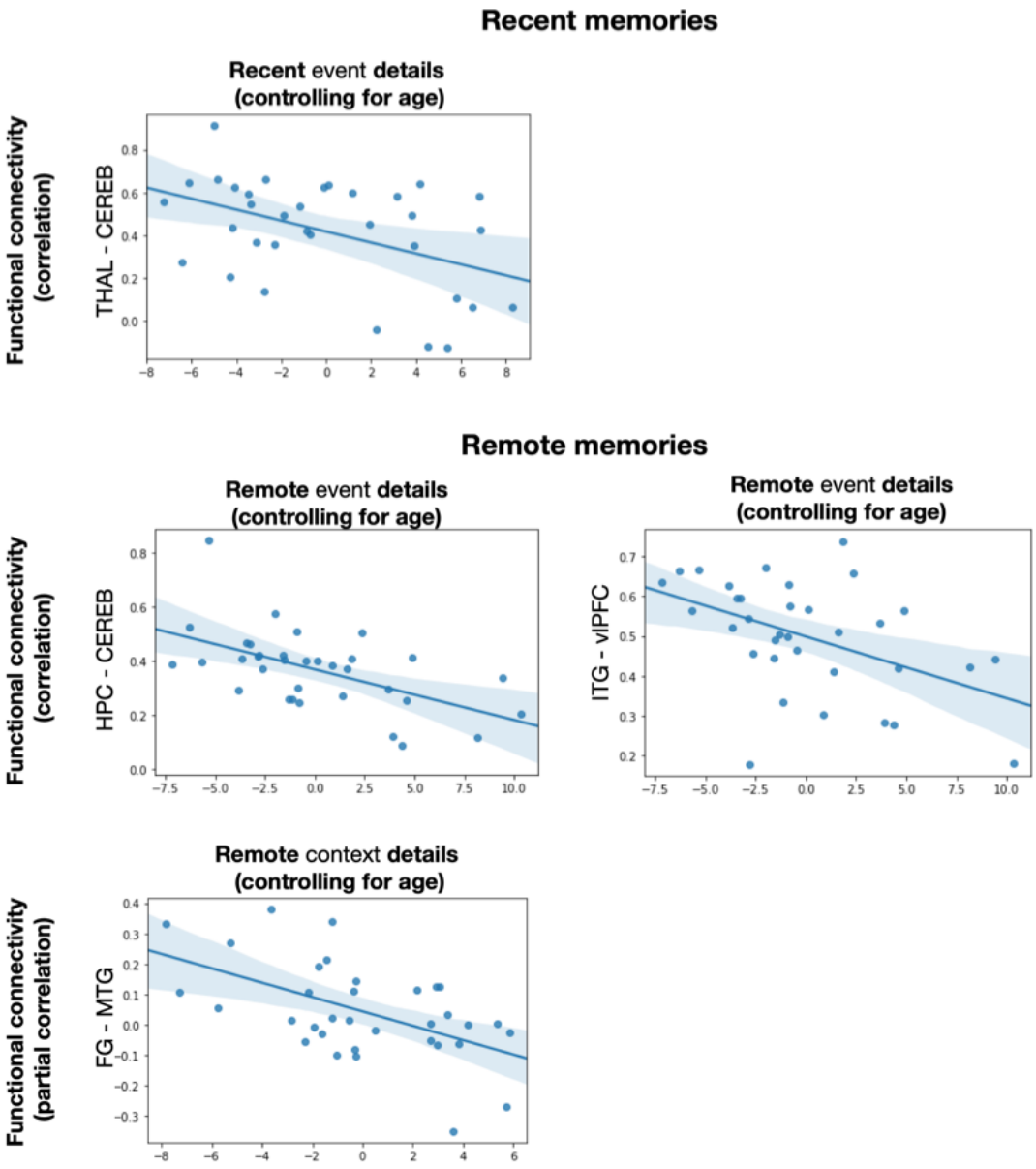

Figure 6. Plots of significant connectivity/behavior association for details in recent memories (upper panel) and remote memories (down). On the x-axis: residuals of the number of recalled AM details controlling for age. On the y-axis: connectivity between a pair of ROIs. Significant associations were found for event details when connectivity=correlation, and for context details when connectivity=partial correlation. THAL=Thalamus. CEREB=Cerebellum. HPC=Hippocampus. ITG=Inferior Temporal Gyrus. vlPFC=ventrolateral Prefrontal Cortex. FG=Fusiform Gyrus. MTG=Middle/Lateral Temporal Gyrus.

Recent memories

For recent memories (connectivity=correlation), the number of event details was associated with thalamo-cerebellar connectivity (t=-2.90, corrected p=0.04).

Additionally, the number of context details in recent memories was associated with the connectivity between the anterior medial temporal lobe and the cerebellum (connectivity=correlation). No associations for recent event details or recent context details were found when partial correlation was the connectivity metric.

Remote memories

For remote memories, event details was significantly associated with the connectivity between the ventrolateral PFC and the inferior temporal gyrus (including the temporal pole) (t=-2.96, corrected p=0.04), as well as by the connectivity between the hippocampus and the cerebellum (t=-3.29, corrected p=0.02) (connectivity=correlation). We found no significant results when connectivity was estimated with partial correlation. For context details in remote memories, the number of context details was significantly associated with functional connectivity between the lateral fusiform gyrus and the middle temporal gyrus (t=-3.84, corrected p=0.02) (connectivity=partial correlation).

3.2.2.2 Other measurements

Semantic details

Semantic details were not significantly associated with functional connectivity, both when using correlation or partial correlation as connectivity metrics, and when assessing semantic details across all memories, or separately for recent and remote memories.

Verbal recall

Long-Delay Free Recall as assessed with the CVLT-c was not associated with functional connectivity, both when using correlation or partial correlation as the connectivity metric.

Age

We also examined whether functional connectivity within the correlation and partial correlation matrices showed age-related differences. This was not the case after correcting for multiple comparisons.

3.2.2.2 Interaction between age and functional connectivity

Finally, we analyzed whether the relationship between AM recall and functional connectivity was moderated by age. We performed the same regression analyses as in the previous section but adding an interaction term between age and AM details. We ran separately models with this interaction term in order to analyze the main effect (i.e., results from the previous subsection) without the influence of the interaction effect. We did not found significant age*autobiographical details interaction effects for all subcategories of autobiographical details.

4. Discussion

We examined the resting-state functional connectivity correlates of AM during childhood. Our main results were: 1) Recall of episodic, but not semantic details was related to age. 2) Functional connectivity was associated with EAM details. Different correlates were found for event and context details, and for details recalled in recent or remote memories. 3) There was no moderating effect of age on the association between recalled details and functional connectivity.

4.1 The number of episodic, but not semantic, autobiographical details are correlated with age

Older children recalled more episodically rich autobiographical memories compared to younger children. These findings echo previous studies showing improvements of EAM recall during childhood and adolescence (see also Picard et al., 2009; Piolino et al., 2007; Willoughby et al., 2012). The number of recalled SAM details was not correlated with age. Some previous studies found age-related improvements of SAM recall (Picard et al., 2009; Willoughby et al., 2012), but to a lesser extent than age-related

improvements of EAM recall. One study, in line with our results, did not find age-related differences of SAM recall (Piolino et al., 2007). While there are discrepancies in the literature regarding the development of SAM, our results are in agreement with the general notion that individual differences in SAM recall are less related to age than individual differences in EAM recall. This is in consistent with the fact that semantic memory matures earlier than episodic memory (e.g., Bouyeure & Noulhiane, 2020).

Among EAM, subcategories were positively correlated with age and also showed similar age-related trajectories. The only exception was the number of event details recalled in remote memories. This echoes findings from Picard et al. (2009) showing age-related differences of EAM for recent memories but not for remote ones, although the remote memories studied by the authors were considerably more remote (several years) than the ones studied here. A possible explanation is that event details of remote memories rely more on semantic information than on specific episodic recollection; their recall would thus more depend on age-invariant processes. However, as the oldest memories studied are not more remote than a year, this explanation only partly fits our data. Therefore, we provide some evidence that the recall of context details is more associated with age than the recall of event details, at least for remote memories.

4.2 Functional connectivity is associated with episodic autobiographical memory recall

Resting-state functional connectivity captures correlations between the spontaneous fluctuations of the BOLD signal in different brain regions, describing the default or task-free functional architecture of the brain. We showed that individual differences in this default architecture were associated with individual differences of EAM recall in children.

Several reasons could explain why functional connectivity at rest is associated with the ability to recall the episodic content of autobiographical memories. As previously mentioned, resting-state functional networks have strong correspondences with networks of regions co-activated to perform specific cognitive tasks (Smith et al.,

2009). In order words, the functional architecture of the brain at rest predicts its architecture during specific cognitive demands. Thus, functional connectivity at rest could be representative of the efficiency with which brain areas communicate during the consolidation of past memories, or during their autonoetic retrieval. However, this relation is peculiar for AM, as regions of the DMN are activated by AM recall (Philippi et al., 2015; Shapira-Lichter et al., 2013). Thus, functional connectivity at rest could particularly convey information on the efficiency with which brain regions interact during the recall of autobiographical memories.

Event	**Context**
Hippocampus/Cerebellum	Cerebellum/dorsomedial PFC
ventrolateral PFC/ Inferior Temporal Gyrus	Fusiform Gyrus/ Middle Temporal Gyrus
Thalamus/Cerebellum	

Table 4. Summary of connections associated with event and context details. PFC=Prefrontal Cortex.

We examined differences between the functional correlates of event and context information within EAM (summarized Table 4). We did not find major differences between these the correlates of these two types of episodic content: for example, both were associated with the cerebellum or with areas of the PFC. The cerebellum and the PFC are known to play an important role in memory retrieval (e.g., Andreasen et al., 1999; Chapados & Petrides, 2015; Peters et al., 2013). Their connectivity at rest could be reflective of the efficiency at which they communicate during AM recall. Interestingly, we found a relationship with cerebellum connectivity both for event and context memories. The cerebellum has been previously associated to verbal episodic memory, long-term episodic memory encoding, and conscious retrieval of episodic memories (Andreasen et al., 1999; Fliessbach et al., 2007). Its involvement in AM has been an object of growing interest in the past decades (e.g., Addis et al., 2016; Fliessbach et al., 2007). Thus, future studies would likely benefit from scrutinizing more closely its role in the retrieval of autobiographical memories. The thalamus has been

associated with the recall of episodic memories; its connectivity with the cerebellum reported here is thus consistent. Finally, given the importance of the hippocampus in episodic and autobiographical memory, finding an association between its connectivity with the cerebellum and the number of recalled event details is consistent with the literature and could be seen as a sign of the conceptual validity of our findings.

We also found that the recall of context details was associated with connectivity between the middle/lateral temporal gyrus and the lateral fusiform gyrus. These two regions, particularly the middle/lateral temporal gyrus are associated with semantic processing of information. Their association with the recall of context details is thus surprising. However, the ability to recall context details or episodic information more generally also builds on the retrieval of semantic representations. For example, searching to retrieve spatial or temporal information about an event could be supported by general semantic information about the location or the year's period. Another possibility is that because these brain areas are also involved in language, this could reflect a relationship with language-related skills rather than with memory processes. The role of language abilities in autobiographical recall might be an important confound of our study as we did not controlled memory-connectivity associations with language abilities. However, we have limited evidence from a pilot study (Supplementary Material, S2) that phenomenological richness of EAM recall is independent of language skills. Moreover, our other findings are consistent with the idea that associations are mainly mediated by memory-driven processes, such as the associations with the hippocampus or the cerebellum. Moreover, context details were associated with cerebellar-dorsomedial PFC connectivity. The dorsomedial PFC has been shown to play a crucial role in the retrieval of mnemonic contextual information (Chapados & Petrides, 2015).

A surprising difference between event and context details was that event details were associated with functional connectivity when correlation was used as the connectivity metric, and context details were associated with connectivity when partial correlation was used as the connectivity metric. We used both types of metrics to estimate functional connectivity as they provide distinct information: while correlation shows the

overall relation between time series, partial correlation is thought to be an approximation of direct connections by controlling for the connectivity of other regions. This result shows the complementarity of using different metrics to estimate functional connectivity. However, this dissociation between connectivity metrics and aspects of behavior needs to be replicated by future studies to be interpretable with confidence. This nevertheless suggest that the recall of context details is associated to the functional organization of the brain at rest through more specific patterns (direct connections) than event details.

Besides the influence of information type, we also examined the effect of the recency of recalled memories (recent/remote), which is summarized Table 5.

Recent	**Remote**
Thalamus/Cerebellum	Fusiform Gyrus/Middle Temporal Gyrus
	Hippocampus/Cerebellum
	Inferior Temporal Gyrus/ventrolateral PFC

Table 5. Summary of connections associated with recent and remote memories. PFC=Prefrontal Cortex.

There was a greater number of connectivity associations with details from remote memories than with details from recent memories. Thus, the functional architecture of the brain at rest seems to be more related to the ability to re-experience more episodic-rich autobiographical memories if they are remote in time. This is consistent with previous findings suggesting that remote memories could engage a more distributed cortical network because of system-level consolidation processes, while recent memories would be more specifically represented in the anterior hippocampus (Bonnici & Maguire, 2012).

Except the association between context details and cerebellar-dorsomedial PFC connectivity, all associations between functional connectivity and EAM recalls were negative correlations. Similar negative relationships were reported by previous developmental studies, such as Østby et al. (2012) on EAM, or studies investigating the functional connectivity correlates of other cognitive functions during childhood (Geng et al., 2021; Riggins et al., 2016). Negative correlations between cognitive measurements and functional connectivity have been hypothesized to be specific to development, since studies in healthy adults generally report positive correlations between functional connectivity and behavior. As mentioned by Østby et al. (2012), the direction of the association between cognitive function and brain anatomy has been shown to change during development (Shaw et al., 2006) and a similar phenomenon could occur for functional connectivity. Lower functional connectivity could be a reflection of the selective elimination of synapses occurring during early development (Østby et al., 2012) which could be associated with better cognitive performance, and a higher quality of AM recall. As the negative relationship described by Østby et al. (2012 was stable across an age range covering late childhood to early adulthood (9 to 21 years), the authors reasoned that the inversion of the direction of this relationship must occur during adulthood. Our results further support this notion, as we did not find a moderating effect of age on functional connectivity. Thus, if changes of the direction of functional-behavioral relationships are to occur, then they should occurr either during early childhood (Riggins et al., 2016) or during later development compared to our age span.

Overall, our study adds to a scarce literature on the functional connectivity correlates of EAM and of episodic memory. The only previous study investigating the functional connectivity correlates of episodic autobiographical memory (Østby et al., 2012) used self-ratings of autonoetic experiences during a cue-word AM task; we show here that such associations were also found with objective ratings. Our results invite to scrutinize further the functional correlates of EAM during childhood and suggest a role of regions outside of the DMN network (e.g., thalamus, cerebellum).

Our results have consequences for our understanding of childhood amnesia. We showed that individual differences in aspects of the brain's functional architecture at rest were related with individual differences in the ability to recall rich episodic autobiographical memories in children. Previous studies have demonstrated that young children forget their earliest memories as they age (Bauer & Larkina, 2014; Peterson et al., 2018). This forgetting could be reflected in changes in the brain's default functional architecture, as well as its progressive offset. We did not find a moderating effect of age on the relation between EAM recall and functional connectivity, suggesting that older children have similar functional connectivity correlates of EAM than younger children. Age-related differences in EAM could thus partly be explained by the fact that younger children use a similar, although more immature, version of the networks of brain areas involved in AM. However, this important question should be further explored. Our findings show that future studies will benefit from using functional connectivity methods to examine the neuroimaging correlates of AM development and childhood amnesia.

4.3 Limitations and future directions

Our study has a number of limitations. First, by contrast with previous resting-state studies on episodic/autobiographical memory, we choose to perform a systematic examination of the contribution of memory to functional connectivity on a region-to-region basis among a selection of regions covering the main autobiographical memory network. This approach is more exhaustive compared to seed-to-voxel or ICA-based analyses but a downfall is a lack of specificity that complicates the interpretability of the findings. Moreover, the amount of statistical tests performed within each connectivity/behavior correlation matrix means that the p-values can survive the correction procedure only in case of strong significance, given that they are adjusted for comparisons among a set of 105 p-values. For this reason, we considered that each correlation matrix (consisting in an association between functional connectivity and a given AM score) could be treated as a distinct model/family of statistical comparisons, and adjustment for multiple comparisons was performed within each model (number of comparisons = 105) although we tested EAM scores that were statistically related with each other. Hence, although we can have strong confidence

in the reliability of the results of a single model, the fact that we compared multiple categories of EAM with the same functional connectivity matrices still represent a risk of Type 1 error inflation. Still, the fact that some connectivity patterns were associated with several categories of EAM details is a sign of reliability. The finding of an overall association between EAM and functional connectivity reported here can be deemed robust. As the association between resting-state functional connectivity and autobiographical memory during development is understudied, future research will likely benefit from investigating more the specific roles of brain regions in AM recall.

Another limitation is that our final sample size was small (34 subjects) particularly given the studied age range (4-12 years old). Sample size limitations caused by difficulties of recruitment and high data attrition are common in developmental studies. It is possible that lack of statistical power prevented us from characterizing potential developmental changes regarding the relationship between functional connectivity and autobiographical recall (moderating effect of age).

A crucial question is how the functional and structural maturation of the brain accompanies the transition from scarce and poorly detailed memories of the childhood amnesia period, to richer and more long-lasting memories during later development. Given that early childhood is a period of rapid increases of episodic memory and EAM abilities, it is possible that patterns of functional and structural maturation contribute specifically to these improvements. Such relationships would also largely benefit from being studied with a longitudinal design instead of a cross-sectional design, which was another limitation of our study. A promising avenue of research could be the longitudinal characterization of the functional correlates of autobiographical memory during early childhood.

5. Conclusion

Our results further support the fascinating observation that the brain’s default functional architecture is reflective of the efficiency with which individuals recall memories from

their past, and show that this relation is found during childhood. As personal memories formed during childhood amnesia are later forgotten, further investigations of the functional correlates of autobiographical recall during childhood could benefit our understanding of this phenomenon and of its progressive offset.

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Supplementary Material

S1. Description of the CAI procedure.

Children were asked to recall personal memories based on cue-words. For example, if given the cue ‘toy’, the child had to recall and narrate an autobiographical memory related to a toy. Words were selected based on their familiarity and appeal to children, and were the same for all participants, presented in the same order. Cue words were not freely chosen by the child among a preselected list as in the original paradigm because word-order had an effect on a subsequent recall task which was administered after the CAI, as part of another study. Children were asked to recall 6 memories in total. Among these 6 memories, children were asked to recall 3 recent memories and 3 remote memories. Recent memories were defined as events that happened between the day of the interview and two weeks before the interview. Remote memories were defined as events that happened between two months and two years before the interview. Children always recalled first 3 recent memories (cues: school, toy/play, family), followed by 3 remote memories (cues: meal, music/drawing, pet). The instructions were as follows: “I am going to ask you to recall something that happened to you in your past. This memory has to be related with the word I am going to give you. For example, if I give you the word ‘Christmas’, I want you to tell me about a memory you have about something you did during a Christmas day. I want you to be as precise as possible. For example, do not tell me about your whole Christmas holidays, but tell me about something you did one specific day, at a particular place, at a particular time. I want you to tell me as much as things as you can recall. Tell me everything that you can remember. It does not matter if it is not important things. We are first going to do a trial. Do you understand?’. Specific instructions about the required time frame (recent/remote memories) where then added. Recall was preceded by one training trials to verify that children understood the instructions. When given the cue-word, children had to recall as much details as possible (free recall

phase). When they had finished their narrative, we used a general probe to elicit the recall of further information: ‘Is there something else that you remember?’. This phase was then followed with specific probes: ‘When did this event take place? Where did this event take place?’. These probes were used to elicit the retrieval of further context information and were also used to ensure that the child understood that they had to recall a specific event. Subsequent phenomenological self-ratings which are often part of the CAI were not administered as our pilot study indicated that self-ratings were poorly understood and poorly reliable by the youngest children of our studied age span. The narratives of each participant were recorded to be subsequently transcribed. Recorded data was anonymized and securely stored to guarantee privacy. Recordings were used to transcribe each narrative, and the transcriptions were used to code autobiographical details in each narrative following the CAI protocol (Levine et al., 2002; Willoughby et al., 2012).

S2. Correlation between the phenomenological richness of episodic autobiographical recall and language comprehension.

We performed a pilot study on 28 children aged from 6 to 12 years. One of its goal was to investigate the relationship between autobiographical recall and language comprehension. Autobiographical recall was measured with the same CAI procedure as described in the article, but coding was performed with a TEMPau-like procedure (e.g., Piolino et al., 2007), which involves rating the phenomenological richness of recalled memories on a discrete scale based on phenomenological criteria (e.g., first-person perspective, spatial and temporal details, etc.). The fact that we did not use the same rating protocol (and when that is less dependent on language) limits the generalization of the findings of this pilot study to the current article. Still, they provide some evidence of a relative independence between phenomenological richness during recall (which is tapped by the number of recalled EAM details) and language comprehension. The TEMPau coding procedure as it is considerably faster than the CAI coding procedure and was thus used for time constraints relative to this pilot study. We thus measured a “Total Episodicity” score which shows the overall Episodicity rating of the subject across all of its recalled memories. Data collection and analysis was done with the assistance Prisca Beejadhur and Suzanne Kretz.

We examined the relation between Total Episodicity as measured with a TEMPau-like rating system and standard scores of the language comprehension subtest of the WISC using linear regressions in which Total Episodicity was the dependent variable. Total Episodicity was not associated with language comprehension from the WISC ($F=0.09$, $R2=0.01$, $p=0.74$). An association was also not found when controlling for language ($t=0.09$, $p=0.92$).

S3. Correlations between mean Framewise-Displacement (FD), EAM recall, and age

Variable	Correlation with mean FD
Age	-0.32, p=0.055
Total episodic details	-0.14, p=0.44
Total semantic details	-0.09, p=0.57

S4. Atlas edition procedure

Two regions were covered by two parcels each as there was no functional parcels covering them adequately: the lateral temporal gyrus (which was covered by a lateral fusiform gyrus parcel and a middle temporal gyrus parcel) and the medial temporal lobe (which was covered by an anterior parahippocampal gyrus parcel and a posterior parahippocampal gyrus parcel). As there was no ROI covering specifically the temporoparietal junction, we chose ROIs covering the temporoparietal junction and the left angular gyrus, a neighboring structure which is also an important correlate of autobiographical and episodic memory (Addis et al., 2017). Because these temporoparietal junction/angular gyrus ROIs were available only separately for the left and right hemispheres, we collapsed them across hemispheres to respect bilaterality as for the other ROIs. We verified that ROIs were not overlapping with each other. This was found only for the temporoparietal junction/angular gyrus ROI which overlapped with parts of the ROI corresponding to posterior tip of the medial temporal gyrus. The medial temporal gyrus ROI was hence edited to avoid overlapping.

The following ROIs were used to create the atlas (original names):

VENTRAL_MEDIAL_PREFRONTAL_CORTEX
DORSOMEDIAL_PREFRONTAL_CORTEX_anterior
VENTROLATERAL_PREFRONTAL_CORTEX
ANTERIOR_CINGULATE_CORTEX_dorsal
MIDDLE_TEMPORAL_GYRUS
INFERIOR_TEMPORAL_GYRUS_and_TEMPORAL_POLE
HIPPOCAMPUS
AMYGDALA
THALAMUS
131@MIST_197
148@MIST_197
FUSIFORM_GYRUS_lateral
POSTERIOR_CINGULATE_CORTEX
75@MIST_197
CEREBELLUM

Complementary analyses

These results show a hiatus between the developmental trajectories of the episodic and semantic aspects of autobiographical memory, as only episodic autobiographical details were positively correlated with age. Functional connectivity of the hippocampus, of neocortical regions (prefrontal, temporal regions), of the cerebellum and of the thalamus was related to episodic autobiographical recall in children. This shows that differences of functional connectivity at rest in the developing brain are related to differences in the capacity to recall episodic autobiographical memories within a large-scale cerebral network.

Complementary analyses

Functional connectivity was specific to episodic autobiographical memory, as it was not related to semantic autobiographical recall, or to episodic verbal recall. We additionally examined a potential contribution of functional connectivity to memory discrimination to investigate the specificity of the brain-behavior relationship between functional connectivity and episodic autobiographical recall.

Methods

Functional connectivity was predicted by the Memory Discrimination index. The same method as the one described in the paper was used.

Results

Functional connectivity was not predicted by the Memory Discrimination index.

Conclusion

Functional connectivity within a large-scale network is related to EAM, but to other components of episodic memory.

Chapter 4. General Discussion

Summary of the results

In this dissertation, we examined brain-behavior relationships between several components of episodic memory on the one hand and structural/functional features of the hippocampus and of connectivity networks involved in episodic memory on the other hand, during development. The main results were:

- **Part 1: Behavioral results**

  Aim 1: Examining the developmental trajectories and relationships between episodic memory components in the developing brain (Study 1).

  - Highlights:
    - Episodic memory components scores were positively correlated with age, except for recognition/item memory.
    - Age-related differences were linear, suggesting that all studied components (except recognition/item memory) have a protracted maturation and develop at a continuous rate.
    - Memory discrimination was behaviorally independent from other components of episodic memory.

- **Part 2: Hippocampal organization**

  Aim 2: Describing how the transversal (subfields) and longitudinal axes of hippocampal organization are related to episodic memory development (Studies 2 and 3).

  - Highlights:
    - Hippocampal subfields, reflecting the transversal (medial-lateral) axis of organization of the hippocampus, were specifically related to memory discrimination but not to other components of episodic memory (Study 2).

        - By contrast, the longitudinal organization of the hippocampus was related to episodic recall but not to memory discrimination (Study 3).
        - Thus, the two axes of hippocampal organization could contribute to distinct components of episodic memory during childhood.

- **Part 3: Cerebral connectivity**

  Aim 3: Describing how cerebral connectivity is related to episodic memory development (Studies 4 and 5).

    - Highlights:
        - The maturity of white matter tracts connecting neocortical regions, and neocortical regions with the MTL, was related to episodic memory recall during childhood. The contribution of tract maturity to episodic memory recall was similar between younger and older children (i.e., not moderated by age) (Study 4).
        - Functional connectivity within a large-scale network of cortical and subcortical regions was related to episodic autobiographical recall but not to other components of episodic memory. The relationship between functional connectivity and episodic memory was also not moderated by age (Study 5).

4.1 Developmental trajectories and relationships of episodic memory components

4.1.1 Protracted development of memory discrimination via pattern separation

Previous studies described important improvements of memory discrimination, the behavioral outcome of pattern separation, during the childhood amnesia period. An absence of age-related differences after this period for memory discrimination tasks involving the discrimination of single items has also been reported (Ngo et al., 2018, 2019). Thus, we expected to show more important age-related differences of memory discrimination in younger children compared to older children. As discussed in Study 1 and 2, our results rather suggest a protracted development of pattern separation (measured with memory discrimination) even when it involves the discrimination of simple items (see also Rollins & Cloude, 2018). Moreover, age-related differences of memory discrimination were best described by a linear model, suggesting that age-related differences could be caused by continuous rates of development in our studied age span. However, this could also be caused by an insufficient number of data points in young children that would have prevented us to detect specific patterns of age-related differences in early childhood. Thus, while the idea of a protracted development of pattern separation is uncontroversial, there is incongruent data regarding its development for the discrimination of single items, and its exact developmental trajectory remains to be further elucidated, for example with a longitudinal design. **Nevertheless, our results clearly show that pattern separation for the discrimination of single items has a more protracted development than previously reported.** If pattern separation for single items has a protracted development from early childhood to early adolescence, then **improvements of episodic memory after late childhood could partly be related to the development of basic pattern separation abilities**.

This protracted development of pattern separation is consistent with the fact that age-related structural differences of hippocampal subfields are observed after early childhood, as we also showed in Study 2. The correlation between age and memory discrimination was smaller than the correlation between age and episodic recall or episodic autobiographical memory (EAM) recall. However, this difference was not significant. The statistical power of the test that was used to assess differences between correlation coefficients is importantly impacted by sample size. Thus, if the development of pattern separation is protracted, but to a lesser extent than the development of episodic recall and EAM recall, we might have been unable to detect it. Future studies will larger sample sizes might characterize differences in the developmental trajectories of these episodic memory components.

4.1.2 Protracted development of episodic memory recall and episodic autobiographical recall

We found a protracted development of episodic recall and EAM recall, in line with previous findings (e.g., Ackerman, 1985; Bauer & Larkina, 2014; Picard et al., 2009, 2012; Piolino et al., 2007). For EAM, we expected to find more important age-related differences during the period of childhood amnesia, given that young children's autobiographical memories are particularly fragile. **Our results instead suggest a linear development of EAM recall**. This could be also be due to the same reasons as for pattern separation discussed above (sample size, insufficient number of young children). Further research is needed to determine this question. The protracted development of EAM and of episodic recall are likely related to the protracted maturation of some of their neural correlates, as we suggested for episodic recall and structural connectivity (Study 4 and discussion section 4.3).

4.1.3 Behavioral independence of memory discrimination

Memory discrimination was behaviorally independent from other episodic memory components (Study 1). Previous studies have reported an absence of correlation between memory discrimination and relational memory performance in children (Ngo

et al., 2018, 2019). **We further confirm the idea of a behavioral independence of memory discrimination (and thus pattern separation) with other episodic memory components** by showing that memory discrimination performance did not correlate with episodic recall and EAM recall. This independence is further suggested by the specific and non-overlapping associations we found regarding the neural correlates of memory discrimination and of the other episodic memory components (Studies 2-5).

The fact that memory discrimination is behaviorally independent from other episodic memory components does not entail that the recall episodic information does not depend on efficient pattern separation abilities. For example, as pattern separation happens during encoding, the ability to recall already pattern-separated autobiographical memories do not need to depend on the pattern separation abilities of the individual when they perform recall. Future studies could further examine the relationships between pattern separation and other episodic memory components, for example with longitudinal designs examining if the pattern separation abilities of children at time point A predicts their recall abilities at time point B. Such designs could provide valuable information on the potential role of impaired pattern separation in the rapid forgetting of early memories. Interestingly, memory discrimination has been shown to correlate with verbal episodic recall in older adults, but not younger adults (Stark et al., 2010, 2013). The specificity of the correlation between episodic recall and memory discrimination in older adults could indicate that, with aging, performance at episodic memory components covary because they share common factors of variance (e.g., expressing senescence), which are absent in children.

To summarize, we provide new results regarding the development and relations of episodic memory components in a developmental period ranging from early childhood to early adolescence. Overall, these results support previous suggestions on the usefulness of using a multi-component approach to study episodic memory development (Ngo, 2019; Ngo et al., 2018, 2019; Raj & Bell, 2010; Sluzenski et al., 2006)**.**

4.2 The transversal and longitudinal axes of hippocampal organization are related with distinct components of episodic memory

Hippocampal subfields reflect the **transversal** axis of organization of the hippocampus as they are cellular layers stretching over the longitudinal axis but superposed over the medial-lateral direction. Hippocampal subfields are not independent units within the hippocampus but are differentially connected with each other following precise connectivity patterns (e.g., trisynaptic and monosynaptic circuits). Functional differences over the transversal axis of the hippocampus (i.e. between-subfields functional differences) are related to differences of between-subfields connectivity (e.g., the function of DG cells is related to their CA3 inputs) (Gómez & Edgin, 2016; Lavenex & Banta Lavenex, 2013; Schlichting et al., 2021). Thus, the transversal axis of organization of the hippocampus is often considered to convey information about its internal connectivity (Riggins et al., 2018; Wael et al., 2018). On the other hand, the **longitudinal axis** of the hippocampus reflects less the internal wiring of the hippocampus than the connectivity of hippocampal the hippocampus with other brain areas (Poppenk et al., 2013; Przeździk et al., 2019; Strange et al., 2014). Indeed, functional changes over the longitudinal axis are related to differences of connectivity of with the rest of the brain (Poppenk et al., 2013; Przeździk et al., 2019; Strange et al., 2014). Thus, if the transversal axis of organization mainly represents the internal circuitry of the hippocampus, the longitudinal axis mainly represents how the hippocampus is integrated to cortical networks.

4.2.1 The transversal axis is specifically related to pattern separation in children

We showed (Study 2) that volumes of hippocampal subfields CA3 and subiculum were related with inter-individual differences in memory discrimination. Hippocampal subfields volumes were not associated with other episodic memory components.

This relationship between the transversal axis of the hippocampus and pattern separation (measured with memory discrimination) contrasts with our examination of the longitudinal axis of organization of the hippocampus (Study 3). The organization of the longitudinal axis was not related to memory discrimination, but was associated with episodic recall. **Thus, we found distinct patterns of brain-behavior relationships between the transversal and longitudinal axes of the hippocampus.**

These differences are consistent with the idea that the transversal axis represents variations in internal connectivity, while the longitudinal axis represents variations in external connectivity. Given that pattern separation is a neural computation mechanism mainly performed within the hippocampus by subfields interacting with each other, it is expected that differences in pattern separation abilities (i.e., memory discrimination) would preferentially relate to structural properties of the transversal axis, rather than on longitudinal axis differences describing the integration of the hippocampus to cortical areas. However, given the importance of the hippocampus for episodic memory, the fact that we found no associations between specific hippocampal subfields and other components of episodic memory do not indicate that structural properties of hippocampal subfields (e.g., volumes) are only related to pattern separation. Indeed, associations between subfields volumes and other components of episodic memory, such as relational memory (Lee et al., 2014), source memory (Canada et al., 2021; Riggins et al., 2018), memory for temporal order (Canada et al., 2020), statistical learning and associative inference (Schlichting et al., 2017), have been described during development. Some of these episodic memory components also importantly rely on the maturity of neocortical regions such as the PFC, e.g. for source memory (Keresztes et al., 2017). Nevertheless, our results suggest that structural properties of specific hippocampal subfields are more likely to covary with individual differences of pattern separation abilities than with individual differences in episodic recall.

Episodic recall (as assessed with tests similar to the Long-Delay Free Recall of the CVLT-c used in our study) was reported to be correlated with subfields volumes by some studies in older adults (e.g., Zammit et al., 2017) and by a study on adolescents

(Tamnes et al., 2014). It is possible that the relations between subfields volumes and verbal recall are less prevalent during early development. As mentioned in section 4.1, episodic recall has been shown to correlate with memory discrimination in older adults but not in young adults (Stark et al., 2010, 2013). This illustrates differences in the cognitive characteristics and thus neural correlates of episodic memory components over the lifespan. However, it is also possible that episodic recall covaries with subfields volumes during development, but that our study was too underpowered to detect this association. Nevertheless, the two latter explanations further highlight the specificity of the association between subfields volumes and memory discrimination/pattern separation during childhood reported here.

4.2.2 The longitudinal axis follows a gradual organization which is related to episodic memory recall

The results of Study 3 showed for the first time in the context of development that the longitudinal specialization of the hippocampus could be described in terms of gradual changes, rather than with segregated anterior/posterior or head/body/tail parcels separated by sharp transitions. Because we showed that individual differences in the organization of these gradual changes on the longitudinal axis were related to individual differences in episodic recall, describing the longitudinal organization of the hippocampus in terms of gradual changes of connectivity is functionally meaningful. An important avenue of future research is thus to elaborate further on methods enabling the description of gradual structural or functional changes on the longitudinal axis of the hippocampus, rather than averaging these changes into segregated parcels (when they are indeed gradual, as for connectivity).

The organization of this longitudinal connectivity gradient did not show age-related differences. However, this does not necessarily mean that the longitudinal axis of organization, as measured with connectivity gradients, do not mature in the age 4-12 period (see discussion of Study 3). The anterior-posterior specialization of the hippocampus was reported to be largely absent in neonates (Howell et al., 2020). This finding indicates that the connectivity gradient of the hippocampus is likely to mature rapidly during the very first years of life, given that we reported that the connectivity

gradients of 4-years-olds were not significantly different from the connectivity gradients of 12-years-olds. If age-related differences are to be found in 4-12 range, they were not sufficiently important to be detected by our study. Thus, they are likely less important than those occurring during the very first years of life. Interestingly, age-related differences of the connectivity of the anterior and posterior hippocampus (studied with segregated parcels) have been reported during early childhood and adolescence (Blankenship et al., 2017; Warren et al., 2021). **Our results could however suggest that the organization of connectivity differences on the longitudinal axis (described by the longitudinal connectivity gradient) could remain overall stable from early childhood to adolescence, e.g. because connectivity changes in the anterior and posterior areas occur at similar rates.** Our study was seminal in the examination of this possibility and suffered from a small sample size; thus, this issue needs to be further studied.

4.2.3 Integrating the transversal and longitudinal axes

Overall, our results show **the complementarity of studying the two axes of hippocampal organization to uncover their relations with distinct components of episodic memory in the context of development.** However, these axes are obviously not independent from each other. As subfields stretch over the longitudinal axis, their inputs and outputs change as a function of their location on this axis. For example, subfields in the anterior hippocampus have been shown to be preferentially connected to the perirhinal cortex (located in the anterior MTL), while subfields in the posterior hippocampus have been shown to be connected with the parahippocampal cortex (located in the posterior MTL) (Poppenk et al., 2013). In adults, subfields have been shown to exhibit distinct functional connectivity patterns with the MTL; importantly, these connectivity patterns varied within each subfield over the longitudinal axis (Dalton, McCormick, De Luca, et al., 2019; Dalton, McCormick, & Maguire, 2019). These between-subfields connectivity differences (transversal axis) and within-subfields differences (longitudinal axis) illustrate the relations between the two axes of hippocampal organization.

A study from Wael et al. (2018) using both microstructural information (T1w/T2w ratio) and functional connectivity data demonstrated that the hippocampal subfields themselves could be described with a longitudinal functional connectivity gradient representing the longitudinal organization of their connectivity with the cortex, and with a microstructural transversal gradient representing their infolding. Besides the whole hippocampus, longitudinal and transversal gradients are thus also present at the finer-grained scale of the hippocampal subfields. Moreover, it is likely that episodic memory components related to specific subfields, such as pattern separation, also show within-subfields differences over the longitudinal axis. For example, pattern separation could vary over the longitudinal axis as a function of the coarse or sharp nature of the information to be pattern-separated. The fact that the posterior hippocampus is associated with sharper, more specific representations, suggest that it would preferentially be associated with pattern separation, while the anterior hippocampus would be associated with pattern completion, which is a generalization process (Poppenk et al., 2013). **Therefore, even if we showed that distinct episodic memory components were associated with distinct axes of hippocampal organization, a fundamental open question is how these two axes of organization relate to each other during development.**

Distinct developmental dynamics are likely to be involved in the maturation of the transversal and longitudinal axes. Given that the longitudinal and transversal gradients are also found at the subfield level (Wael et al., 2018), hippocampal maturation is likely the product of the complex interactions between several modes of organization which both reflect changes of internal (between-subfields) and external (hippocampo-cortical) connectivity which are integrated at multiple scales. **Combined, the maturation of these two axes of organization would represent how experience-dependent changes reflect the way the hippocampus "learns how to remember" during childhood (Alberini & Travaglia, 2017). An important avenue of future research is thus to further estimate the developmental trajectories and the relations between the transversal and longitudinal axes of hippocampal organization on episodic memory development.**

4.3 Connectivity within brain networks and episodic memory

While the hippocampus is pivotal to episodic memory, its importance is related to its central position in a network of brain areas which are the source and destination of its inputs and outputs (Ranganath & Ritchey, 2012; Riggins et al., 2020). Consequently, the integration of the hippocampus to this large-scale network underpinning memory-guided behavior has been shown play an important role in episodic memory development (Geng et al., 2019, 2021; Mabbott et al., 2009; Ngo et al., 2017; Riggins et al., 2016, 2020; Samara et al., 2018). The protracted maturation of connectivity within this network could be an important factor contributing to childhood amnesia and to its progressive offset: the immaturity of connectivity between episodic memory regions could contribute to the fragility of early memories (Josselyn & Frankland, 2012; Riggins et al., 2020). Indeed, immature structural or functional connectivity could cause impaired information processing because brain regions that interact together for memory functions communicate less efficiently. Still, many aspects of the contribution of connectivity between regions involved in episodic memory during development remain unstudied or poorly understood. **Our results provide new insights on the relation between structural and functional connectivity and episodic memory development and function.**

4.3.1 The maturity of white matter microstructure is related to episodic memory recall

Previous studies have indicated that structural connectivity between the MTL/hippocampus and the PFC was related to episodic memory function in adults and older children. However the association between late-maturing tracts connecting the PFC and other neocortical regions (parietal cortex) and episodic memory during early childhood is unclear. The only evidence so far was an absence of relation between

episodic recall and hippocampus/PFC structural connectivity, suggesting that prefrontal-limbic connectivity could be too immature during early childhood to be associated with episodic memory performance (Ngo et al., 2017).

On the contrary, we showed that the maturity of the structural connectivity between prefronto-limbic and prefronto-parietal regions was related with episodic recall in a sample of 4-12 years old children (Study 4). The microstructural maturity of late-maturing tracts, such as the Uncinate Fasciculus (UF) and the dorsal Cingulum Bundle (CB), was assessed with a multivariate representation of the association of their microstructure with age. The obtained "tract maturity scores" were significantly correlated with distinct aspects of episodic memory, i.e. Short-Delay Free Recall for the dorsal CB, and Long-Delay Free and Cued Recall for the UF. We did not find a moderating effect of age on the relation between tract maturity and episodic recall performance. These results can be considered as evidence against the assumption that age-related differences of episodic memory are importantly related to neocortical maturation from middle childhood and/or adolescence onwards but not or less during prior development (discussed and reviewed in Ghetti and Bunge, 2012). On the contrary, **they suggest an early specialization of white matter tracts for distinct aspects of episodic recall,** since the length of delay in episodic recall tasks influenced of tract-behavior associations. Our results could thus be seen as an invitation **to reconsider how the contribution of structural connectivity to episodic memory development unfolds during childhood, particularly for late-maturing white matter tracts.**

4.3.2 The functional organization of the brain at rest is related to episodic autobiographical memory recall

We found that the **functional organization of large-scale brain networks at rest was related with the ability to recall rich episodic autobiographical memories during development** (Study 5). Thus, besides the role of hippocampal connectivity (which we also found in some cases) or of the DMN, we also provide evidence regarding an important functional role of other regions, such as the cerebellum. We

also found that the recall of episodic details in recent memories was more associated with functional connectivity than the recall of episodic details in recent memories. **As childhood amnesia involves the progressive forgetting of distant memories over the course of childhood** (Bauer & Larkina, 2014b; Peterson, 2021), **the functional organization of the brain at rest could convey meaningful information about childhood amnesia and its progressive offset, which should be further examined by future studies.**

4.3.3 Relations between structural and functional connectivity

Structural connectivity was specifically associated with episodic recall but not with other components of memory, while functional connectivity was specifically associated with EAM recall but not with other components of memory. Our result show specific associations between connectivity and episodic memory components as a result of the modality with which connectivity is studied. But this should obviously not be taken as evidence of an absence of relation between structural connectivity and EAM recall, or an absence of relation between functional connectivity and episodic recall during childhood. For example, in adults, the microstructure of white matter tracts has been associated with EAM recall, particularly the fornix (Hodgetts et al., 2017), which we did not replicate. Although there is no data in the literature on the structural connectivity correlates of EAM in children, there are no theoretical reasons to suppose that the Fornix microstructure should not convey information about the ability to recall autobiographical memories in children, particularly given its early maturation (Dubois et al., 2008). Further research is necessary to describe this relation, eventually by using more “advanced” assessments of white matter microstructure than those derived from diffusion tensor imaging methods.

The relations between structural and functional connectivity are complex and poorly understood. Structural and functional connectivity patterns have been reported to be either correlated with each other or independent, depending on the methodological approach (Baum et al., 2020; Fjell et al., 2017; Ford & Kensinger, 2014; Uddin, 2013). Thus, an important question is how these two forms of connectivity are related with each other during development.

In adults, age-related differences of functional and structural connectivity have been reported to be independent from each other (Fjell et al., 2017). Such relations (or absence thereof) remain to be described during childhood relatively to episodic memory development.

Overall, our structural and functional connectivity results suggest a specialization of connectivity between specific regions for distinct components of episodic memory, and for distinct aspects of these components, in children.

4.4 Specificity of brain-behavior relationships and their development

The present works brings new data describing specific, non-overlapping brain-behavior relationships related to episodic memory during childhood. Based on the previous sections of the discussion, we summarize in Table 4 below these relationships and indicate the likeliness that they are truly specific (i.e., are our negative results likely indicators of an absence of relation). Our results are also summarized Figure 7.

Brain-behavior relationship	**Hippocampal subfields (transversal axis of hippocampal organization)**	**Hippocampal connectivity gradient (longitudinal axis of hippocampal organization)**	**Prefrontal-limbic and prefrontal-parietal structural connectivity**	**Functional connectivity within a large-scale brain network**	**Likely to be a specific association ?**
Pattern separation	Yes	No	No	No	Overall likely as PS has been shown to be strongly related with specific subfields.
Episodic verbal recall (short-long delay, free or cued)	No	Yes	Yes	No	Probably also related to some functional connectivity between regions.
Episodic autobiographical memory	Not tested	Not tested	No	Yes	Probably also related to structural connectivity between regions.

Table 4. Brain-behavior relationships found in our studies and likeliness that these associations are truly specific (i.e., is a true association likely whereas we described negative results).

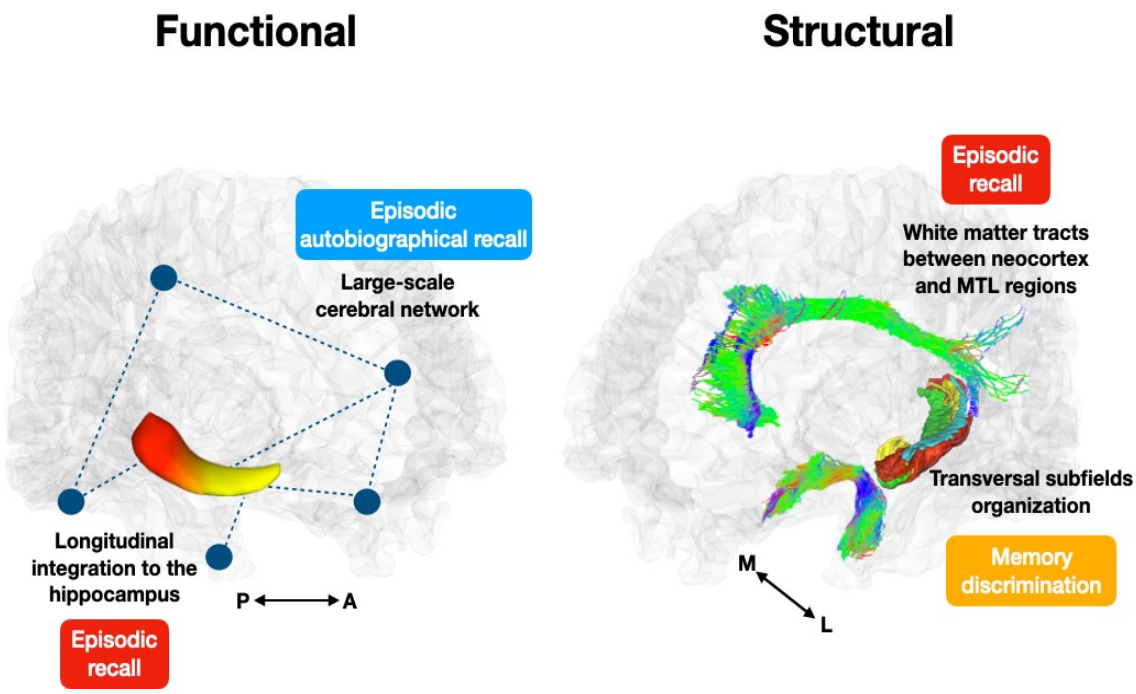

Figure 7. Summary of our results. Left: Functional results. The hippocampus is organized on its longitudinal axis as a gradient spanning the anterior-posterior direction (from yellow to red in the image). Differences in this gradual organization are related to differences of episodic recall. Brain areas involved in episodic memory (blue dots) are functionally connected with each other and with the hippocampus (dotted lines). Functional connectivity is related to episodic autobiographical recall. **Right: Structural results.** On its transversal axis, the hippocampus is composed of distinct subfields (red:CA1; green: subiculum; Yellow: CA23; Cyan: DG). Volumetric differences of these subfields are associated with memory discrimination performance, the behavioral proxy of pattern separation. The microstructure of white matter tracts such as the dorsal Cingulum Bundle and the Uncinate Fasciculus, represented on the figure, are associated with episodic recall.P-A: posterior-anterior axis. M-L: medial-lateral axis. Structures are not to scale.

Conclusion 1. These results suggest a specialization of distinct features of the brain (transversal and longitudinal organizations of the hippocampus; structural connectivity between neocortical and limbic regions; functional connectivity within a large-scale brain network) for distinct components of episodic memory in children. We provide new insights about the relations between episodic memory components and their neural correlates in the developing brain.

As discussed in the previous sections, some of the negative results indicating an absence of relation between a given brain feature (e.g., prefrontal-limbic structural connectivity) and a given episodic memory component (e.g., EAM recall) could be idiosyncrasies of our dataset. Future studies might find positive relations were we described an absence of relations. This could be particularly the case for structural and functional connectivity, given that studying connectivity means studying an important possible range of relations between brain areas. Still, **the specific brain-behavior associations found in our work are indications of ways in which the brain could specialize for distinct episodic memory components during childhood.**

Besides this specialization found in children, an important question is how **these specific brain-behavior associations are influenced by age, i.e. if they differ between younger and older children**, which is discussed below.

4.4.1 Influence of age on brain-behavior associations

Besides describing brain-behavior associations specific to episodic memory components, our second main objective was to describe the potential influence of age on these relations. Our theoretical contributions (Introduction section) led us to formulate the hypothesis that some brain-behavior relations could be moderated by age during development. Indeed, **if the development of episodic memory is multi-stepped with important improvements during early childhood, then distinct patterns of brain-behavior relations between children during and after childhood amnesia** (or between younger and older children of our sample more generally) could be interpreted as neuroimaging "signatures" of immature episodic memory.

We hypothesized in our introduction (section 1.4, and 1.6.3) that episodic memory components could contribute to the overall development of episodic memory with distinct timings. Because the age-related trajectories of episodic memory components were all linear and not significantly different, except for recognition memory, **we only partly verified this hypothesis**.

Further research is necessary to assess potential differences in the developmental trajectories of pattern separation, episodic recall, and episodic autobiographical recall, in order to contrast the differences of their putative contributions to the overall development of EM.

We also **hypothesized that age-related differences of episodic recall and of EAM recall could be related to different neural correlates as a function of age** (e.g., hippocampal maturation in the early years of childhood, neocortical maturation in the later years) because of the heterogeneous maturation of the brain. **Our results rather show that brain-behavior relationships for episodic recall and EAM recall are similar between younger and older children. However, in the case of pattern separation and the hippocampus, we evidenced a moderating effect of age.**

4.4.2 Two developmental dynamics?

In regard with what precedes and the existing literature, we suggest that our results **could describe two main dynamics in the development of episodic memory.**

The moderating effect of age on the relationship between pattern separation and the hippocampus reported in Study 2 adds to previous findings **showing non-linearities in hippocampal development** (Canada et al., 2019; Riggins et al., 2018, for experimental findings; Newcombe et al., 2007; Olson & Newcombe, 2013, for discussions and theoretical models). For example, volumes of given subfields have been shown to decrease or augment with age depending on the developmental period (Canada et al., 2021). This, in turn, affects the nature of brain-behavior relations between episodic memory performance (pattern separation, but also source memory) and subfields volumes (Canada et al., 2018; Riggins et al., 2018). For example, for younger children, a bigger volume for a given subfield could be associated with better memory performance, while for older children, the opposite relation could be found, or conversely (e.g., Study 2, Canada et al., 2018; Riggins et al., 2018). Qualitative changes of brain-behavior relationships for hippocampal-neocortical connectivity have also been reported during childhood (Riggins et al., 2016). Overall, there is converging evidence showing that the relation between the maturation of the hippocampus and episodic memory development differs as a function

of age. **In other words, there are qualitative differences in the brain-behavior relationships of younger and older children when it comes to the hippocampus**, and particularly its transversal organization. These qualitative differences could be caused by distinct developmental factors intervening with distinct timings, such as neurogenesis (in the DG), myelination, or synaptic pruning.

Therefore, a dynamic of development could be specific to the hippocampus, and particularly to its transversal (subfields) organization, leading to qualitatively changes of brain-behavior relationships with age.

By contrast, the fact that we did not find age-moderated relations between episodic recall and EAM recall on the one hand, and connectivity on the other hand, suggest that differences in these brain-behavior relationships between younger and older children in our sample are not qualitatively different, but solely quantitatively different (for example, increased efficiency of transmission of neuronal signal reflected by increased fractional anisotropy could be related with increased memory recall, and this relation does not qualitatively change over development). However, as previously discussed, the absence of this age-moderating effects reported in our study could be caused by methodological limitations such as the insufficient number of 4-6 years old children (i.e., during the childhood amnesia period) in our final samples. As our results show an absence of age-moderated effects in the age 4-12 period, we can hypothesize that if connectivity-behavior relationships are moderated by age, these qualitative changes might occur either mostly during early development (e.g., age 2-6 years), either during late adolescence or adulthood (as suggested by Østby et al. (2012) for functional connectivity and discussed in Study 5). Still, these results could suggest that for episodic recall and EAM recall, younger children **could use a similar but more immature version of functional brain networks compared to older children** (e.g., Mecklinger et al., 2010), at least approximately during the age 4-12 period.

A second dynamic could thus concern connectivity within large-scale brain networks, which association with **some episodic memory components** (episodic recall and EAM recall, but potentially others) in the age 4-12 period would consist mainly in **quantitative and linear changes. The developmental trajectories of episodic memory components, and of episodic memory as a whole, might depend from the interaction between these two developmental dynamics.**

4.4.3 Implications for childhood amnesia

What do our results bring to the understanding of childhood amnesia? Childhood amnesia has been related to a multitude of factors, mainly in relation with hippocampal maturation (e.g., Alberini & Travaglia, 2017; Donato et al., 2021; Josselyn & Frankland, 2012; Li et al., 2014). The role of the protracted maturation of the connectivity of the hippocampus with neocortical regions is also hypothesized, but its remains unclear (Josselyn & Frankland, 2012; Riggins et al., 2020). Based on the results of our dissertation and on the current literature, we propose the hypothesis that hippocampal maturation and the maturation of connectivity between extra-hippocampal (e.g. neocortical) areas could contribute distinctively to childhood amnesia. As qualitative differences in brain-behavior relationships have frequently been reported for the hippocampus, it is possible that **hippocampal maturation contributes to the offset of childhood amnesia through an approximation of a threshold function**: a “sufficient maturity state” of the hippocampus has to be reached for memories to lose their fragility inherent to childhood amnesia. On the other hand, **connectivity between extra-hippocampal regions could contribute to the offset of childhood amnesia through a linear function**: more efficient communication between brain areas could be associated to more efficient encoding and retrieval of episodic information, meaning that memories are progressively less likely to be rapidly forgotten because they are more complex and more easily retrieved. This distinction is speculative and could be seen as a program for future research.

Conclusion 2. **Two distinct developmental dynamics, one specific to the hippocampus, and one to brain networks, might be differentially related to the development of distinct episodic memory components and thus to childhood amnesia. This conclusion is speculative and provisional given that many aspects of episodic memory development remain insufficiently studied.**

To summarize, **our results show a specialization of distinct aspects of the brain for distinct components of episodic memory. They show that some previously understudied or unstudied aspects (such as the role of structural/functional connectivity) are factors related to memory development and function. This underlines the interest of studying other factors than hippocampal maturation or cortical maturation in the prism of its relationship with the hippocampus. Still, our results also emphasize the particular role of hippocampal maturation. In regards with our results and the current literature, we suggest that episodic memory development and childhood amnesia could be related to two developmental dynamics, one specific to the hippocampus, and one for connectivity within brain networks.**

4.5 Limitations and future directions

4.5.1 Limitations

Our work has several limitations. One of our goals was to study a broad developmental period (4-12 years) to describe the progressive ontogeny of episodic memory. This age range was chosen to include both children during and after the period of infantile amnesia and children old enough to describe the eventual point at which some components of episodic memory reach adult-like maturation. An alternative to our acquisition strategy might have been to separate the acquisition of data into distinct age groups (e.g., 4 year-olds, 6-year-olds, 8-year-olds; or children of age 4-6 year, 8-10, and 12-14). Another possibility would have been not to separate the subjects into age groups but to study a sample covering a smaller age range (e.g., 4-8 years). These two alternatives share similar advantages: reducing the studied age range would have reduced some of the variability due to age by having a larger number of data points for each age.

These approaches were not chosen for both theoretic and pragmatic reasons. In the case of a narrower age range (e.g. 4-8), our conclusions about memory development would have been more limited by the lack of data regarding later development as they would have covered less of the hypothesized developmental periods. In case of a group design, missing data between age groups can obscure interpretation of what happens between these age groups and prevent the use of polynomial or logarithmic age models to describe age-related differences with more precision. However, another reason that weighted in our decision to study a broad, continuous age range was related to timing. Recruiting children, especially young children, to participate in neuroimaging protocols is time-consuming, as it is less easy to recruit children than adults. Studying specific age groups or a narrower age range would have meant that we would have had to narrow down the potential number of studied children over a limited period of time, taking into account the fact that data attrition is high in children. Indeed, our data acquisition process took a year and a half and began after several

months of design, planning, and pilot testing; yet, doctoral studies must be completed in a limited time frame.

Another major limitation of our work is the sample size. Although we recruited 50 children, missing data and exclusion of data to preserve satisfactory data quality led to a sample size that was quite small in the cases of Study 2 and 3. For the other studies, the number of subjects was between 30 and 40, which may be low by current standards in the adult neuroimaging literature, but can be deemed satisfying for developmental studies. Still, we potentially lacked statistical power to describe some effects, which limits the generalizability of our findings.

One way to avoid data attrition would have been to narrow the focus of our investigations. Our research protocol included, for neuroimaging, 4 different modalities with an acquisition time of 45 minutes. For behavioral assessments, our protocol included 3 memory tests plus a control test, whose total average duration was 45 minutes to one hour. Of course, it is not easy for children to participate for almost two hours in tasks requiring high levels of concentration and attention. A shorter protocol focusing on fewer aspects of memory development and brain maturation would probably have led to less data attrition.

However, it is possible to consider that, independently of the duration of our protocol, one of its limitation comes from the fact that it covers too many different aspects of episodic memory development. Given that episodic memory development is underpinned by a multitude of factors at the cerebral and cognitive levels (as we have discussed in the Introduction of this dissertation), we have chosen to develop a data acquisition protocol partially representing this multiplicity. Nevertheless, for an equivalent amount of acquired data, investigating different aspects of fewer components of episodic memory would have allowed us to elaborate more specific conclusions, but this greater specificity would also have been a limitation of this alternative approach.

Another limitation of our work is its cross-sectional design. Age-related differences described in cross-sectional designs result from a combination of 'true' maturational changes across developmental time, and differences related to between-subject variability. Longitudinal designs reduce confounding factors related to between-subject variability by highlighting how within-subject variability is related to age, describing age-related changes. All estimates of developmental effects made by cross-sectional designs are therefore statistical approximations that can sometimes lead to conflicting results between studies. However, given the ease of this type of design compared to longitudinal designs, they remain the most widely used in developmental neuroscience.

4.5.2 Future directions

Besides these methodological or theoretical limitations, our findings provide new data on the relationship between episodic memory development and brain maturation and highlight a number of promising future directions.

We showed that the transversal and longitudinal axes of hippocampal organization were related with distinct aspects of episodic memory. Understanding how these two axes of variability are related to each other (i.e., between-subfields, and within the longitudinal axis at the level of the whole hippocampus or within each subfield) and how these relations unfold over development is critical to understand hippocampal maturation and hence episodic memory. So far, few studies in adults and even fewer in children have investigated these relations. The fact that adult studies have found longitudinal and transversal gradients at the subfield level shows that hippocampal maturation can be addressed at more fine-grained level of description which lack during development so far. We provided the first description of the gradual organization of the hippocampus on its longitudinal axis during childhood, but how such gradient organization is found within hippocampal subfields remain to be described during development. It is likely that these fine-grained levels of description would bring important information on the contribution of the hippocampus to memory development. For example, we showed that pattern separation-related abilities (memory

discrimination) was associated with specific hippocampal subfields. It is possible that the contributions of subfields to pattern separation/completion vary as a function of the longitudinal axis based on the coarse or sharp nature of the information to be pattern-separated or completed. Studying this question in the context of development would be an major illustration of how the multivariate maturation of the hippocampus contributes to the ontogeny of episodic memory.

We showed the relation of structural and functional connectivity with episodic memory function during development. Further research is necessary to determine how the maturation of brain networks contribute to episodic memory development. We showed that features of the brain's default architecture (resting-state functional connectivity) was related to children's ability to recall episodic autobiographical memories, i.e. the memories affected by childhood amnesia. Thus patterns in the brain's 'default' functional organization reflect the ability of children to recall the memories they have. Studying further this relation in early childhood might also provide clues about how this relates with memories they will lose. For example, a longitudinal designs measuring the relation between young children's ability to recall autobiographical memories, as well as this relation as assessed a few years later, might provide important information on how differences in the brain functional organization covary with differences in the ability to recall one's past. Relatedly, such longitudinal designs could also beneficially applied to the structural/functional study of the hippocampus (subfields and anterior-posterior organization).

Finally, an important future direction is the applications of the study of "normal" episodic memory development to pathological contexts. During our PhD program, we were involved in several projects studying episodic memory function in several pediatric pathologies, as well as, in some cases, pathologies in adults. These works are summarized in the appendix of this dissertation (Appendix 1).

5. Conclusion

Little is known about the development of the different components of episodic memory in relation to brain maturation. In this thesis, we sought to shed light on this issue by adopting a multi-component approach. This approach aimed to show the relationships between the components of episodic memory and their neural correlates in the context of development. It also aimed to highlight potential developmental differences in brain-behavior relationships between episodic memory components and their neural correlates. Our results revealed that episodic memory components were associated with different neural correlates. In particular, the transversal and longitudinal axes of the hippocampus were associated with different components, pattern separation and episodic recall respectively. In addition, functional and structural connectivity were also associated with different components, episodic recall and episodic autobiographical recall respectively. These results provide new insights about the specialization of the brain for different components of episodic memory during childhood. We also found that brain-behavior relationships were not qualitatively different for the association between connectivity and episodic recall or episodic autobiographical recall. This could suggest that the brain networks used by younger children to recall information are overall similar but more immature versions of the networks used by older children. By contrast, the relationship of hippocampal subfields (transversal organization) with pattern separation was, in the case of the subiculum, moderated by age. This suggests qualitative differences in brain-behavior relationships in the case of hippocampal subfields. Distinct developmental dynamics for the hippocampus and large-scale brain networks might contribute differently to the maturation of episodic memory components, and play complementary roles in the offset of childhood amnesia.

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List of figures

Figures in the studies follow the numbering system specific to each study. Only figures following the numbering system of the entire thesis (in the Introduction, Methods, and Discussion chapters) are listed here.

List of tables

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Appendix

Appendix I: application to pathologies.

I report here the abstracts of several studies evaluating the components of episodic memory in the context of different pathologies in children or adults. I participated in the methodological design and co-supervised these studies with Marion Noulhiane. These studies were conducted by Master students (Master in Neuropsychology of the University of Paris, Master in Neuropsychology of the University of Grenoble, Master..

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Clara Champy – Master 2 Neuropsychologie, Université de Paris.
Episodic memory difficulties in children born extremely premature: a model for studying the long-term effect of neonatal hypoxia.
Supervision: M. Noulhiane, **co-supervision**: A. Bouyeure
Abstract : Children born very prematurely show an alteration of episodic memory in relation with hippocampal atrophy. This atrophy results from neonatal hypoxic phenomena due to the immaturity of the lungs and the presence of apneas characteristic of the preterm infant. The objectives of this study were to replicate the results of pre-existing studies concerning the alteration of episodic memory but with a specific interest in a population of very premature children, i.e. before 28 weeks of amenorrhea, and to investigate their autobiographical episodic memory capacities. Six very preterm infants aged 4 years 11 months to 11 years 1 month and six age- and sex-matched control participants were therefore recruited and completed memory tests (the CVLT-C and an episodic autobiographical memory task). Nonparametric statistical analyses revealed lower performance than the control group during the learning phase of the CVLT-C, during immediate recall and delayed recall but not during the recognition task. These results could reflect an alteration in the volume of the hippocampus, involved in recollection, and a preservation of the perirhinal cortex involved in the feeling of familiarity. Furthermore, the episodic autobiographical memory narratives of the extreme preterm infants contained less temporal detail than the memory narratives of the control group, which could indicate a disruption of the developmental trajectory of episodic autobiographical memory also related to a

reduction in hippocampal volume. These hypotheses would need to be tested in future brain imaging and behavioral studies with larger numbers of participants.

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Eliot Gerretsen - Master 2 Neuropsychologie et Neurosciences Cliniques, Université Grenoble-Alpes.

Mnemonic Discrimination and Item Memory Capacities in Children with Temporal Lobe Epilepsy and Roland Paroxysmal Epilepsy.

Supervision: M. Noulhiane, **co-supervision** : A. Bouyeure.

Abstract : During childhood, temporal lobe epilepsy and epilepsy with rolandic paroxysms can alter the functioning of the hippocampus and thus affect the development of episodic memory. Episodic memory involves different memory processes, some of which evolve later in relation to the prolonged development of certain subfields, such as the dentate gyrus, the seat of neoneurogenesis, whose maturation is closely linked to the emergence of episodic memory around the age of 7 years because of its capacity to perform pattern separation, i.e. the orthogonalization of similar representations, which reduces interference between memories. Conversely, the extrahippocampal capacity for item memory would develop earlier. Given the location of the epileptogenic focus in temporal lobe epilepsy and the impairment of memory consolidation in rolandic paroxysmal epilepsy, the present study sought to demonstrate a disturbance in neoneurogenesis and thus in the capacity for pattern separation, measured by a lure discrimination task, in children with temporal lobe epilepsy or epilepsy with rolandic paroxysms compared to a control group, opposed to a preservation of item memory. The results showed a deleterious effect of epilepsy on the global success of the task, but not on the item memory taken individually, which was successful in both patients and controls, nor on pattern separation, even if its efficiency was demonstrated in controls and not in patients.

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Gaelle Bleuzen - Master 2 Neuropsychologie, Université de Paris.

Mémoire épisodique et Syndrome de Fatigue Chronique : évaluation via une tâche de pattern separation.

Supervision: M. Noulhiane, **co-supervision**: A. Bouyeure

Abstract: Objective. The preliminary study presented here suggests to assess episodic memory (EM) and particularly the process of discriminating highly similar but non identical informations in memory (i.e pattern separation, PS) in an adult population with a Chronic Fatigue Syndrome (CFS). The other goal of this study was also to disentangle the link between memory performance and individual factors as the subject's psychological state or their fatigue. Methods. After a standard neuropsychological evaluation to screen cognitive
functions, a computerized task of PS has been proposed to CFS patients. Questionnaires investigating anxiety and depression as well as a subjective evaluation of fatigue in daily life were also administrated to the participants. Results. The pattern separation task partially permitted to distinguish CFS participants from controls over lure discrimation. Different response patterns could be identified within the experimental group. The PS performance was correlated to subjective mental fatigue. Conclusions. The present study shows that refining EM evaluation is possible, and in particular the process of PS, for patients who could not be differentiated with traditional neuropsychological EM evaluations. The intragroup differences highlighted here put forward that the memory profile of CFS patients is heterogenous. They also question the influence of several individual factors as perceived fatigue on memory for these patients.

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Laura Rioult - Master STAPS, Université de Rouen Normandie.

CrossFit : une influence sur la mémoire épisodique ?

Supervision : M. Noulhiane, F. Lemaitre. **Collaboration** : A. Bouyeure.

Abstract : While physical activity (PA) has long been proposed to slow the cognitive and physical decline associated with aging, few studies have examined the impact of PA on memory systems in young adults. Recently, intermittent physical activities have been the most coveted by athletes looking for an effective way to improve their performance. Several studies have shown that memory improves during a single

session of moderate exercise, but few studies have focused on high-intensity intermittent exercise. In young adults, the effects of such intense intermittent exercise on cognitive performance are conflicting. It is therefore important to ask whether popular high-intensity intermittent exercise such as CrossFit can improve episodic memory (EM) abilities in young adults or, on the contrary, damage key brain structures of memory. Two groups of participants were recruited: a control group (GT, n=24; age=21.58±0.88; PA level=3.15±3.13) and an experimental group (GE) (n=16; age=22.12±1.55; PA level=4.10±2.73). Participants in the GE completed two EM tests: the Pattern Separation performed before (T0) and after (T1) a high-intensity CrossFit session and the California Verbal Learning Test performed post hoc. The results showed no significant difference between T0 and T1 ($X2(1)=1.704$, $p=0.192$, Kendall's W -31239.573). This research indicates that CrossFit does not have an acute effect on episodic memory, either positive or negative, on EM. However, it would be interesting to further investigate the effects of this type of training in the short and long term on memory.

Appendix II: Dissemination of the results and science outreach

The findings presented in this dissertation were presented and discussed during several international conferences, listed below:

Talks

- Bouyeure, A., Champy, S., Poiret, C., Sandesh, P. Noulhiane, M. *Functional connectivity correlates of autobiographical memory in the developing brain.* OHBM 2021, Virtual Conference.
- Poiret, C., Bouyeure, A., Patil, S., Duchesnay, E., Grigis, A., Lemaître, F., Noulhiane, M. *Viewpoint Equivariance: Are 3D CapsNets Any Good for Hippocampal Segmentation?.* OHBM 2021, Virtual Conference.
- Bouyeure, A., Chauvin, R., Haak, K.V., Beckmann, C.F.., Noulhiane, M. *Functional organization of the hippocampus on its anteroposterior axis during childhood.* OHBM 2020, Virtual Conference.
- Bouyeure, A., Patil, S., Noulhiane, M. *Hippocampal subfields volume predict memory discrimination performance in the developping brain.* OHBM 2020, Virtual Conference.
- Bouyeure, A., Bekha, D., Hertz-Pannier, L., Noulhiane, M. *White matter microstructure is associated to episodic memory performance in the developping brain.* European Brain and Behaviour Society 2019, Prague, Czech Republic.
- Bouyeure, A., Bekha, D., Noulhiane, M. *Resting-state functional connectivity is correlated to episodic memory performance in the developping brain.* Society for Neurosciences 2018, San Diego, CA, USA.
- Bouyeure A., Bekha D., Germanaud D, Delattre V, Rivière D., Mangin JF, Chiron C, Hertz-Pannier L, Noulhiane M. *Sulcal morphology of the medial temporal lobe in children and adolescents.* OHBM 2017, Vancouver, Canada.
- Bouyeure A., Bekha D., Germanaud D, Delattre V, Rivière D., Mangin JF, Chiron C, Hertz-Pannier L, Noulhiane M. *Sulcal morphology of the medial temporal lobe in healthy preterm infants.* OHBM 2017, Vancouver, Canada.

I was also involved in several science outreach activities during my PhD student years, listed below:

Science outreach

- **Semaine du Cerveau**
  Moderator of Jessica Dubois' general public conference during a science outreach event organized by the CEA.
- **Cognitive sciences on the stage**
  General public conference in a Parisian theater.
- **Les Savanturiers**
  Scientific workshops and activities in an elementary school of the Paris region.
- **Projet Declics**
  Workshop about scientific research in a Parisian highschool.

Résumé long en français

Introduction - La mémoire épisodique (ME) est le système mnésique dédié à la mémorisation à long-terme d'évènements précis avec leur contexte spatio-temporel, cognitif, perceptif et émotionnel. Les souvenirs épisodiques sont donc notamment ceux qui composent notre histoire personnelle, notre autobiographie. A l'âge adulte, il nous reste peu de souvenirs d'avant l'âge de 6 ans : ce phénomène, appelé « amnésie de l'enfance », illustre le développement considérable de la ME au cours des premières années de la vie. En effet, de nombreuses études ont montré que les jeunes enfants étaient capables de former des souvenirs épisodiques ; ces souvenirs des premières années de la vie sont donc manquants durant le développement ultérieur parce qu'ils sont sujets à un oubli accéléré au cours de l'enfance. Au niveau cérébral, l'hippocampe, structure diencéphalique bilatérale, est le principal corrélat neuronal de la ME. Plusieurs études ont mis en évidence un parallèle entre la maturation prolongée de l'hippocampe au cours de l'enfance, tant sur les plans anatomique que fonctionnel, et le développement progressif des compétences en ME du point de vue cognitif. Cependant, à un niveau plus fin de description, la ME s'avère être une fonction cognitive multiforme comprenant des « composantes » cognitives dédiée à des processus distincts (mémoire relationnelle, séparation de motif, mémoire de la source…). Ces composantes de la ME sont sous-tendues par des corrélats cérébraux différents. Le développement global de la ME durant l'enfance pourrait donc résulter de trajectoires développementales propres à ses composantes. En effet, la maturation cérébrale étant hétérogène, le développement de la ME pourrait résulter de rythmes de maturation différents des composantes de la ME, en relation avec des rythmes de maturation différents des corrélats cérébraux de ses composantes. La question de la contribution et de la spécificité des composantes de la ME dans le développement global de la ME, notamment en relation avec le phénomène d'amnésie de l'enfance, reste cependant mal comprise dans la littérature actuelle sur le développement, où les composantes de la ME sont le plus souvent étudiées indépendamment les unes des autres. Dans cette thèse, notre objectif était donc de suppléer à cette carence en examinant le développement général de la ME durant l'enfance via l'étude des associations entre plusieurs composantes cognitives de la ME et leurs corrélats cérébraux à travers différents stades de développement. Cette approche multi-composantes permettrait ainsi d'étudier dans un cadre méthodologique et théorique unifié différents aspects contribuant au développement de la ME. Pour ce faire, nous avons commencé par élaborer une contribution théorique sur les corrélats cérébraux de la ME et leur développement. Celle-ci a mis en évidence l'existence de deux principaux types de corrélats cérébraux essentiels pour le développement de la ME : premièrement, la maturation de l'hippocampe, tant sur son axe transversal (sous-champs hippocampiques) que longitudinal (spécialisation antéro-postérieure de l'hippocampe) ; deuxièmement, la connectivité au sein d'un réseau cérébral à large échelle comprenant l'hippocampe, ainsi que des régions néocorticales (notamment le cortex préfrontal), corticales (cervelet) et sous-corticales. Notre étude s'est donc focalisée sur la caractérisation de trois composantes distinctes de la ME, choisies en raison de la différence entre leurs corrélats cérébraux et leurs trajectoires développementales putatives : 1) la séparation de motif, processus permettant d'assurer la spécificité des souvenirs à l'encodage, dont il a été montré chez l'adulte qu'il était réalisé spécifiquement par les sous-champs de l'hippocampe ; 2) le rappel épisodique, processus permettant d'assurer la récupération d'informations épisodiques, dont il a été montré chez l'adulte qu'il était réalisé par des interactions hippocampo-préfrontales ; 3) le rappel épisodique autobiographique, processus permettant d'assurer la récupération d'informations épisodiques de nature autobiographique (souvenirs personnels), dont il a été montré chez l'adulte qu'il était réalisé par les interactions au sein d'un large réseau comprenant l'hippocampe ainsi que des régions corticales et sous-corticales. L'objectif de cette thèse était donc : (1) de mettre en évidence des corrélats cerveau-comportement spécifiques à chaque composante étudiée de la ME, afin de décrire la spécialisation du cerveau pour différentes composantes

cognitives de la ME durant l'enfance ; (2) de décrire les éventuels effets de l'âge sur ces corrélats cerveau-comportement, afin de décrire l'influence du développement sur cette spécialisation cérébrale. Le but de cette approche multi-composante était donc de montrer comment le cerveau se spécialise durant l'enfance pour différentes composantes de la ME, et comment cette spécialisation cérébrale évolue au cours de l'enfance, éclairant le développement général de la ME et potentiellement des facteurs pouvant contribuer au phénomène d'amnésie de l'enfance.

Méthode - Nous avons acquis des données comportementales de ME et de neuroimagerie multimodale chez 50 enfants âgés de 4 à 12 ans avec un design transversal. Cette tranche d'âge a été choisie dans la mesure où elle permettait d'étudier tant des enfants dans la période de l'amnésie de l'enfance (avant 6 ans) que des enfants hors de la période de l'amnésie de l'enfance (après 6 ans). Notre protocole comportemental incluait un test de rappel épisodique (California Verbal Learning Test for children), un test de rappel épisodique-autobiographique (tâche de rappel autobiographique basé sur un indiçage), et un test de séparation de motifs (Memory Similarity Task). Notre protocole de neuroimagerie incluait plusieurs séquences d'IRM 3T afin de caractériser différents aspects du développement cérébral : une séquence anatomique T1 cerveau entier, une séquence anatomique T2 à haute résolution centrée sur l'hippocampe pour permettre la segmentation des sous-champs hippocampiques, une séquence de d'IRM fonctionnelle au repos pour examiner la connectivité fonctionnelle entre les corrélats de la ME, et une séquence d'IRM de diffusion pour examiner la connectivité structurelle entre les corrélats de la ME. Nous avons également réalisé une contribution méthodologique développant une nouvelle méthode pour l'influence de facteurs anatomique sur la localisation des structures hippocampiques et parahippocampiques, un préalable à notre étude dans la mesure où celle-ci comportait la segmentation anatomique de l'hippocampe.

Résultats – La première partie de nos résultats portait sur la description des trajectoires développementales des composantes de la ME au niveau comportemental, et sur les relations entre les différentes composantes de la ME. Nos résultats ont mis en évidence que les performances à l'ensemble des composantes de la ME étudiées (séparation de motif, rappel épisodique, rappel épisodique autobiographique) étaient corrélées avec l'âge, montrant une amélioration progressive des compétences en ME durant le développement pour différentes composantes. Ces trajectoires développementales étaient linéaires et n'étaient pas significativement différentes, suggérant un développement continu et globalement similaire des composantes de la ME dans la tranche d'âge étudiée. Par ailleurs, les performances de rappel épisodique et de rappel épisodique autobiographique étaient corrélées entre elles, mais les performances de séparation de motif n'étaient pas corrélées avec les performance de rappel épisodique et de rappel épisodique autobiographique. La deuxième partie de nos résultats s'est focalisée sur la relation entre maturation de l'hippocampe et développement des composantes de la ME. Dans une première sous-partie, nous avons étudié la relation entre l'organisation transversale de l'hippocampe en via les volumes des sous-champs hippocampiques, obtenus par segmentation manuelle de l'hippocampe, et les performances des enfants aux tests évaluant différentes composantes de la ME. Nos résultats ont montré que les performances en séparation de motif était corrélée à l'âge dans la population étudiée (4-12 ans), et que les performances en séparation de motif étaient associées aux volumes de sous-champs hippocampiques spécifiques (subiculum et CA3), et que cette relation était modérée par l'âge dans le cas du subiculum. En revanche, le volume des sous-champs hippocampiques n'était pas associé aux performances aux tests évaluant les autres composantes de la ME (rappel épisodique, rappel épisodique autobiographique). Dans une deuxième sous-partie, nous avons étudié la relation entre l'organisation longitudinale de l'hippocampe, examinée avec une méthode de connectopie décrivant le gradient de connectivité fonctionnelle hippocampe sur son axe antéropostérieur, et les composantes de la ME. Nos résultats ont montré que l'organisation de l'hippocampe sur son axe longitudinal était associé aux performances de rappel épisodique, mais pas à la séparation de motif et au rappel épisodique autobiographique. Ces relations n'étaient pas modérées par l'âge. La troisième partie de nos résultats s'est focalisé sur la relation entre connectivité cérébrale et développement des composantes de la ME. Dans une première sous-partie, nos résultats ont montré que la maturation de la connectivité structurelle entre les régions médiotemporales (comprenant l'hippocampe) et des régions néocorticales (cortex préfrontal et pariétal) était associée au développement des performances de rappel épisodique, mais pas de rappel épisodique autobiographique ou de la séparation de motif. Ces relations

n'étaient pas modérées par l'âge. Dans une deuxième sous-partie, nos résultats ont montré que la connectivité fonctionnelle au sein d'un large réseau comprenant des régions néocorticales, corticales et sous-corticales était associé au rappel épisodique autobiographique, mais pas au rappel épisodique ou à la séparation de motif. Ces relations n'étaient pas modérées par l'âge.

Discussion - Nos résultats contribuent à la compréhension du développement de la ME pendant l'enfance de trois manières principales. Premièrement, nos résultats apportent de nouvelles informations sur le développement des composantes de la ME au cours de l'enfance d'un point de vue comportemental. Contrairement à certaines données de la littérature, nous montrons que les compétences en séparation de motif ont un développement continu dans la tranche d'âge 4-12 ans, soit un développement plus prolongé que rapporté précédemment. Nous confirmons par ailleurs l'indépendance comportementale de la séparation de motif relativement à d'autres composantes de la ME, probablement causée par la spécificité de ses corrélats cérébraux, comme montré dans la deuxième partie de nos résultats. Deuxièmement, nos résultats mettent en évidence chez l'enfant une spécialisation des corrélats cérébraux de la ME pour différents types de composantes de la ME. Ces résultats contribuent ainsi à la compréhension des bases cérébrales de la ME dans les mesure où ils proposent les premières descriptions des corrélats cérébraux du rappel épisodique autobiographique, et parmi les première descriptions des corrélats cérébraux de la séparation de motif et du rappel épisodique dans une tranche d'âge incluant des jeunes enfants. Cette spécialisation cérébrale était observable au sein même de l'hippocampe, dans la mesure où son organisation transversale (sous-champs) était associée aux performances de séparation de motif et pas aux autres composantes de la ME, alors que son organisation longitudinale (gradient antéropostérieur) était associée aux performances de rappel épisodique, mais pas aux autres composantes de la ME. Cette spécialisation était également observable en terme de connectivité entre les corrélats de la ME, dans la mesure où la connectivité structurelle hippocampo-préfrontale et préfronto-pariétale était associée au rappel épisodique, mais pas aux autres composantes de la ME, et que la connectivité fonctionnelle était associée au rappel épisodique autobiographique, mais pas aux autres composantes de la ME. L'examen de ces résultats dans le contexte de la littérature chez l'enfant et l'adulte suggère que la séparation de motif dépend bien spécifiquement des sous-champs hippocampiques, comme montré dans notre étude ainsi que dans le reste de la littérature. En revanche, la spécificité de la connectivité structurelle et fonctionnelle pour le rappel épisodique et épisodique autobiographique respectivement pourraient être des idiosyncrasies de notre travail, dans la mesure où la littérature chez l'adulte (faute de littérature disponible chez l'enfant) suggère une association entre connectivité structurelle et rappel épisodique autobiographique, et connectivité fonctionnelle et rappel épisodique. Néanmoins, ces résultats dans leur ensemble démontrent que le cerveau est spécialisé dès l'enfance pour différentes composantes de la ME, démontrant des relations spécifiques entre corrélats cérébraux et composantes de la ME. Troisièmement, l'étude de l'influence de l'âge sur les relations entre composantes de la ME et leurs corrélats cérébraux suggère deux dynamiques développementales différentes à l'œuvre dans cette spécialisation. D'une part, une dynamique développementale serait propre à l'hippocampe, dans la mesure où nous avons trouvé un effet de modération de l'âge sur les relations entre séparation de motif et sous-champs hippocampiques. Dans le contexte de la littérature actuelle montrant de semblables effets de modération de l'âge sur les relations entre maturation de l'hippocampes et performances de ME, nous suggérons qu'il est une dynamique développementale spécifique à l'hippocampe dans laquelle le développement de la ME est associée à des changements quantitatifs avec l'âge (amélioration des compétences mnésiques en relation avec la maturation cérébrale), ainsi qu'à des changements qualitatifs (changement de la nature des relations entre développement de la ME et maturation cérébrale avec l'âge, illustrant l'effet de facteurs de maturation cérébrale différents avec le développement). Ces changements qualitatifs pourrait être liés à des facteurs de développements différents avec le temps développemental, tel que la neurogenèse, la synaptogenèse, ou l'élagage synaptique. Par contraste, l'absence d'effet de modération de l'âge sur les relations entre connectivité cérébrale et composantes de la ME suggère une autre dynamique développementale propre aux réseau de la ME à large-échelle, dans lesquels les changements seraient quantitatifs et non qualitatifs. En d'autres termes, les enfants plus jeunes utiliseraient une version similaire, mais plus immature, des réseaux cérébraux comprenant des régions néocorticales, corticales et sous-corticales, comparés aux enfants plus âgés. Des dynamiques développementales différentes, l'une spécifique à l'hippocampe et l'autre à la connectivité entre aires cérébrales, pourraient donc contribuer ensemble au

développement des composantes de la ME et, de la sorte, à l’arrêt progressif de l'amnésie de l’enfance. Dans l’ensemble, les résultats de cette thèse apportent de nouveaux éléments à notre compréhension des facteurs contribuant au développement de la ME pendant l’enfance en lien avec la maturation cérébrale.