

Memory and the developing brain: From description to explanation with innovation in methods



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ABSTRACT

Recent advances in human cognitive neuroscience show great promise in extending our understanding of the neural basis of memory development. We briefly review the current state of knowledge, highlighting that most work has focused on describing the neural correlates of memory in cross-sectional studies. We then delineate three examples of the application of innovative methods in addressing questions that go beyond description, towards a mechanistic understanding of memory development. First, structural brain imaging and the harmonization of measurements across laboratories may uncover ways in which the maturation of the brain constrains the development of specific aspects of memory. Second, longitudinal designs and sophisticated modeling of the data may identify age-driven changes and the factors that determine individual developmental trajectories. Third, recording memory-related activity directly from the developing brain presents an unprecedented opportunity to examine how distinct brain structures support memory in real time. Finally, the growing prevalence of data sharing offers additional means to tackle questions that demand large-scale datasets, ambitious designs, and access to rare samples. We propose that the use of such innovative methods will move our understanding of memory development from a focus on describing trends to explaining the causal factors that shape behavior.

1. Introduction

The ability to remember detailed information about past experiences is crucial for human existence and continues to develop from childhood into adulthood. Researchers in the field of cognitive development, observing dramatic changes in memory performance from childhood to adulthood, have grappled with two important research goals: to characterize memory development and to identify the sources of such development (Bjorklund and Schneider, 1996; Ghetti and Angelini, 2008; Schneider and Ornstein, 2015; Schneider and Pressley, 1989). In characterizing memory development with behavioral data, researchers have observed a dichotomy, with relative stability from middle childhood to adulthood on tasks of memory recognition that require few contextual details and protracted development (i.e., gains continuing after middle childhood) on tasks that require retention of detailed information (Keresztes et al., 2017; Ngo et al., 2018; Ofen, 2012; Ofen et al., 2016). Regarding the sources of such development, researchers have highlighted the importance of related cognitive

constructs in explaining individual differences in memory performance, such as working memory capacity, prior knowledge, and metacognitive knowledge of mnemonic strategies and the use of such strategies (Schneider and Ornstein, 2015; Schneider and Pressley, 1989). Advances in neuroimaging methodologies have propelled investigation into the neural basis of age-related gains in memory performance. The guiding logic of the neuroscientific study of memory development is that researchers can use the brain to link known factors such as chronological age to observable memory outcomes, and ultimately to use measures from the brain to develop a mechanistic understanding of the links between age and memory performance. Alongside an increase in behavioral investigations of memory development, the use of neuroimaging techniques to probe memory and its development has risen sharply in recent years (Ofen, 2012) (Fig. 1). This increase in the prevalence of studies of brain and behavior conducted with participants across a wide age range holds the potential to uncover mechanisms of developmental change, prompting timely evaluation of outstanding inquiries and best practices in the developmental cognitive

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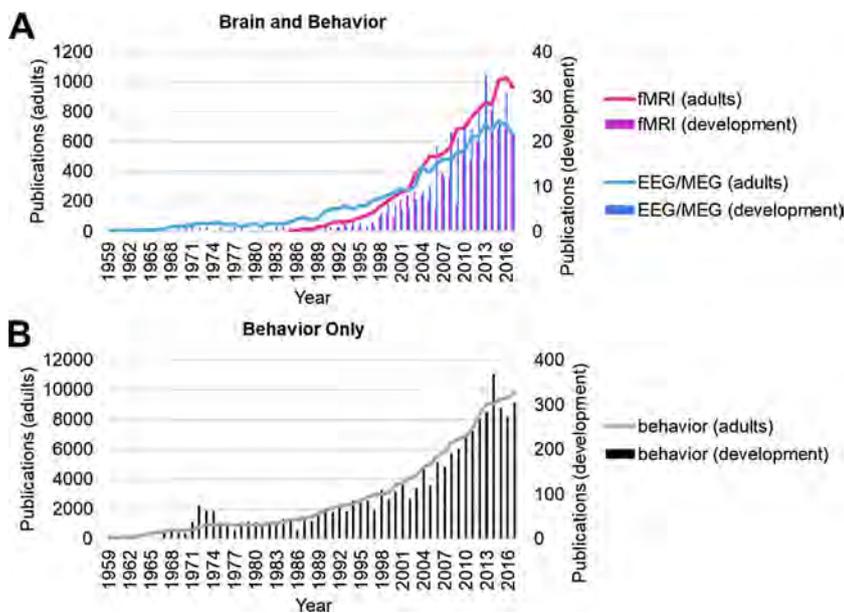


Fig. 1. Number of publications on memory in adults and developing samples, by methodology, 1959-2017. (A) Number of publications in PubMed using the search term “memory” (excluding “working”) and either: (1) “fMRI,” “child,” “development;” (2) “fMRI” (excluding “child,” “development”); (3) “EEG” or “MEG” and “child,” “development” (excluding “iEEG,” “ECoG,” “sEEG”); or (4) “EEG” or “MEG” (excluding “child,” “development,” “iEEG,” “ECoG,” “sEEG”). The number of publications in adults is plotted as lines on the left axis and the number of publications conducted in developing samples is plotted as bars on the right axis at 1:30 scale. Note that the earliest search result was dated 1959. EEG, electroencephalogram; MEG, magnetoencephalogram. (B) Number of publications in PubMed using the search term “memory” (excluding “working”) and either: (1) “child,” “development” (excluding “fMRI,” “EEG,” “MEG,” “iEEG,” “ECoG,” “sEEG”); or (2) (excluding “fMRI,” “EEG,” “MEG,” “iEEG,” “ECoG,” “sEEG,” “child,” “development”). As in (A), the number of publications in adults is plotted as lines on the left axis and the number of publications conducted in developing samples is plotted as bars on the right axis at 1:30 scale. Note that this search returned entries in adults that date back to 1842, not shown.

neuroscience of memory.

In this review, we start with a brief overview of the current state of knowledge about the neural basis of memory development as it pertains to future directions (Section 2). We then provide three examples in the use of innovation in structural imaging, longitudinal design, and direct brain recordings (Section 3), and briefly consider opportunities which are made feasible with data sharing and novel analytical approaches (Section 4). Taken together, we argue that the careful use of innovative methods will yield mechanistic explanations of *how* the development of the brain drives the development of memory. We do not aim to provide an exhaustive review of current questions or currently available methodologies. Instead, our goal is to demonstrate the process by which careful use of innovative methodologies can provide insights into specific questions and advance our understanding of the development of memory. Although the examples we provide concern research into the development of memory, the principle of tailoring a question to be addressed with the use of innovative methods can be applied broadly to the study of other cognitive functions. We aim to illustrate the ways in which brain data may be used to investigate specific questions that propel us forward from describing age differences in the neural correlates of memory to testing whether (and how) the development of the brain drives the development of memory.

2. Using functional MRI (fMRI) to map the neural correlates of memory development

Many neuroimaging studies of memory development have utilized functional MRI (fMRI) to assess age differences in memory-related brain activations gleaned from the contrast between functional brain maps across different task conditions, as measured in participants across a wide age range. In adults, memory-related activations are consistently found across several brain regions, including the medial temporal lobes (MTL) and prefrontal cortex (PFC) (Brewer et al., 1998; Kim, 2011; Schacter and Wagner, 1999; Spaniol et al., 2009). Investigations of age differences in functional neuroimaging measures within these regions evidence both relative stability and differences across age groups, which partly depend on the specific task—comparable to the dichotomy observed in behavior. For example, in the first study that employed a rapid event-related fMRI design to assess age differences in memory-related activations predictive of subsequent memory formation (i.e., contrasting trials that were later remembered versus forgotten; Fig. 2A), Ofen and colleagues demonstrated differential developmental

trajectories in the PFC and MTL (Ofen et al., 2007). The characterization of age differences within the PFC and MTL, including the hippocampus, continues to be a focus of research today.

The PFC appears to continue its development well beyond age 8 to support improved memory outcomes from childhood through young adulthood (Ofen et al., 2007). Specifically, the inferior frontal gyrus consistently shows age-related increases in activation during the encoding and retrieval of remembered stimuli (Ofen et al., 2012; Tang et al., 2018). Furthermore, it was recently found that different subregions of the PFC show dissociable developmental patterns, with the nearby middle/superior frontal gyrus and medial frontal regions showing concurrent age-related increases in deactivation (Tang et al., 2018) (Fig. 2B). Taken together, findings of age differences in PFC activation patterns suggest that the development of attentional and strategic control processes involved in the encoding and retrieval of detailed representations of experiences is key to predicting age-related differences in memory performance.

In the MTL, extant literature points to more subtle patterns of age differences. For example, in the same study that indicated increased PFC activations during the encoding of scenes that were subsequently remembered, activations extracted from regions in the MTL did not differ by age (Ofen et al., 2007). Similarly, stability in memory-related activations in the MTL across age groups has been observed in studies utilizing other memory tasks (Shing et al., 2016). However, age differences in MTL activations have been shown in certain cases, such as when a subset of scene stimuli selected for higher complexity were analyzed (Chai et al., 2010), when analyses focused on memory for recollective details (Ghetti et al., 2010), or when analyses were limited a priori to the anterior or posterior MTL (DeMaster and Ghetti, 2013). These studies suggest that stimuli, task characteristics, and the resolution of the region under investigation are important factors in delineating developmental effects in the MTL and understanding the ways by which MTL maturation supports memory development.

Specific challenges for interpreting differences in the functional correlates of memory development stem from shifting theoretical perspectives about the ‘elements’ of memory (Brunec et al., 2018; Cohen and Eichenbaum, 1993; Henke, 2010; Lee et al., 2012; Nadel and Hardt, 2011; Shimamura et al., 1991; Tulving, 1983)—i.e., characterizing memory as a critical step in studying its developmental trajectory. For example, agreement on theoretical perspective about the functional organization of memory along the long axis of the hippocampus has proven quite elusive (Duncan and Schlichting, 2018; Poppenk et al.,

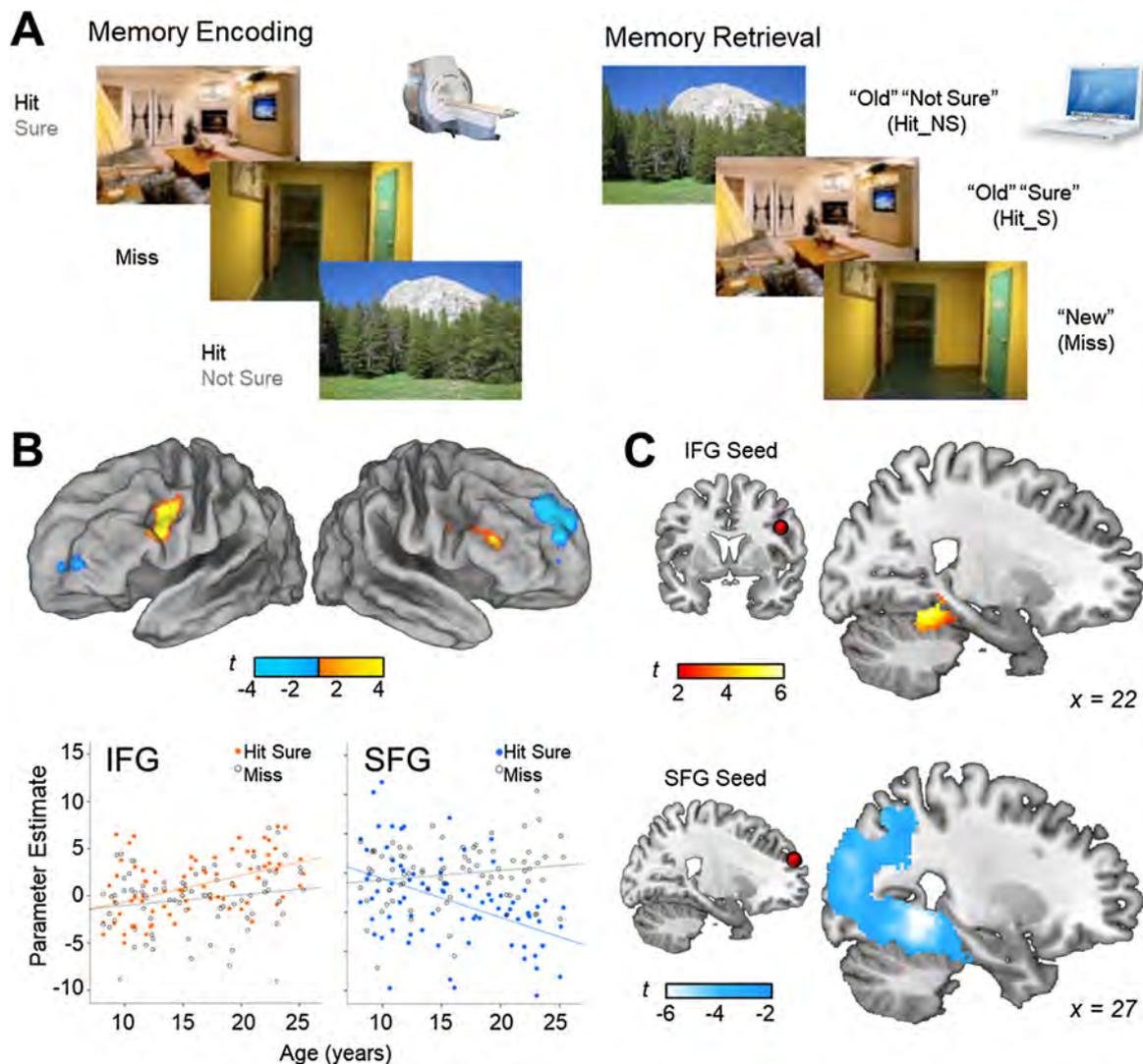


Fig. 2. Using a subsequent memory paradigm and fMRI to map the neural correlates of memory development. (A) Subsequent memory paradigm. Participants studied indoor and outdoor scenes while fMRI data were collected, and then completed a self-paced recognition test after a delay. Encoding trials were labeled as Hit or Miss based on whether the scenes were later correctly recognized as “Old” (Hit) or incorrectly judged as “New” (Miss). Hit trials were further classified as Hit Sure (Hit_S) or Hit Not Sure (Hit_NS) based on the “Sure”/“Not Sure” rating given at test. Positive subsequent memory effects and negative subsequent memory effects were calculated by the Hit_S > Miss and Miss > Hit_S contrasts. (B) PFC regions showing age-related differences in subsequent memory effects. Positive subsequent memory effects in bilateral inferior frontal gyrus (IFG) increased with age, while negative effects in bilateral superior frontal gyrus (SFG) increased with age. The significance threshold for the t-maps shown on top is $p < 0.05$, corrected. Orange, positive effects; blue, negative effects. Adapted with permission from (Tang et al., 2018). (C) PFC regions showing age-related differences in the functional connectivity linked to memory formation. Connectivity between the IFG and parahippocampal gyrus (PHG) increased with age, while anti-correlated connectivity between the SFG and PHG increased with age. The significance threshold for the t-maps is $p < 0.05$, corrected. Orange, positive effects; blue, negative effects. Adapted with permission from (Tang et al., 2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2013; Strange et al., 2014). Some argue for a gradient along the long axis of the hippocampus, with the anterior region supporting coarse or gist-like memory representations and the posterior region supporting more detailed representations (Poppenk et al., 2013). Others suggest a distinction between the integration and separation of information in the same regions, governed by temporally distinct cellular events or ‘coding schemas’ (Duncan and Schlichting, 2018). Yet, others suggest that the anterior/posterior distinction may simply reflect the need for flexibility in memory retrieval (DeMaster et al., 2016). In going through this specific example, one can appreciate the many unknowns that limit robust interpretation of the neural correlates of memory in cross-sectional samples. Striving to reach agreement across laboratories on a conceptual framework and operationalization of the best practices to assess different aspects of memory is critical for adequate interpretation of developmental differences.

2.1. Using fMRI to go beyond regional brain mapping of memory development

Although investigating developmental effects within brain regions has been productive, using this approach does not provide insight into age differences in functional connectivity between regions. Earlier reports demonstrated increased functional coupling between the inferior frontal gyrus and MTL with age during memory encoding (Menon et al., 2005) and retrieval (Ofen et al., 2012; Paz-Alonso et al., 2013). In recent years, investigators are increasingly adopting network-level methods and proposing network-based descriptions of the neural substrates of memory development. Indeed, recent work demonstrated that age-related differences in functional coupling between the PFC and MTL partially account for age-related increases in memory performance (Tang et al., 2018) (Fig. 2C). By demonstrating not only age-related

differences in functional coupling, but also a predictive relationship between such coupling and behavior, these reports illuminate the characterization of neural networks in describing and understanding memory development.

In addition to measuring brain function during memory-related tasks, there is growing popularity in characterizing the brain's organization into networks 'at rest'. Using such methods, one can identify task-positive and task-negative networks—i.e., sets of interconnected regions defined based on studies in which task-induced activation would typically either increase or decrease compared to an 'at rest' baseline (Fox et al., 2005; Fransson, 2005; Kim et al., 2010; Vincent et al., 2006). Interestingly, age differences in the connectivity profiles of these networks are commonly found, prompting an interest in linking age differences in 'at rest' brain networks to performance on a range of cognitive tasks, including memory (Barber et al., 2013; Betzel et al., 2014; Chai et al., 2014b; Fair et al., 2007; Hwang et al., 2013). Among others, main findings indicate age-related increases in connectivity within task-positive networks, as well as in anticorrelations between task-positive and task-negative networks (Blankenship et al., 2017; Chai et al., 2014a, b; Tang et al., 2018). These studies further underscore the relevance of characterizing functional connectivity patterns in understanding memory development.

An important reason for the growing popularity of studying neural networks by measuring the brain 'at rest' is that this approach makes it possible to test aspects of brain development in very young children, even toddlers and babies, who cannot complete complex memory tasks in the scanner. Indeed, recent years have witnessed more studies assessing the neural correlates of memory in young children by linking functional brain measures gathered 'at rest' with performance on behavioral tasks completed in the laboratory (Blankenship et al., 2017; Riggins et al., 2016). Findings from these studies indicate early age-related dissociations, with 4-year-olds exhibiting an opposite pattern of correlation between memory performance and activation in regions within versus outside a postulated 'hippocampal memory network' than 6-year-olds (Riggins et al., 2016). By considering neural networks 'at rest', these studies suggest that early memory development is linked to shifts in the functional relationship between memory-related regions, providing evidence that extends above and beyond regional activations. These notions, if replicated and validated using longitudinal designs, may prove instrumental in moving us towards an explanation of the factors governing developmental change in memory.

Overall, with the use of innovative analyses of fMRI data, including multivariate voxel pattern analysis or inter-subject cross correlation, it will become possible to tackle questions that will take us from describing age-related trends in brain function that map onto age-related trends in memory performance and move into to a more mechanistic understanding of memory development. In Section 3, we provide specific examples of outstanding inquiries and best practices in the use of other innovative approaches to take investigations in the developmental cognitive neuroscience of memory in that direction.

3. Innovative methods: what should we aim for?

Below we provide three examples of outstanding inquiries that, given the innovative applications of currently available methods and recent advances in human neuroscientific techniques, may now be addressed. We first provide a brief description of the scope of each question, followed by the proposed innovation in methodology that is best suited to address it. Each example offers a proposal to propel our understanding of memory development from description to mechanistic explanation, with the goal of constructing predictive models and identifying causal links between brain development and memory development.

3.1. Linking brain development to cognitive development: maturation of the hippocampus

A central aim of developmental cognitive neuroscience is to demonstrate that brain development provides endogenous constraints on cognitive abilities. Considered under the purview of memory and given the critical role of the hippocampus in memory, we may ask whether (and how) hippocampal maturation supports the development of memory.

Reliable and valid estimates of brain structures, such as hippocampal volume, can be used to address the question of how hippocampal maturation supports age-related gains in memory performance. Indeed, prior work supports the notion that individual differences in hippocampal volume are related to individual differences in memory performance, and that these relationships differ by age and specific aspect of memory tested (Keresztes et al., 2018; Lavenex and Lavenex, 2013; Van Petten, 2004). A key advantage of structural imaging approaches, as compared to functional measures of hippocampal activation, is that structural measures are not based on the performance of a specific task (or the brain 'at rest'). However, the question of whether (and how) hippocampal development drives memory development remains untested, and the related evidence in humans remains sparse.

The first step in addressing this question is to characterize age differences in hippocampal structure. In a sense, the field must agree on a means to reliably measure hippocampal volume to capture hippocampal maturation. Although postmortem studies in primates (Jabes et al., 2010, 2011) and humans (Abraham et al., 2010; Insausti et al., 2010) suggest that the hippocampus undergoes protracted structural changes over development, and that hippocampal total volume differs over the adult lifespan (Raz et al., 2010, 2005) and in certain clinical populations (Schuff et al., 2009), variability in total hippocampal volume appears to be unrelated to age across development (Gogtay et al., 2006). The hippocampus, however, is a complex structure composed of cytoarchitecturally distinct *subfields* (dentate gyrus [DG], Cornu Ammonis [CA] 1–3 regions, and subicular complex/subiculum) (Duvernoy, 2005), which are thought to serve unique roles in memory (Aimone et al., 2006; Duvernoy, 2005; Gao et al., 2018; Leutgeb et al., 2007; Marr, 1971). Therefore, there is growing interest in generating reliable and valid measures of hippocampal subfields. Recent advances have made it possible to reliably measure hippocampal subfield volumes in humans in vivo and thus to chart differential age effects. For example, in a large cross-sectional sample of participants aged 8–82 years, Daugherty and colleagues demonstrated that CA1-2 volumes showed a linear decrease, whereas CA3-DG volumes showed a quadratic decrease, with age (Daugherty et al., 2016), which were mirrored, albeit with slight differences due to the limited age range, in a developmental sample of participants aged 8–25 (Daugherty et al., 2017) (Fig. 3A-B). Such advances in quantifying individual structural variability have sparked growing interest in characterizing the maturation of hippocampal subfields and testing the extent to which fine-grained maturational profiles constrain memory development.

Importantly, recent studies link hippocampal subfield volumes to memory outcomes in developing samples, including associative memory test performance (Daugherty et al., 2017; Lee et al., 2014; Riggins et al., 2018), correctly rejecting unstudied items, discriminating studied items from similar lures (Keresztes et al., 2017), and statistical learning (Schlichting et al., 2017). However, although several reports document links between hippocampal subfield volumes and memory, we note a large degree of variability among findings. For example, volumes of the right CA3-DG were shown to correlate positively with item-color associative memory in a sample of participants aged 8–14 years (Lee et al., 2014), but negatively with word-pair associative memory in a sample of participants aged 8–25 years (Daugherty et al., 2017) (Fig. 3C). With the data currently available, evidence exists but is inconsistent for age differences in the relationship between hippocampal subfield volumes and memory performance—which may be due

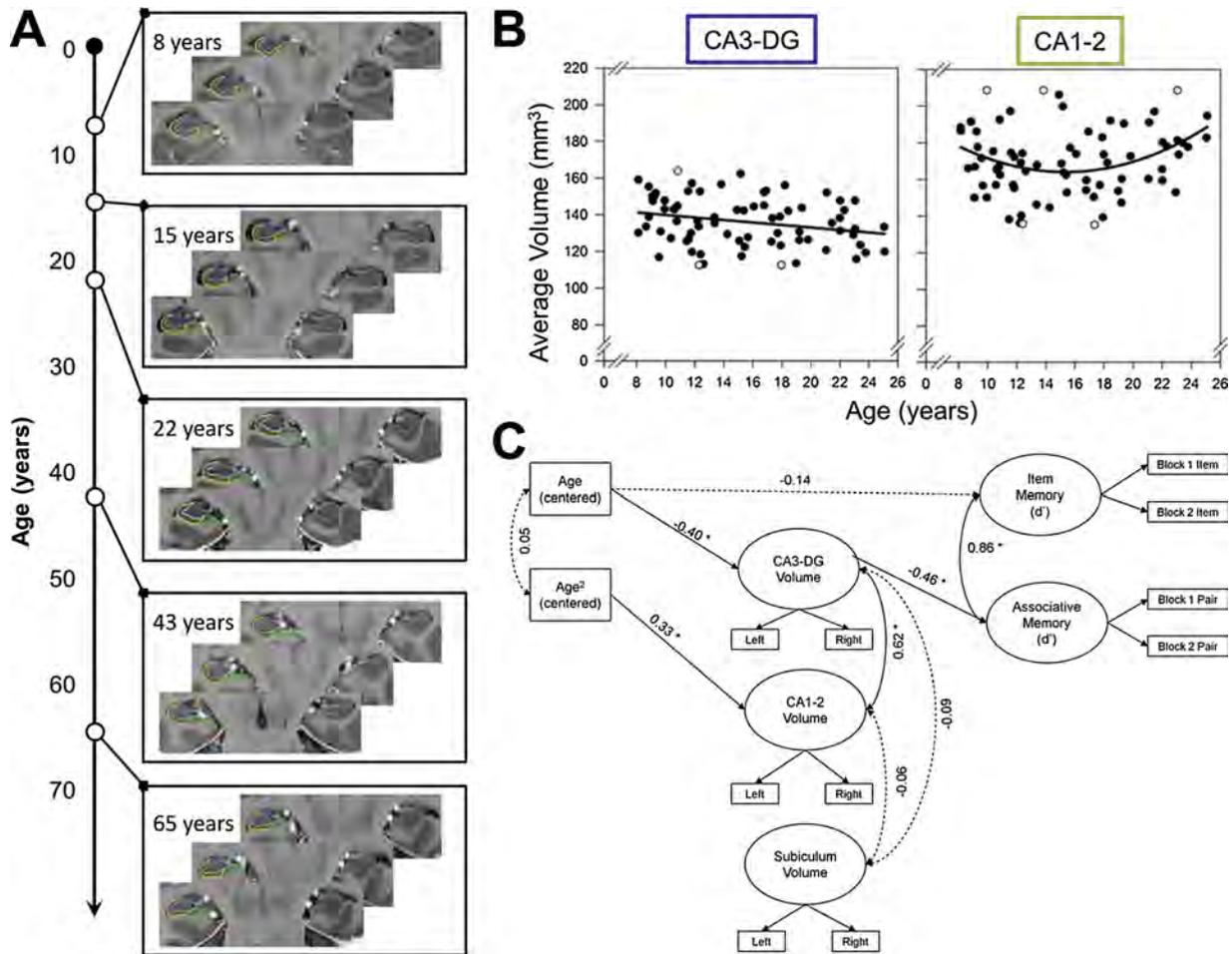


Fig. 3. Age-related differences in hippocampal subfield volumetry. (A) Representative images from individuals sampled across the lifespan. Within each individual dataset, the three images are contiguous slices (0.4×0.4 in-plane resolution, 2-mm slice thickness) showing the range sampled for hippocampal subfield volumetry. Blue, CA3-DG; yellow, CA1-2; green, subiculum; red, entorhinal cortex. Adapted with permission from (Daugherty, et al., 2016). (B) Differences in select hippocampal subfield volumes from 8 to 26 years of age. Left: CA3-DG (age $p = 0.02$; age² $p = 0.62$; $R^2 = 0.12$). Right: CA1-2 (age $p = 0.56$; age² $p = 0.01$; $R^2 = 0.12$). Standardized effect coefficients are reported from the latent modeling that estimated linear and quadratic age differences in all regions simultaneously, accounting for correlations among subregions. Adapted with permission from (Daugherty et al., 2017). (C) Model testing age-related differences in recognition memory (indirect age effect $p = 0.04$; $R^2 = 0.21$). All coefficients are standardized. *, $p < 0.05$; dashed lines, non-significant covariate effects. Adapted with permission from (Daugherty et al., 2017) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

to limitations in research and analytical protocols, as discussed below.

These studies present a step forward in illustrating how age differences in hippocampal structure provide endogenous constraints on the behavioral expression of memory phenomena. Yet, several limitations should be addressed in ongoing efforts to examine how hippocampal maturation might explain age differences in memory performance. First, extant data are based on different hippocampal segmentation protocols, limiting the integration of findings across studies. By acknowledging the lack of harmonization in measures of hippocampal subfield volumetry (Yushkevich et al., 2015), ongoing efforts may develop consistent and reliable segmentation tools. Notably, the Hippocampal Subfields Group has been working toward a harmonized protocol to segment hippocampal subfields along the anterior-posterior axis (Wisse et al., 2017), which is particularly important for the head and tail portions where limited visualization exists (Yushkevich et al., 2015). Second, individual differences exist in hippocampal structural measures and in memory performance that are unrelated to chronological age. Advanced statistics may prove critical in testing the extent to which age differences in hippocampal subfield volumes are linked to age differences in memory. For instance, Keresztes and colleagues applied partial least squares correlation analysis to identify variance in

subfield volume measures that are associated with chronological age to index hippocampal ‘maturity’, thereby linking ‘maturity’ indices to performance on specific tasks (Keresztes et al., 2017). This approach identifies the variance attributable to a variable of specific interest, in this case, the variance in hippocampal subfields that are age-related—so-called ‘maturity’. In another recent study, Daugherty and colleagues applied structural equation modeling to demonstrate that age-related increases in associative memory are partially mediated by age differences in DG-CA3 subfield volumes (Daugherty et al., 2017). In contrast to traditional approaches that use single-indicator measurements to reflect memory constructs, these approaches are privileged in their ability to isolate variables of interest and model them using multiple indicators. Indeed, we are not the first to argue that the application of statistical models which consider multiple indicators should ensure the fidelity of construct representations of brain and cognition across development (Little et al., 1999).

In this subsection, we highlighted one example of how innovation in the application of current methodologies—implementing reliable measures of hippocampal subfield volumes—may allow researchers to tackle the question of whether hippocampal maturation provides endogenous constraints on the maturation of the memory. In the next

subsection, we argue that a key element of developmental neuroscience is glaringly missing: longitudinal design. Only with longitudinal data will it be possible to explain how an individual's brain and behavior *change over time*. We thus illustrate the promise of employing longitudinal designs with large numbers of participants, across wide age ranges, to investigate developmental change.

3.2. Understanding developmental change in memory with longitudinal data

Here, we consider how methodological advances and collaborations increase the feasibility of using brain data to better *predict* developmental changes in memory. We aim to outline the critical need for longitudinal data in pursuing this fundamental question.

Longitudinal data are crucial if an attempt is made to characterize age-driven changes within an individual, to identify the unique or combined effects of possible factors which determine observable age differences in brain and behavior, and the possible changes in the composition of constructs over time (Chan, 1998). Yet, except for a few reports (e.g., (Kail, 2007; Schleeper and Jonkman, 2014; Schneider et al., 2004)), studies of memory development typically report findings based on comparisons across groups of participants who differ by age, attributing inter-individual differences to age in cross-sectional samples (Schneider and Ornstein, 2015). Some consider this approach problematic, as cross-sectional age variance extraction provides limited evidence in support of hypotheses about cognitive development (Lindenberger et al., 2011; Maxwell and Cole, 2007). However, because the extant data linking brain development to cognitive development are mostly cross-sectional, with a nod to the preferential use of longitudinal designs, researchers often argue for the validity of interpretations based on cross-sectional data (Ofen et al., 2007). We argue that, although there is an overall correspondence between findings based on cross-sectional data and findings based on longitudinal data (Lebel and Beaulieu, 2011), longitudinal designs provide the unique opportunity to investigate true developmental changes.

For instance, behavioral data about memory performance, collected from a sample of 100 kindergarten children with three measurements over one year, revealed enormous variability in the early acquisition of memory strategies (Schneider et al., 2004). Such patterns of change were observed by means of a longitudinal design that included several measures of memory obtained from a large sample of children, thereby controlling for inter-individual sources of variability and isolating a complex pattern of effects to age—that is, the intra-individual source of variability in question. To add important insights about brain development to our understanding of memory development, longitudinal data are necessary to disentangle complex developmental patterns and uncover the factors that determine future memory outcomes.

Longitudinal data may be particularly important within the domain of memory because, as we highlighted above in Section 2, specific challenges for studying developmental changes in the domain of memory stem from shifting theoretical perspectives about the 'elements' of memory (Brunec et al., 2018; Cohen and Eichenbaum, 1993; Henke, 2010; Lee et al., 2012; Nadel and Hardt, 2011; Shimamura et al., 1991; Tulving, 1983). In this regard, longitudinal studies may contribute to the harmonization of theoretical accounts across laboratories by providing the requisite evidence to claim that dual variance in neural and behavioral measures may be attributed to age, uniquely alleviating the primary unknowns of interest in developmental neuroscience.

Not limited to the domain of memory research, utilizing longitudinal designs goes beyond the detailed characterization of patterns of brain development and the development of cognitive abilities within individuals. With careful designs, one may start identifying *causal* links between brain development and cognitive development by assessing the modifiers of brain development that influence behavioral outcomes. Furthermore, by tackling the controversial issue of causality, insights into modifiers of brain development may also address concerns around

atypical brain development, with relevance to educational and clinical settings. For instance, the longitudinal assessment of socioeconomic status has linked poverty to poor school performance via structural changes in hippocampal maturation over time (Hair et al., 2015). This important finding presents an instance of how longitudinal designs may infer causality from a known environmental factor to the observed modification of neural and behavioral outcomes. Indeed, because the hippocampus is critical for memory functions and it is at risk for certain neurodevelopmental psychopathology, dually charting trajectories of hippocampal maturation and specific aspects of memory are instrumental in understanding how biological and environmental factors modify developmental trajectories of memory via hippocampal change (Yu et al., 2018).

We note, however, that conducting longitudinal studies that aim to link brain development to the development of any cognitive domain is a challenging endeavor. Nonetheless, with growing efforts to generate and share large-scale longitudinal data (e.g., ABCD), there is now the feasibility to pinpoint developmental changes in brain structure with validity and precision (Giedd et al., 2015; Mills et al., 2016; Mills and Tamnes, 2014). There is also burgeoning interest in identifying appropriate practical considerations in longitudinal study design, such as task selection and reliability, practice effects, consistency in assessments, and application of statistical models and analyses (Kievit et al., 2017; Telzer et al., 2018). Recent progress has been made in tackling these challenges in the investigations of developmental effects in other cognitive domains using fMRI (Crone and Elzinga, 2015; Finn et al., 2010; Koolschijn et al., 2011; Ordaz et al., 2013; Qin et al., 2014). Still, demonstrated quantitative reliability remains elusive in fMRI paradigms (Herting et al., 2017; Telzer et al., 2018; Vetter et al., 2017). Because fMRI data are typically interpreted at the group level, even simple comparisons across (age) groups become increasingly difficult to interpret when assumptions of equivalence in sources of variability, such as head movements or task strategies, are not met; and it is well documented that motion-induced artefacts are particularly detrimental in developmental studies (Chai et al., 2014b; Engelhardt et al., 2017). Thus, differences in motion and other variables by age may confound differences which systematically vary with the variable of interest: age. With longitudinal data, it will become possible to assess changes across multiple indicators and better account for the lack of equivalence in sources of variability that are not of interest.

Although practically challenging, we propose that longitudinal designs conducted in large numbers of participants with a wide range of targeted measures of brain and behavior should serve as the gold standard for any assessment of true change. With growing understanding that chronological age is but one of many sources that shape individual differences in behavior, there is increasing acceptance of individual-differences approaches to developmental research. As well, methodological advances in data-sharing and analysis make researchers more capable than ever before in accounting for issues such as reliability, and in promoting the large-scale investigation of the factors driving individual differences in memory development.

3.3. Measuring memory directly from the developing brain

In the previous subsections, we outlined recommendations to associate the maturational trajectories of key memory structures with age differences in behavior and proposed the careful implementation of longitudinal designs to track developmental changes. In short, we have covered the where of age-related variability in memory and begun to address the controversial issue of causality, the results of which together would evidence that the development of the brain indeed drives the development of memory. In this section, we tackle the missing link: *how*. How might real-time neural activity in key memory structures vary with age, potentially giving rise to the improvements observed in memory from childhood to young adulthood?

Although fMRI techniques measure the developing brain with

millimeter resolution, the hemodynamic response is observed over the course of several seconds, making it ill-suited to track the cascade of sub-second neural processes that underlie memory formation. Likewise, non-invasive electrophysiology (EEG/MEG) (Banaschewski and Brandeis, 2007; Werkle-Bergner et al., 2006; Taylor and Baldeweg, 2002) and eye-tracking (Eckstein et al., 2017; Hannula et al., 2010) techniques offer immense potential to measure the developing brain in real time during the performance of memory tasks, but they are limited in spatial resolution. To effectively delineate how a memory is successfully formed, maintained, and retrieved demands a view of the brain that is both spatially and temporally precise (Johnson and Knight, 2015). Until recently, no such method was considered feasible for use in pediatric populations.

However, the last few decades have witnessed a dramatic growth in the application of invasive clinical recordings of the brain—that is, EEG traces recorded intracranially from awake, behaving humans—to address questions in basic science (Chiong et al., 2017; Parvizi and Kastner, 2018). These electrodes are placed intracranially for clinical monitoring, usually to diagnose and/or prepare for surgical resection of a focal epileptic source, and once placed, may remain implanted for up to several days. Electrodes are placed subdurally in strips or grids to sample the cortical surface (as in ECoG) and/or stereotactically into deeper structures such as the hippocampus (sEEG) (Fig. 4). With electrode spacing generally between 4–10 mm and sampling rates of 500–10k Hz, ECoG/sEEG data offer unprecedented spatiotemporal precision in studies of human cognitive neuroscience. As well, direct access to neural tissue circumvents the signal-to-noise confounds that preclude reliable measurement of spectral activity at high frequencies (> 70 Hz) through the scalp, which is especially noteworthy as high-frequency activity in the EEG is a proxy for multi-unit neuronal firing (Hermes et al., 2017; Miller et al., 2014; Ray et al., 2008; Rich and Wallis, 2017; Watson et al., 2017).

Approximately 1% of the population is affected with epilepsy, and surgical management is recommended in medication-resistant cases to minimize the risks of neurocognitive dysfunction and premature death (Kwan et al., 2011). This 1% includes children, who may be at increased risk of long-term cognitive and behavioral deficits due to the early age of onset compared to adults—and, so, for whom surgical management is believed to be under-utilized (Ravindra et al., 2017). Though collecting the data is not without logistical challenges (Chiong et al., 2017), it is important to note that ECoG/sEEG data may be obtained during performance of experimental tasks and free of seizure activity between episodes; and the traces recorded from non-pathologic sites likely represent healthy tissue (Rossini et al., 2017).

Intracranial studies have been conducted in adults during the performance of memory tasks and findings have begun to address foundational questions in the neuroscientific study of memory (Johnson and Knight, 2015). In a large-scale investigation of word list encoding, high-frequency responses and theta (3–8 Hz) rhythms recorded from frontal, temporal, and parietal sites revealed that these key memory regions—as identified in fMRI studies of memory formation (Kim, 2011)—reflect

temporally distinct networks (Burke et al., 2014). As high-frequency responses also correlate with the hemodynamic response in fMRI (Jacques et al., 2016; Khurshheed et al., 2011; Mukamel et al., 2005), ECoG/sEEG data offer a bridge between the fMRI data available on memory development and examination of activity in the same regions with millisecond precision. Likewise, sEEG recordings of the hippocampus have shown that the theta rhythms reported in the animal literature also play a central role in human memory formation (Lega et al., 2012; Zhang and Jacobs, 2015), effectively bridging memory research across species. Further explorations of functional connectivity suggest that the PFC serves a key role as a hub during memory formation (Burke et al., 2013), and show that communications between the PFC and MTL occur via multiple rhythms simultaneously during the selection (Johnson et al., 2018a) and retrieval (Watrous et al., 2013) of everyday associations in memory.

Taken together, intracranial recordings afford unparalleled spatio-temporal resolution in the study of human memory and, in so doing, offer unique insights into multi-unit neuronal activity and dynamic functional connectivity, linking research across modalities and species. Reports of intracranial research studies in developing samples are rare (Taylor and Baldeweg, 2002). A recent study addressed working memory in patients aged 6–44 years (Kambara et al., 2017), localizing the time-course of load-dependent responses to the precentral gyrus across the whole sample; however, the authors did not consider patient age as a source of variability. We propose that with deliberate collaboration between clinicians and developmental and cognitive neuroscientists, intracranial recordings from children, adolescents, and adults be used to probe whether and how the spatiotemporal dynamics of neural activity in key memory structures vary with age.

Foundational work in pediatric intracranial research has begun addressing open questions in the *how* of memory development indicated by the current landscape of fMRI evidence. For instance, in our recent work we asked how the spatiotemporal propagation of activity across regions of the PFC might link age differences in brain structure to age differences in memory outcomes (Johnson et al., 2018b). Yet, many open questions remain. Do communications between the PFC and MTL occur along multiple rhythms simultaneously in children, comparable to those observed in adults? And, importantly, do theta rhythms recorded directly from the developing hippocampus predict subsequent memory?

Finally, invasive clinical recordings offer the rare opportunity to temporarily perturb neural systems via direct electrical stimulation. Just as intracranial electrodes record activity from the underlying neural tissue, they can also be used to deliver spatiotemporally precise electric pulses to the same tissue (Gallentine and Mikati, 2009; Parvizi and Kastner, 2018; Ritaccio et al., 2018). Clinicians generally use intra- or extra-operative stimulation in the gamma range (50–60 Hz) to perform functional mapping of primary motor sites and the eloquent cortex, defining the boundaries so that these critical brain regions may be spared from surgical resection. Mapping results yield reliable and

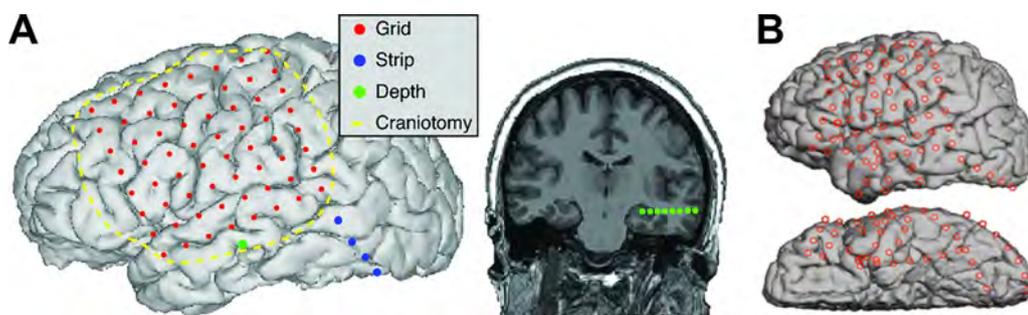


Fig. 4. Techniques for intracranial electrode placement. (A) Left: Reconstruction of a post-operative image from an epilepsy patient undergoing intracranial monitoring, illustrating two types of subdural ECoG (i.e., grid and strip) and penetrating sEEG (depth) placements. Right: Volumetric MRI coronal slice from the same patient showing sEEG placement to target the hippocampus. Red, grid (ECoG); blue, strip (ECoG); green, depth (sEEG); yellow, margin of craniotomy performed for placement of grid electrodes. Adapted with permission from (Chiong et al., 2017). (B) Reconstruction of ECoG placements in an 11-year-old patient (included in Johnson et al., 2018b), shown in lateral (top) and ventral (bottom) views (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

formed for placement of grid electrodes. Adapted with permission from (Chiong et al., 2017). (B) Reconstruction of ECoG placements in an 11-year-old patient (included in Johnson et al., 2018b), shown in lateral (top) and ventral (bottom) views (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

highly specific data that link brain structure with millimeter precision directly to behavioral outcomes (Ritaccio et al., 2018), making these data appropriate to address the controversial issue of causality. When applied to research, mapping has linked the fusiform face area directly to face perception in adults (Parvizi et al., 2012; Rangarajan et al., 2014), and also been shown to elicit more elusive behavioral phenomena such as intentionality, volition, anxiety, and even laughter (Parvizi and Kastner, 2018). Clinical mapping is performed in pediatric patients (Gallentine and Mikati, 2009). We suggest that by parcellating the activity at sites of known function during performance of memory tasks, these data may be additionally applied to infer how specific brain structures impact memory outcomes by age.

4. Future directions made possible by the utilization of big data

Lastly, we briefly consider future directions made possible by the utilization of large neuroimaging datasets, which are being collected and made available by advances in computing systems. There is an enormous promise for advancing our understanding of factors that determine memory development by the availability of large datasets which researchers can use to conduct data-driven investigations of age differences in neural and behavioral measures along dimensions of interest. Made feasible with data sharing and the computational power needed to tackle large datasets, data-driven approaches utilize machine learning and multivariate statistics to analyze large-scale data collected at multiple test sites (Biswal et al., 2010). Indeed, by using methods that quantify global patterns of activation or 'brain states', researchers have successfully predicted the fate of a memory from fMRI data (Balci et al., 2008; Rissman et al., 2010; Rissman and Wagner, 2012). In another instance, using data from the Human Connectome Project (HCP) and the United Kingdom Biobank Project, researchers can combine genetic and brain connectome metrics to investigate the dual influences of genetic and environmental factors in the development of cognitive abilities (Barch, 2017; Rosenberg et al., 2016; Shen et al., 2017). Although studies utilizing connectome data to investigate the development of memory are scarce, progress in the application of novel multivariate methods to understand memory in adults presents a promising direction for investigating the sources of its development in younger samples. Creative analyses of multi-site data offer the potential to reevaluate and even discover previously untapped neural substrates underlying memory, thereby providing novel foundations for understanding its development.

5. Conclusions

In this review, we briefly presented the current state of knowledge on the neural basis of memory development and the methods commonly used to study this important issue, and illuminated several examples of how innovative methodologies may be applied to generate novel insights. We highlighted promising opportunities to move beyond a focus on characterizing and describing the neural correlates of memory toward a more mechanistic explanation, using the brain to solve for outstanding questions in the field of memory development. Given the availability of 'big data', commitment to open-source data sharing and collaborative efforts, and innovative analytic techniques paired with advances in measurement techniques and computational power, now is an excellent time to evaluate outstanding inquiries and best practices to gain further insights about the development of memory.

A primary guiding principle in the application of developmental cognitive neuroscience approaches to the study of memory development is defining the appropriate question for which innovative methods may be implemented to answer, and then matching the methods accordingly. We offered three examples of how the current landscape of methodological innovations may allow us to move beyond description into explanation. First, we highlighted the promise of improved theoretical grounding and best practices in the harmonization of brain measures to study structural development. Second, we highlighted the

promise of careful longitudinal designs to allow researchers to tease apart sources of individual differences and ultimately provide predictive models of the environmental and biological modifiers of the brain and cognitive development. Pertaining to these two examples, we argue that tracking effects by chronological age, a prominent approach in published work, should be reframed in a larger context that identifies age as but one aggregate descriptor of an individual—allowing for estimation of effects of multiple variables in longitudinal designs. Longitudinal data, specifically, afford great promise in solving some of the many unknowns behind individual differences in memory development. In effect, with structural imaging we will be able to provide answers about the *where* of memory development, and with longitudinal designs we will be able to provide answers to questions that tap into *why* certain individuals differ from others. With our last example, we illustrated how innovative applications of clinical data may provide answers to novel questions that extend our understanding of *how* memory is implemented in the developing brain.

Across the examples provided here, we argue, there is immense potential to enhance our understanding of memory development and make a big leap from where the field is now. Perhaps the greatest challenge in making a leap forward is identifying the ways by which innovative methodologies can provide fundamental new information that informs theoretical perspectives. Indeed, new data, methods, and analytical approaches are exciting. Yet, with an overarching goal of using brain measurements to provide mechanistic links between chronological age and memory development, clear identification of outstanding questions is critical. Given shifting theoretical perspectives about the elements that make up memory, and little agreement on terminology and best practices in operationalizing memory processes, there is a risk of missing opportunities to derive cumulative knowledge. Collaborative efforts across laboratories may be instrumental in reaching agreement about what to ask, and how to frame and test converging hypotheses across multiple modalities. It is our hope that the field challenges the limits of neuroimaging, going beyond the characterization of functional brain-behavior correlates toward explanations of memory development based on predictive modeling, real-time measurement, causal perturbation and assessment, and data-driven exploration.

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Conflict of Interest

None.

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