New perspectives on the aging brain

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Abstract

According to popular literature, late life development progresses along a linear trajectory of monotonic age-related decline. Emerging research on brain and cognitive aging is now challenging this view. Healthy aging comprises a complex set of functional, structural, and cognitive changes marked by gains and losses. These complex patterns suggest that human development continues as an active process into later life, yet how they intersect remains poorly understood. In three cross-sectional studies, deep behavioral phenotyping and novel neuroimaging techniques were used to examine age differences in brain function, structure, and their relationships to cognition at both the whole-brain and smaller systems levels. The overarching goal was to characterize these interactions against a backdrop of late life development that involves both adaptive and maladaptive change.

Study 1 adopted a whole-brain, data-driven approach to examine whether functional network dedifferentiation, a defining feature of functional brain aging, is a global property of brain aging or a network-level phenomenon, and how this could inform cognitive differences. Multi-echo resting state functional images and cognitive assessments were collected from 181 younger and 120 older healthy adults. We found evidence for both global and network-specific dedifferentiation in older versus younger adults, with direct implications for aging cognition.

Through the lens of autobiographical memory (AM), studies 2 and 3 involved more targeted assessments of age differences to brain structure and function in association with cognition (158 younger, 105 older adults). Study 2 tested for differences in grey matter volume of regions implicated in AM—anterior/posterior hippocampus (AHIPP/PHIPP) and temporal poles (TP)—and whether volume differences were associated with AM performance in each cohort. Older adults had smaller PHIPP volumes compared to younger adults, but episodic AM was positively related to AHIPP and TP volumes in older adults.

Study 3 examined age group differences in resting-state functional connectivity of a local circuit implicated in AM and its association to AM. Older adults' connectivity profile was marked by TP integration with regions across the default network, and were associated with smaller PHIPP volumes. An age-invariant pattern dissociated connectivity related to episodic and semantic AM, suggesting a preservation of functional circuits related to AM. Younger adults also demonstrated a unique pattern of connectivity related to overall recollection. These results

provided strong evidence that variance in a local functional circuit is sensitive to systematic variation in recollection that coincides with shifts in older age.

These studies advance our understanding of the complex contours of brain aging, underscoring that structural and functional changes may index both adaptive and maladaptive processes associated with cognition in older adulthood. Taken together, the findings from these studies offer initial support for an adaptive neuroplasticity account of neurocognitive aging, and bear import on outlooks for real-world functioning in late life.

Résumé

Selon la littérature populaire, le développement en fin de vie progresse le long d'une trajectoire linéaire de déclin monotone lié à l'âge. Les recherches émergentes sur le vieillissement cérébral et cognitif remettent aujourd'hui en question cette vision. Le vieillissement sain comprend un ensemble complexe de changements fonctionnels, structurels et cognitifs qui est marqué par des gains et des pertes. Ces modèles complexes suggèrent que le développement humain se poursuit comme un processus actif jusqu'à un âge avancé, mais la façon dont ils s'entrecroisent restent mal compris. Dans trois études transversales, un phénotypage comportemental approfondi et de nouvelles techniques de neuro-imagerie ont été utilisés pour examiner les différences d'âge dans la fonction et la structure du cerveau, ainsi que leurs relations avec la cognition, tant au niveau du cerveau entier que des systèmes plus petits. L'objectif principal était de caractériser ces interactions dans le contexte d'un développement tardif de la vie qui implique des changements adaptatifs et inadaptés.

La première étude a adopté une approche axée sur les données pour l'ensemble du cerveau afin de déterminer si la dédifférenciation du réseau fonctionnel, une caractéristique du vieillissement cérébral fonctionnel, est une propriété globale du vieillissement cérébral ou un phénomène au niveau du réseau, et comment cela pourrait influencer les différences cognitives. Des images fonctionnelles multi-écho au repos et des évaluations cognitives ont été recueillies auprès de 181 jeunes adultes et 120 adultes plus âgés en bonne santé. Nous avons trouvé des preuves d'une dédifférenciation à la fois globale et spécifique au réseau chez les adultes plus âgés par rapport aux adultes plus jeunes, avec des implications directes sur le vieillissement cognitif.

À travers le prisme de la mémoire autobiographique (AM), la deuxième et la troisième étude ont consisté en des évaluations plus ciblées des différences d'âge au niveau de la structure et de la fonction cérébrales en association avec la cognition (158 adultes plus jeunes, 105 plus âgés). La deuxième étude a testé les différences de volume de matière grise des régions impliquées dans la AM - hippocampe antérieur/postérieur (AHIPP/PHIPP) et pôles temporaux (TP) - et a vérifié si les différences de volume étaient associées aux performances de la AM dans chaque cohorte. Les adultes plus âgés avaient des volumes de PHIPP plus petits que les adultes plus jeunes, mais la AM épisodique était positivement liée aux volumes du AHIPP et du TP chez les adultes plus âgés.

La troisième étude a examiné les effets différentiels de l''âge sur la connectivité fonctionnelle d'un circuit local lié à la AM, ainsi que son association avec la AM. Les profils de connectivité des adultes plus âgés étaient marqués par une intégration étendue du TP avec les régions du réseau par défaut et était associée à une réduction du volume de la PHIPP. Un modèle invariant en fonction de l'âge a dissocié la connectivité liée à la AM épisodique de celle lié à la AM sémantique, suggérant une préservation des circuits fonctionnels associés à la AM. Les jeunes adultes ont également démontré un modèle unique de connectivité lié au souvenir global. Ces résultats fournissent des preuves solides que la variance dans la connectivité fonctionnelle d'un circuit local est sensible à la variation systématique du souvenir qui coïncide avec des changements dans âge avancé.

Ces études font progresser notre compréhension des contours complexes du vieillissement cérébral, soulignant que les changements structurels et fonctionnels peuvent indexer les processus adaptatifs et inadaptés associés à la cognition chez les adultes âgés. Dans l'ensemble, les résultats de ces études offrent un support initial pour un compte rendu de la neuroplasticité adaptative du vieillissement neurocognitif, et sont importants pour les perspectives de fonctionnement du monde réel à un âge avancé.

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In high school I wrote an essay that began: “We are but an amalgamation of the people we encounter, the experiences we have with them, and the impressions they leave upon us.” I thought it was profound at the time. Fifteen years later, that sentence has never rung more true.

Thank you to my supervisor, Nathan Spreng. Your kindness, empathy, and bottomless reserve of patience have guided me through this degree. Thank you for your rigor, your trust in me, and the reminders not to undermine myself. Thank you for always having your door open, for reading draft after draft (ad nauseam), and for all the nuggets of wisdom. Most of all, thank you for your mentorship.

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Contribution to Original Knowledge

Adults aged 65 and above are projected to make up nearly 30 percent of the population by 2068 (World Bank Data), yet surprisingly little is understood about the aging brain beyond decline. Distinguishing between adaptive and maladaptive change is extremely important to better characterize mechanisms of vulnerability, appropriately tailor interventions, and perhaps most critically, optimize well-being and quality of life. The studies contained within this thesis used novel neuroimaging techniques to employ a comprehensive multi-scale investigation of brain function, structure, and cognition differences between younger and older adults. Across three studies, we characterize brain differences that offer initial evidence for an adaptive neuroplasticity account of late life brain development.

Study 1 examined whether reduced specialization in older age is a global property of older brain function or if it emerges from specific network changes. Global integration increased with age, but large-scale functional connectivity profiles were relatively preserved. Specific integration of visual, somatomotor, and dorsal attention networks across the brain were prominent features of older adult connectomes, with tentative links to better executive functioning. Findings from Study 1 demonstrated that global age-related trends may not sufficiently characterize age-related cognitive change. Functional coupling of specific brain networks may offer an adaptive benefit to declining complex cognition.

In Studies 2 and 3 we describe localized structural and functional differences between younger and older adults in the hippocampus and temporal pole that may support autobiographical memory in older age. In line with general declines to complex cognition, episodic autobiographical memory was lower in older versus younger adults. However older adults recalled more semantic details about their personal pasts. At the level of the brain, older adults had smaller posterior hippocampus volumes, but this was unrelated to the amount of episodic detail they recalled. Instead, older adult episodic detail was related to volumes of regions associated with semantic processing in younger adults. These findings suggested an age-related shift in how regional grey matter may impact cognitive functioning in older adulthood. Study 3 provided supporting evidence for this shift within the functional connectivity profiles of the hippocampus and temporal poles. A distinct pattern of integration with regions across the default network distinguished older adult functional connectivity from young, and was associated with posterior hippocampus volumes. Shared and unique age group patterns of functional

connectivity associated with AM were identified. These indicated an overall preservation in how the default network may be readily recruited for AM across the lifespan, most highly influenced by systematic variation in the balance of episodic versus semantic details. Yet, an age-related shift in this balance distinguished connectivity associated with recollection as a whole in younger adults. Together, Studies 2 and 3 showed that local structural changes may alter both the functional brain architecture underpinning AM and the contents of autobiographical recall. This suggests that age-related functional brain adaptation may emerge to support complex cognition in later life.

Results across the three studies demonstrated that patterns of decline cannot be examined in isolation. On both global and local levels, age-related changes that could be conceived as decline may in some ways reflect adaptive plasticity to support cognitive abilities in older age. The present thesis highlights the need to consider the intersection of age-related functional, structural, and cognitive gains and losses to better understand and accommodate an ever-growing segment of the population.

Contribution of Authors

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Roni Setton*: managed, processed, and quality assessed all neuroimaging data, analyzed behavioral data, analyzed neuroimaging data, created visualizations, wrote and edited the manuscript; **Laetitia Mwilambwe-Tshilobo*:** created in-house code for individualized parcellation schemes, analyzed neuroimaging data, created visualizations, wrote and edited the manuscript; **Manesh Girn:** analyzed neuroimaging data, created visualizations, edited the manuscript; **Amber W. Lockrow:** collected data, managed behavioral data, reviewed the manuscript; **Giulia Baracchini:** involved in neuroimaging data processing, parcellation, and management, reviewed the manuscript; **Colleen Hughes:** involved in neuroimaging parcellation; **Alexander J. Lowe:** contributed code to the manuscript, reviewed the manuscript; **Benjamin N. Cassidy:** collected data, reviewed the manuscript; **Jian Li:** provided software, reviewed the manuscript; **Wen-Ming Luh:** involved in conceptualization and methodology for neuroimaging data collection; **Danilo Bzdok:** reviewed the manuscript; **Richard M. Leahy:** conceptualized individualized parcellation, reviewed the manuscript;
Tian Ge: provided initial code for individualized parcellation, reviewed the manuscript; **Daniel S. Margulies:** reviewed the manuscript; **Bratislav Misic:** provided methodological feedback, reviewed the manuscript; **Boris C. Bernhardt:** provided methodological feedback, reviewed the manuscript; **W. Dale Stevens:** conceptualized the study and methodology, supervised data collection, wrote and edited the manuscript; **Felipe De Brigard:** reviewed the manuscript; **Prantik Kundu:** provided initial code for neuroimage processing, provided methodological feedback, contributed additional developmental data, reviewed the manuscript; **Gary R. Turner:** conceptualized the study and methodology, provided funding, supervised data collection, wrote and edited the manuscript; **R. Nathan Spreng:** conceptualized the study and methodology, provided funding, supervised data collection, wrote and edited the manuscript;

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Roni Setton: managed, processed, and quality assessed all neuroimaging data, oversaw management of autobiographical interview transcription, scoring, and quality checking, scored interviews, analyzed all neuroimaging and behavioral data, created visualizations, wrote and edited the manuscript; **Signy Sheldon:** edited the manuscript; **Gary R. Turner:** provided funding, supervised data collection, edited the manuscript; **R. Nathan Spreng:** provided funding, supervised data collection, edited the manuscript, provided supervision;

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Roni Setton: managed, processed, and quality assessed all neuroimaging data, oversaw management of autobiographical interview transcription, scoring, and quality checking, scored interviews, analyzed all neuroimaging and behavioral data, created visualizations, wrote and edited the manuscript; **Laetitia Mwilambwe-Tshilobo:** created in-house code for individualized parcellation schemes, provided methodological feedback, reviewed the manuscript; **Signy Sheldon:** edited the manuscript; **Gary R. Turner:** provided funding, supervised data collection, edited the manuscript; **R. Nathan Spreng:** provided funding, supervised data collection, edited the manuscript, provided supervision;

Chapter 1: General Introduction

Normal aging encompasses both gains and losses in brain and cognitive function: Functional brain networks degrade while cross-network connections proliferate; global grey matter atrophy occurs in the context of preserved regional volumes; fluid abilities decline while crystallized capacities accrue over the lifespan. How these complex changes in brain and behavior intersect is poorly understood. The present thesis examines brain-behavior relationships in healthy younger and older adults to better characterize differences in associations among brain function, structure, and cognition in normative neurocognitive aging.

Literature Review

Mounting evidence suggests that age-related functional, structural, and cognitive changes do not follow a uniform pattern of decline. Rather, the aging brain is marked both by losses, preservation, and gains in each of these domains. Functional brain activity and connectivity show a widespread pattern of dedifferentiation, or reduced specialization, of brain regions during task and at rest. Yet reduced differentiation is driven, at least in part, by increased functional integration. This is seen in task-evoked fMRI studies as less asymmetrical activity (Cabeza, 2002) and more prefrontal activity (Davis et al., 2008). Properties of brain structure, including grey matter volume, cortical thickness, and white matter integrity, follow a net pattern of decline as increasing brain age incurs cell death and shrinkage, loss of dendritic spines, and deterioration of myelin (see Raz et al., 2005 for a review). Yet, some regions are more susceptible to atrophy and thinning while others remain stable over the lifespan (Raz et al., 2005; Salat et al., 2004; Fjell et al., 2009; Ziegler et al., 2010). White matter hyperintensities, distributed lesions to the white matter signaling a range of possible neuropathologies or cerebrovascular risk factors (see Raz et al., 2005 for review), also accrue with age, but disproportionately affect frontal region microstructure and generally have less impact on the rest of the brain. Lastly, fluid cognitive abilities including attention, inhibition, working memory, and episodic memory, worsen (Park & Reuter-Lorenz, 2009). Complementary to these losses, crystallized cognition, including vocabulary and world knowledge accumulated over one's lifetime, peaks in older age (Li et al., 2013). Yet, much of the attention in aging research is focused on how brain change abets cognitive decline.

Two frameworks of neurocognitive aging propose an account to relate and resolve these multiplex changes: adaptive plasticity. The Scaffolding Theory of Aging and Cognition (STAC; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) is a lifespan theory outlining age-related functional change as compensatory neural scaffolding in response to structural impairment. The STAC model predicts that individuals with less degeneration will age more successfully and will require less compensation (subject to other neural enrichment and depletion factors). With inevitable age-related changes, older adults with a greater ability to recruit compensatory resources, indicative of a greater propensity for adaptive plasticity, will fare better. The STAC model also notes that at some critical point in the aging trajectory, pathology may overtake the brain's capacity for compensation. Growing of Lifelong Differences Explains Normal aging (GOLDEN aging; Fabiani, 2012) is a developmental continuity framework that views healthy aging as the amplification of individual differences, present in early adulthood, over the course of one's lifetime. Drawing on some of the same ideas as STAC, the crux of GOLDEN is that maturation, in the absence of disease, is a process that continues to shape and transform brains. Despite their emphasis on adaptive change, both STAC and GOLDEN attempt to explain brain change in the context of cognitive losses.

Losses, maintenance, and gains in brain function, structure, and cognition suggest that plastic mechanisms may respond to and potentially buffer against decline. Distinguishing between plastic changes that confer benefits rather than vulnerabilities may seem intractable given the heterogeneity across individuals, functional networks, functional regions, gross anatomy, and cellular composition. This thesis takes a two-pronged approach by looking at both whole-brain and smaller-systems brain change in relation to cognitive gains and losses. At the whole-brain level, we can ask how large-scale functional network patterns across the brain differ in older age, and whether specific differences impact cognition more than others. At the smaller-systems level, we can examine function and structure within regions implicated in domain-specific cognitive gains and losses to narrow in on age-related brain-behavior differences that may be imperceptible at a larger scale. In this way, we can begin to characterize age differences in brain function that help or hurt cognitive function in older age.

Age Differences in Global Patterns of Brain Function and Cognition

Resting-state fMRI studies, which measure the low frequency spontaneous oscillations in BOLD signal underlying large-scale functionally distinct brain networks (Biswal et al., 1995), demonstrate an analogous pattern of functional gains and losses as task-fMRI studies. Less asymmetrical and more prefrontal brain activity during task (Davis et al., 2008) is paralleled by reduced connectivity within networks and more connectivity between networks at rest (Chan et al., 2014; Geerligs et al., 2015; Wig, 2017). In combination, these connectivity changes are interpreted as a pattern of dedifferentiation, whereby networks become less associated with discrete functions (e.g., visual network in occipital cortex and visual perception) and are rendered less specialized. Although age-related dedifferentiation occurs in most networks, higher-order organization is relatively preserved compared to younger adults. This has been demonstrated with global efficiency, which quantifies how efficiently distant information is transmitted across the brain, and gradients of connectivity, which identify functional connectivity similarity profiles across the brain (Cao et al., 2014; Bethlehem et al., 2020). More prominent age-related changes have been observed in association networks including the default, frontoparietal control, and dorsal attention networks. Older adult association networks show less local efficiency and are less modular, suggesting more long-range between-network connectivity (Cao et al., 2014; Geerligs et al., 2015). Reduced segregation of association networks has even been related to declining episodic memory across the adult lifespan (Chan et al., 2014). The default network is particularly susceptible to age-related change, with its core regions the first to be afflicted by amyloid plaques in Alzheimer's Disease (Buckner et al., 2005). Thus far, measures of functional dedifferentiation, and the gains and losses that characterize it, summarize non-specific properties of the aging connectome and associate with more global measures of cognitive losses. It is unclear whether and/or how specific network connectivity changes contribute, and whether quantitative measurement of such changes would reveal more subtle relationships to cognitive gains and losses.

Age Differences in Local Brain Function and Cognition: Autobiographical Memory as a Test Case

Autobiographical Memory

Autobiographical memory (AM), the repository of our past experiences, is one domain in which both age-related cognitive gains and losses are observed. AM recollections naturally contain information that varies in level of detail. This information can be categorized into more event-specific, episodic versus more general, semantic detail. Age-related changes to episodic and semantic components of AM mirror general cognitive trends: older adults recount fewer episodic and more semantic details compared to younger adults (e.g., Levine et al., 2002).

A leading model of AM posits that memory details are stored within hierarchical levels of specificity (e.g., lifetime periods, general events, and event-specific knowledge), and that access to successive levels is constrained by a "working self," a combination of working-memory control processes and self-schemas that direct our beliefs and goals at any given point in time (Conway & Pleydell-Pearce, 2000). AM is naturally dynamic: a hierarchical organization enables personal memories to be reconstructed in a variety of ways (Addis et al., 2009), with a "working self" exerting top-down control to construe memories according to an individual's current goals and beliefs (Prebble et al., 2013). Changes to older adult recollections may reflect limited retrieval to more specific levels within an AM hierarchy, in parallel with other executive control declines. Some evidence suggests that individuals, and more so older adults, offer additional semantic information when episodic specificity is impoverished (Devitt et al., 2017). Alternatively, age-related AM changes may reflect an updated belief system, newfound goals, and an altogether different outlook on life. Indeed, shifting perceptions of time horizons are predicted to guide motivations and goals (Carstensen, 2006). Young adults, who view time as more open-ended, are motivated to gather information, experience novelty, and expand their knowledge base in the service of knowledge acquisition goals. Older adults, who view time as more limited, are motivated to regulate their emotional states and optimize psychological wellbeing in the service of meaning-making goals. Constrained time horizons may also motivate older adults to seek a sense of self-continuity. Semantic AM is important for the formation and maintenance of a coherent self-concept in the present moment and a continuous mental representation of self over time (although the relationship is thought to be bidirectional; Prebble et al., 2013). In contrast, episodic AM contributes to present self-awareness and the ability to mentally travel into the past and future. Inclusion of more semantic detail in older adults' AM recollections may therefore reflect an inclination toward semantic continuity. As such, semantic AM need not be characterized merely as a consequence of declining episodic abilities. As

discussed below, examining age-related brain change in relation to episodic and semantic AM separately will be critical for understanding how brain reorganization may impact both cognitive gains and losses.

Brain Activity Associated with Autobiographical Memory

When individuals recall specific memories during AM, a form of internally-directed cognition, they reliably engage regions of the default network (Benoit & Schacter, 2015; Svoboda et al., 2006; Spreng et al., 2009). Similar AM activation is observed in older adults, with notable differences in the temporal lobe (Addis et al., 2011; Viard et al., 2007; Martinelli et al., 2013). One representative study found that younger adults activated posterior hippocampus and parahippocampal cortex more than older adults during earlier stages of an AM task (Addis et al., 2011). Older adults recruited lateral temporal regions, including the temporal pole, and anterior hippocampus later on and more than younger adults, who recruited these regions in a semantic control condition. These findings highlighted two key considerations for understanding how AM changes into older age: 1) different regions of the hippocampus offer unique support to AM, which may change as a function of age, and 2) lateral temporal activity may be an important feature of older adult AM. Until recently, in-scanner AM tasks have involved silent elaboration on past experiences, leaving researchers to infer the interpretation of differential age group activations. Late recruitment of anterior hippocampus during AM was interpreted as differential hippocampal recruitment of younger and older adults during construction versus elaboration stages of AM. A plausible alternative is that mnemonic specialization of anterior and posterior hippocampus (e.g., Brunec et al., 2018; Sheldon et al., 2019) differs in older adults. Older adult recruitment of the temporal pole was speculated to contribute to their more semantic AM recollections, as the temporal pole is widely associated with semantic aspects of memory (e.g., Lambon Ralph et al., 2017). Similar reverse inference has been applied to findings of older adult repetition suppression in the temporal pole for negative, but not positive future episodic simulations (Devitt et al., 2020). As per an age-related positivity bias, older adults preferentially attend to and remember more positive information (see Carstensen & DeLiema, 2018 for a review). This result was therefore construed as older adults distancing themselves from more unpleasant mental simulations by processing them in a more semantic way. Clarification is

needed on how age-related structural and functional differences in AM-associated regions— namely the hippocampus and temporal pole— map onto differences in AM performance. Specifically, how brain changes in these regions each associate with semantic and episodic aspects of AM will provide a better understanding of how local brain change supports cognitive gains and/or losses.

Rationale

Across three cross-sectional studies, novel neuroimaging techniques were used to examine age differences in i) whole brain function and cognitive associations as well as targeted ii) structure-cognition and iii) function-cognition associations. Multi-echo resting-state fMRI, anatomical neuroimages, and an in-depth collection of cognitive measures were collected from a large sample of healthy younger and older adults. Multi-echo fMRI affords a boost in BOLD signal detectability, particularly within regions that are prone to signal drop-out, such as the temporal pole. An individualized parcellation approach was implemented on functional data to account for person-specific shifts in functional boundaries. An automated segmentation protocol, developed specifically for use in older adult populations, was applied to anatomical images to segment each participant's hippocampus. Deep behavioral phenotyping enabled us to obtain global composite measures of cognition, including episodic memory, semantic memory, and executive function. Finally, the Autobiographical Interview (Levine et al., 2002) was administered as a rich measure of AM that yields separate metrics for episodic and semantic recollection. The methodological steps taken here, which respect individual differences in functional and structural regional boundaries, paired with behavioral data from a well-powered sample, made it possible to confidently test for whole-brain and systems-level brain-behavior relationships. The overarching goal of these studies was to better characterize age differences in these associations at each level and explore whether brain reorganization could support cognition in older age, in line with adaptive plasticity. Support for an adaptive plasticity account would have a number of implications for the field of neurocognitive aging, with the potential to redefine the current loss of integrity, loss of function approach to healthy aging research (Andrews-Hanna et al., 2019). Such evidence will offer valuable insight into how plasticity can be leveraged for better health, well-being, and quality of life in older age.

Study 1. A multiscale comparison of younger and older functional connectomes was conducted to investigate whether dedifferentiation of brain networks is a global or network-

specific phenomenon of functional brain aging. To this end, we calculated a global metric of network dedifferentiation, gradients of functional connectivity, and whole-brain functional connectivity matrices and quantitatively compared them across groups. At each level of analysis, metrics were correlated to cognition. Results from this study will provide a backdrop for global functional age change, its effect on systems throughout cortex, and potential links to global measures of cognition.

Study 2. Here we take a more targeted approach by investigating brain-behavior associations with AM and AM-associated regions. It remains to be determined how age-related differences in hippocampal and temporal pole activity during AM speak to episodic versus semantic detailed recollections. The aim of Study 2 was to first identify whether involvement of these regions in AM was rooted in structure. We first tested for age group differences in anterior hippocampus, posterior hippocampus, and temporal pole grey matter volumes. We then tested whether episodic or semantic AM could predict grey matter volume in each of these regions. Findings from this study will reveal which structures show volume differences in older age. Moreover, we will observe whether volume differences, or the lack thereof, predict better episodic or semantic AM performance in each age group.

Study 3. In a direct follow-up to Study 2, we asked how resting-state functional connectivity may differ between these regions and the rest of the default network, due to its role in AM, as a function of age. We also conducted a multivariate analysis to examine how these connectivity differences covaried with episodic and semantic AM separately. Results from this study will reveal functional connectivity differences in a local circuit, which may be overshadowed by whole brain differences in Study 1. Critically, covariance patterns with episodic and semantic AM will shed light on how functional connections in each age group may be readily recruited for different aspects of AM in the context of AM performance differences. This latter result will extend our current understanding of how age-related brain change supports cognition, amid gains and losses.

Chapter 2: Age differences in the functional architecture of the human brain

Adapted from: Setton, R.*, Mwilambwe-Tshilobo, L.*, Girn, M. Lockrow, A.W., Baracchini, G., Hughes, C., Lowe, A.J., Cassidy, B.N., Li, J., Bzdok, D., Leahy, R.M., Ge, T., Margulies, D.S., Misic, B., Stevens, W.D., Bernhardt, B.C., Kundu, P., De Brigard, F., Turner, G.R., & Spreng, R.N. (*Under Revision*). Functional architecture of the aging brain. *Cerebral Cortex*.

Abstract

The intrinsic functional organization of the brain changes into older adulthood. Age differences are observed at multiple spatial scales, from global reductions in modularity and segregation of distributed brain systems, to network-specific patterns of dedifferentiation. Whether dedifferentiation reflects an inevitable, global shift in brain function with age, circumscribed, experience dependent changes, or both, is uncertain. We employed a multi-method strategy to interrogate dedifferentiation at multiple spatial scales. Multi-echo (ME) resting-state fMRI was collected in younger (n=181) and older (n=120) adults. Cortical parcellation sensitive to individual variation was implemented for precision functional mapping of each participant, while preserving group-level parcel and network labels. ME-ICA denoising and gradient mapping identified global and macroscale network differences. Multivariate functional connectivity methods tested for microscale, edge-level differences. Older adults had lower ME-ICA derived BOLD signal dimensionality, consistent with global network dedifferentiation. Gradients were largely age-invariant. Edge-level analyses revealed discrete, network-specific dedifferentiation patterns in older adults. Visual and somatosensory regions were more integrated within the functional connectome; default and frontoparietal control network regions showed greater connectivity; and the dorsal attention network was more integrated with transmodal regions. These findings highlight the importance of multi-scale, multi-method approaches to characterize the architecture of functional brain aging.

Introduction

Spontaneous oscillations in brain activity provide the basis for characterizing large-scale functional networks (Biswal et al., 2010; Fox and Raichle, 2007; Yeo et al., 2011). This intrinsic functional network architecture is determined by both genetic factors and experience-dependent neuroplastic changes occurring across timescales, from moments to decades (Stevens and Spreng, 2014). Studying these networks in older adulthood can yield important insights into the aging brain. Key organizational features of the aging connectome include reduced within- and greater between- network connectivity (Chan et al., 2014; Geerligs et al., 2015), resulting in a dedifferentiated, or less segregated, network architecture (Wig, 2017). However, the specific nature of age-related network dedifferentiation remains uncertain.

There are (at least) two tenable hypotheses. First, network dedifferentiation may represent a global feature of functional brain aging. Global shifts may result from systemic structural, neurophysiological or metabolic alterations, paralleling domain-general changes in cognitive aging. Second, the aging connectome may comprise experience-dependent, network specific patterns of dedifferentiation, paralleling domain-specific changes in cognitive abilities in later life (Stevens and Spreng, 2014; Spreng and Turner, 2019a). Examples of network specific changes include greater connectivity between default and frontoparietal control networks, associated with age differences in autobiographical memory (Spreng et al., 2018); or, reduced segregation among distributed association networks predicting decline in processing speed (Ng et al., 2016; Malagurski et al., 2020). Testing these hypotheses presents significant methodological and conceptual challenges. Mitigating persistent and pervasive methodological limitations that confront resting-state functional connectivity (RSFC) investigations is critically necessary to fully leverage the value of this imaging modality as an indicator of brain, and ultimately cognitive, health in older adulthood.

Here we adopted a multimethod data acquisition and analysis protocol to interrogate patterns of network dedifferentiation in younger and older adults across multiple spatial scales from global to edgel-level differences. We implemented three novel approaches to characterize the functional network architecture of the aging brain. First, we examined global differences in spatiotemporal patterns of BOLD signal covariance across the cortex. We refer to this metric as BOLD dimensionality, or the number of BOLD signal components derived from multi-echo fMRI (ME-fMRI) data acquisition and multi-echo independent components analysis (ME-ICA)

processing (Kundu et al., 2017). Second, we investigated age differences in the macroscale connectivity profile of the brain using functional connectivity gradient analyses (Huntenburg et al., 2018; Margulies et al., 2016; Paquola et al., 2019; Vos de Wael et al., 2020). Third, we identified age differences in edge-level connectomics using partial least squares analyses (PLS, Krishnan et al., 2011; McIntosh and Misic, 2013). PLS enables whole-brain contrasts of unthresholded connectivity matrices, allowing more precise mapping of age differences. Combined, these techniques offer a broad window into the functional architecture of the aging brain, spanning global covariance patterns across the cortex to precision-mapping of edge-level connections. Below we briefly summarize each methodological approach, and associated age-related predictions.

Innovations in ME-fMRI data acquisition protocols, combined with a TE-dependence model of BOLD signal denoising using ME-ICA, enables one to reliably separate BOLD from non-BOLD (i.e. noise) signals into different components (Kundu et al., 2017). ME-ICA processing eliminates distant-dependent motion confounds (Power et al., 2018) and the need for multiple confound regression, including the global signal (Spreng et al. 2019). These analytical features are critical for cross-group comparisons, where it is difficult to adjudicate between group differences in noise versus non-noise components in the BOLD signal. Further, eliminating the need for mean signal regression denoising allows for valid between-group comparisons of the full range of positive and negative RSFC values. ME-fMRI processed data provides excellent reliability and temporal signal-to-noise, sufficient for individual-subject precision mapping (Lynch et al., 2020; Lynch, Elbau, and Liston, 2021). While this metric has not heretofore been examined in older adulthood, we predict that BOLD dimensionality, as a proxy for differentiated brain networks, will be significantly lower for older versus younger adults. This prediction is consistent with previous reports of age-related network dedifferentiation (Betzel et al., 2014; Chan et al., 2014; Geerligs et al., 2015; Madden et al., 2020; Malagurski et al., 2020; Ng et al., 2016; Stumme et al., 2020; Zonneveld et al., 2019) and previously reported declines in BOLD dimensionality from childhood into middle-age (Kundu et al., 2018).

Gradient mapping identifies transitions in regional connectivity patterns across the cortical mantle (Margulies et al., 2016). Age differences in connectivity gradients would signal macroscale functional brain reorganization. As gradients are robust, phylogenetic features of the connectome (Margulies et al., 2016), we predict that these patterns would be resistant to normal ontogenetic

changes. However, changes may emerge for regionally-specific connectivity profiles within the macroscale gradient architecture, reflecting network or node specific shifts in connectivity patterns. We are aware of only one previous investigation of connectivity gradients in older adults. The authors reported that the organization of functional communities (networks) within gradient space was generally stable, while the communities themselves became more dispersed with increasing age, particularly within frontoparietal and default network regions (Bethlehem et al., 2020). Consistent with these previous findings, we predict that the overall gradient architecture will be similar between younger and older adults. However, given the increase in signal to noise associated with ME-EPI and ME-ICA denoising, we predict that additional age-related differences in regional connectivity profiles will emerge that reflect network specific patterns of dedifferentiation, consistent with our previous works (Spreng et al., 2016; Turner and Spreng, 2015).

Edge-level precision to detect age differences in the organization of functional brain networks is enabled by PLS. This multivariate approach analyzes the full edge-level connectivity matrix in a single statistical step, eliminating the need for additional thresholding within an *a priori* defined network parcellation scheme, and resulting in reliable age differences across the full matrix. Here, we first examined edge-level connectomics within a canonical seven-network solution (Yeo et al., 2011). Next, based on previous work, we conducted an *a priori analysis* of the sub-network topography for the default, frontoparietal and dorsal attention networks, derived from the 17-network solution by Yeo and colleagues (2011). Based on our own work and others (Chan et al., 2014; Geerligs et al., 2015; Grady et al., 2016; Spreng & Schacter, 2012; Spreng et al., 2016; Sullivan et al., 2019; Turner and Spreng, 2015), we predicted a global pattern of age-related network dedifferentiation, marked by integration of default and frontoparietal regions and reduced anti-correlations between the default and dorsal attention networks.

Finally, we implemented a novel, individualized functional parcellation approach to identify person-specific functional network nodes (Chong et al., 2017). These individualized parcellations were used in both the gradient and edge-level connectivity analyses. This is an innovative approach designed to facilitate comparisons of RSFC between younger and older adults. Poor registration to standardized templates may fail to capture individual variability in functional organization of the cortex, and these registration problems may systematically differ across age groups (Braga and Buckner, 2017; Chong et al., 2017; Gordon, et al. 2017; Kong et

al., 2019; Kong et al., 2021; Laumann et al., 2015; Wang et al., 2015). Deriving functionally-defined, person-specific cortical parcellations can account for differences at the level of the individual, thereby mitigating systematic registration biases in between-group comparisons. Adopting an individualized parcellation approach may also lessen the impact of noise artifacts that can obscure small yet reliable group differences, increasing power to detect reliable brain-behavior associations (Kong et al., 2021).

Leveraging a multifaceted analysis protocol (see Figure 1), this study addressed two core aims towards advancing our understanding of functional brain aging. The first was to identify age differences in the resting-state connectome, with a specific focus on discerning global, macroscale and edge-level connectivity patterns of network dedifferentiation. A second, supporting aim was to apply a series of novel methodological approaches to (i) reduce the impacts of common confounds in network neuroscience research and (ii) conduct a spatial multiscale (whole-brain to region- and edge- specific) analysis of functional connectivity differences in the aging brain. In light of aims one and two, a third exploratory aim was to ascertain whether functional dedifferentiation, either at global or local levels, was associated with age differences in cognition.

Figure 1

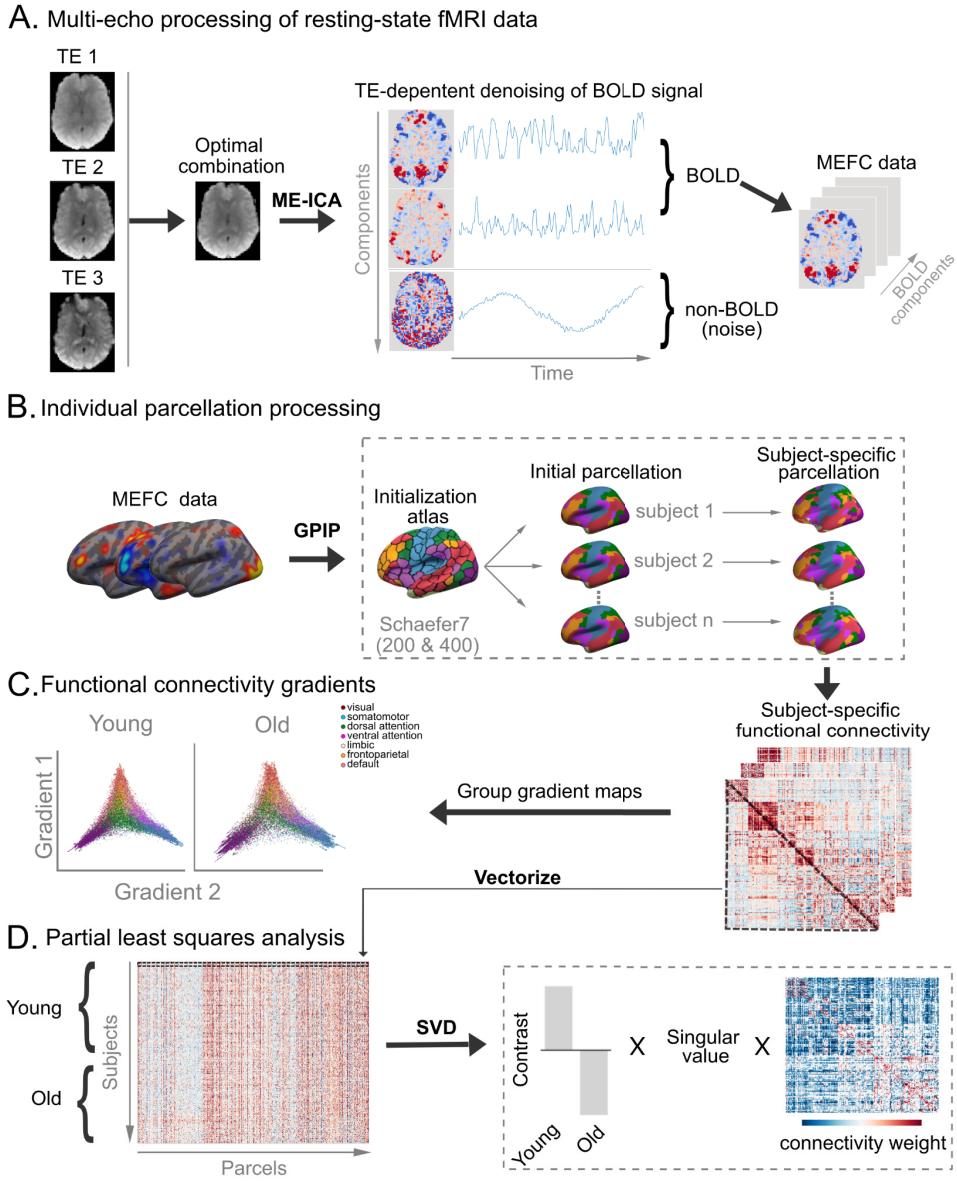

Figure 1 Caption: Workflow of study methods. (A) Processing of multi-echo resting-state fMRI images. For each functional run, three echoes (TE_1, TE_2, TE_3) were combined and denoised using multi-echo independent component analysis (ME-ICA). The denoising process involved removing components with non-BOLD signal (noise) and retaining the BOLD components. MEFC images are made up of the BOLD component coefficient sets. (B) Individualized parcellations were generated. The MEFC data for all participants were resampled to a common cortical surface. All participants were first initialized to a pre-defined cortical parcellation atlas (Schaefer atlas). Parcellations were then refined by participant (subject-specific parcellation). For each participant, MEFC data were extracted from and correlated with each parcel to create a subject-specific functional connectivity matrix. These matrices were used to (C) compute cortical gradients in younger and older adults and (D) assess age-related differences in functional connectivity using partial least squares, which performs a singular value decomposition (SVD).

Materials and Methods

Participants

Participants were 181 younger (M_{age}=22.59y, *SD*=3.27; 57% female) and 120 older (M_{age}=68.63y, *SD*=6.44; 55% female) healthy adults from Ithaca, New York, and Toronto, Canada (Table 1), rendering a total sample size of 301. Standard inclusion and exclusion criteria were implemented to ensure all participants were healthy without evidence of neurological, psychiatric or other underlying medical conditions known to impact brain or cognitive functioning. Specifically, participants were screened to rule out individuals with acute or chronic psychiatric illness, those undergoing current or recent treatment with psychotropic medication, and those having experienced significant changes to health status within three months of the eligibility interview. Younger and older participants were screened for depressive symptoms using the Beck Depression Inventory (Beck et al., 1996) or the Geriatric Depression Scale (Yesavage et al., 1982), respectively. Two older adults were excluded due to a rating of "moderate depression". Older adults were additionally administered the Mini-Mental State Examination (MMSE; Folstein et al., 1975) to rule out mild cognitive impairment or sub-clinical dementia. Participants with MMSE scores below 27/30 were excluded if fluid cognition scores (Gershon et al., 2013) also fell below an age-adjusted national percentile of 25%. All participants were right-handed with normal or corrected-to-normal vision. Procedures were administered in compliance with the Institutional Review Board at Cornell University and the Research Ethics Board at York University.

Table 1

Sample Demographics

	Descriptive Statistics		Inferential Statistics				
	Younger Adults	Older Adults	*T*	df	*p*	95% CI	Cohen's *d*
N							
Cornell	154 (86 female)	84 (47 female)					
York	27 (17 female)	36 (19 female)					
Age (years)							
Range	18-34	60-89					
M	22.6	68.6					
SD	3.3	6.4					
Education (years)*			-7.20	285	< .001	[-2.5, -1.48]	0.86
Range	12-24	12-24					
M	15.2	17.2					
SD	1.9	2.9					
MMSE*			3.09	281	< .005	[.17, .75]	0.37
Range	22-30	25-30					
M	29.09	28.630					
SD	1.22	1.27					
Episodic Memory*			17.51	281	< .001	[1.1, 1.38]	2.11
Range	-1.75-1.59	-1.99-0.70					
M	0.52	-0.71					
SD	0.53	0.66					
Semantic Memory*			-9.18	281	< .001	[-1.00, -.65]	1.10
Range	-2.78-1.39	-1.29-1.91					
M	-0.35	0.48					
SD	0.77	0.71					
Executive Function*			12.67	281	< .001	[.71, .97]	1.52
Range	-1.15-1.80	-2.03-0.76					
M	0.36	-0.48					
SD	0.56	0.53					
Processing Speed*			15.03	281	< .001	[1.17, 1.53]	1.81
Range	-2.26-3.05	-2.40-.050					
M	0.57	-0.78					
SD	0.86	0.56					

Table 1 Note: Episodic Memory, Semantic Memory, and Executive Function are index scores. Processing Speed is a z-score on Symbol Digit Modalities Task, Oral. * significant group differences. Education was not recorded for 14 participants. Age group differences in MMSE, episodic memory, semantic memory, executive function, and processing speed were tested in 283 participants. Positive T values reflect higher scores in younger adults, negative values reflect higher scores in older adults. Statistical results were nearly identical when including sex, education, site, and estimated whole brain volume as covariates in an ANCOVA.

Cognitive Assessment

We first characterized our sample with a deep cognitive assessment. 283 of 301 individuals (163/181 younger adults, 120/120 older adults) underwent cognitive testing prior to brain scanning. Index scores were created for cognitive domains of episodic memory, semantic memory, executive function, and processing speed (descriptives in Table 1). Episodic memory tasks included Verbal Paired Associates from the Wechsler Memory Scale-IV (Wechsler, 2009), the Associative Recall Paradigm (Brainerd et al., 2014), and NIH Cognition Toolbox Rey Auditory Verbal Learning and Picture Sequence Memory Tests (Gershon et al., 2013). Semantic memory tasks included Shipley-2 Vocabulary (Shipley et al., 2009), and NIH Cognition Toolbox Picture Vocabulary and Oral Reading Recognition Tests (Gershon et al., 2013). Executive function comprised the Trail Making Test (B-A; Reitan, 1958), the Reading Span Task (Daneman & Carpenter, 1980), NIH Cognition Toolbox Flanker Inhibitory Control and Attention task, Dimensional Change Card Sort, and List Sort Working Memory Tests (Gershon et al., 2013). Processing speed was tested with the Symbol Digit Modalities Test, Oral (Smith, 1982).

All data were z-scored. Index scores represent the average z-score for all measures included within a cognitive domain. Across the four domains, higher scores represent better performance. Brain-behavior product-moment correlations were conducted at an alpha level of .05 with 95% confidence intervals. Bonferroni adjustments for multiple comparisons were set at $p < .013$ for the four index score tests.

Neuroimaging

Image Acquisition

Imaging data were acquired on a 3T GE750 Discovery series MRI scanner with a 32-channel head coil at the Cornell Magnetic Resonance Imaging Facility or on a 3T Siemens Tim Trio MRI scanner with a 32-channel head coil at the York University Neuroimaging Center in Toronto. Scanning protocols were closely matched across sites. Anatomical scans at Cornell were acquired using a T1-weighted volumetric magnetization prepared rapid gradient echo sequence (TR=2530ms; TE=3.4ms; 7° flip angle; 1mm isotropic voxels, 176 slices, 5m25s) with 2x acceleration with sensitivity encoding. At York, anatomical scans were acquired using a T1-weighted volumetric magnetization prepared rapid gradient echo sequence (TR=1900ms;

TE=2.52ms; 9° flip angle; 1mm isotropic voxels, 192 slices, 4m26s) with 2x acceleration and generalized auto calibrating partially parallel acquisition (GRAPPA) encoding at an iPAT acceleration factor of 2. Two 10m06s resting-state runs were acquired using a multi-echo (ME) EPI sequence at Cornell University (TR=3000ms; TE_1=13.7ms, TE_2=30ms, TE_3=47ms; 83° flip angle; matrix size=72x72; field of view (FOV)=210mm; 46 axial slices; 3mm isotropic voxels; 204 volumes, 2.5x acceleration with sensitivity encoding) and York University (TR=3000ms; TE_1=14ms, TE_2=29.96ms, TE_3=45.92ms; 83° flip angle; matrix size=64x64; FOV=216mm; 43 axial slices; 3.4x3.4x3mm voxels; 200 volumes, 3x acceleration and GRAPPA encoding). Participants were instructed to stay awake and lie still with their eyes open, breathing and blinking normally in the darkened scanner bay.

Image Processing

Anatomical images were skull stripped using the default parameters in FSL BET (Smith, 2002). Brain-extracted anatomical and functional images were submitted to ME independent component analysis (ME-ICA; version 3.2 beta; https://github.com/ME-ICA/me-ica; Kundu et al., 2011; Kundu et al., 2013). ME-ICA relies on the TE-dependence model of BOLD signal to determine T2* in every voxel and separates BOLD signal from non-BOLD sources of noise. Prior to TE-dependent denoising, time series data were minimally preprocessed: the first 4 volumes were discarded, images were computed for de-obliquing, motion correction, and anatomical-functional coregistration, and volumes were brought into spatial alignment across TEs. The T2* maps were then used for anatomical-functional coregistration. Grey matter and cerebrospinal fluid compartments are more precisely delineated by the T2* map than by raw EPI images (Speck et al., 2001; Kundu et al., 2017), which is an important consideration in aging research where these boundaries are often blurred by enlarged ventricles and greater subarachnoid space. Volumes were then optimally combined across TEs and denoised. The outputs of interest included: 1) spatial maps consisting of the BOLD components, 2) reconstructed time series containing only BOLD components, and 3) the BOLD component coefficient sets.

Image quality assessment was performed on the denoised time series in native space to identify and exclude participants with unsuccessful coregistration, residual noise (framewise displacement > .50 mm coupled with denoised time series showing DVARS >1, Power et al.,

2012), temporal signal to noise ratio < 50, or fewer than 10 retained BOLD-like components (see Supplementary Figure 1 for the group temporal signal to noise map).

The denoised BOLD component coefficient sets in native space, optimized for functional connectivity analyses (Kundu et al., 2013), were used in subsequent steps. We refer to these as multi-echo functional connectivity (MEFC) data. Additional measures were taken to account for variation in the number of independent components from ME-ICA once connectivity matrices were estimated, as detailed below. MEFC neuroimages were mapped to a common cortical surface for each participant using FreeSurfer v6.0.1 (Fischl et al., 2012). To maximize alignment between intensity gradients of structural and functional data (Greve & Fischl, 2009), MEFC data were first linearly registered to the T1-weighted image by run. The inverse of this registration was used to project the T1-weighted image to native space and resample the MEFC data onto a cortical surface (fsaverage5) with trilinear volume-to-surface interpolation. This produces a cortical surface map where each vertex, or surface point, is interpolated from the voxel data. Once on the surface, runs were concatenated and MEFC data at each vertex were normalized to zero mean and unit variance.

Individualized Parcellation. We generated participant-specific functional parcellations to examine individual differences in functional brain network organization using the Group Prior Individual Parcellation (GPIP; Chong et al., 2017). This approach enables a more accurate estimation of participant-specific individual functional areas (Chong et al., 2017) and is more sensitive to detecting RSFC associations with behavior (e.g. Kong et al., 2019; Mwilambwe-Tshilobo et al., 2019). The main advantage of this approach is that the correspondence among parcel labels is preserved across participants, while the parcel boundaries are allowed to shift based on the individual-specific functional network organization of each participant—thus providing a similar connectivity pattern that is shared across the population. Starting from an initial pre-defined group parcellation atlas, GPIP first refines each individual's parcel boundaries relative to their resting-state fMRI data. Next, the concentration (inverse covariance/partial correlation) matrices from all subjects are jointly estimated using a group sparsity constraint. GPIP iterates between these two steps to continuously update the parcel labels until convergence, defined as no more than one vertex changing per parcel or 40 iterations. Compared to other group-based parcellation approaches, GPIP has shown to improve the homogeneity of the BOLD signal within parcels and the delineation between regions of functional specialization (Chong et al., 2017).

We extracted MEFC data from each vertex and applied the above parcellation across the entire cohort of 301 participants at resolutions of 200 and 400 parcels. For each resolution, MEFC data were initialized to a group parcellation atlas developed by Schaefer et al. (2018). We use this cortical parcellation scheme both as the initialization reference for our individualized cortical parcellation maps, as well as for our edge-level connectomic analyses described below. We selected the Schaefer atlas for three reasons: (i) It is functionally-derived, and thus more closely aligned with the current study aims, (ii) it has high spatial resolution and can offer different granularities (we report findings from both 400 and 200 node parcellations here), and (iii) it is among the most commonly reported cortical parcellation atlases in the literature, and provides an intrinsic partitioning of nodes within Yeo 7- and 17- network solutions used in our edge-level connectomics analyses (Yeo et al., 2011).

Following initialization with the Schaefer parcellations, the two-step iterative process was repeated 20 times to produce a final parcellation representing the optimal partition with respect to the entire cortical surface. We calculated homogeneity by taking the average correlation coefficient of all pairs of vertices in a given parcel and then averaging across all parcels. This was repeated at each repetition to observe the incremental change in homogeneity as the iterative parcellation proceeded. Homogeneity was calculated first at the participant level and then averaged across the entire cohort for a group estimate. For a subset of participants, some parcels from the final partition merged into the medial wall (where no data existed) or into parcels belonging to the contralateral hemisphere. Because partitions likely reflect participant-specific neurobiological variations in functional organization, parcels assigned to the contralateral hemisphere were allowed to retain their original group atlas label. With the 400-parcel resolution, parcels merging with the medial wall occurred in 69 older adults and 35 younger adults, averaging 2-3 parcels in these participants; parcels migrating to the contralateral hemisphere occurred in 62 older adults and 24 younger adults, averaging 2-3 parcels. With the 200-parcel resolution, parcels merging with the medial wall occurred in 18 older adults and 10 younger adults, averaging 1 parcel in these participants. No parcels migrated to the contralateral hemisphere at this resolution.

Functional Connectivity Matrix. A connectivity matrix was constructed for each participant according to their individualized parcel solution. We extracted and spatially averaged the resulting MEFC data from each parcel and computed the product-moment correlation between each pair, resulting in a $n_{parcels} \times n_{parcels}$ functional connectivity matrix (Ge, Holmes, Buckner, Smoller,

& Sabuncu, 2017). In this approach, RSFC was calculated as the correlation of the ICA coefficients across parcels, rather than a correlation across BOLD signal time-series, as is typically done (see Kundu et al., 2013). The canonical Fisher's r-to-z transformation was then applied to normalize the distribution of correlation values and account for variation in MEFC data degrees of freedom, or the number of denoised ICA coefficients (i.e. number of BOLD components), across individuals (Kundu et al., 2013):

$$Z = \text{arctanh}(\text{R}) \cdot \sqrt{df - 3}$$

where R is the product-moment correlation value and *df* is the number of denoised ICA coefficients. Computing functional connectivity with approximately independent component coefficients rendered global signal regression unnecessary (Spreng et al., 2019). Critically, ME-ICA effectively removes distance-dependent RSFC motion confounds from fMRI data (Power et al., 2018). As shown in Supplemental Figure 2 (see also Supplemental Material), framewise displacement had a comparable impact on younger and older adult RSFC, ruling out motion as a potential confound in the results reported below.

Analysis

BOLD Dimensionality

A unique advantage of ME-fMRI and the ME-ICA processing framework is that BOLD- and non-BOLD-like signals are separated into independent components. A novel metric of "BOLD dimensionality," the number of BOLD components identified by ME-ICA, may then be examined (e.g. Kundu et al., 2018). We assessed the test-retest reliability of BOLD dimensionality across two runs of data. Total BOLD dimensionality was then compared between groups with an independent samples *t*-test and an ANCOVA controlling for sex, education, site and estimated whole brain volume (eWBV; sum of grey and white matter divided by total intracranial volume, derived from FreeSurfer). To observe the trajectory of BOLD dimensionality with increasing age across the lifespan, BOLD dimensionality data from an independent developmental sample (N = 51, 10 female; M_{age}=21.9 years; age range, 8.3 – 46.2 years; see Kundu et al., 2018 for details) were pooled with the current data. To render the samples comparable and account for differences in acquisition across datasets, BOLD dimensionality was scaled by the number of timepoints acquired. The relationship between age and BOLD dimensionality was then fit to a power law function (see Supplemental Figure 3 for unscaled version). Further characterization of BOLD signal dimensionality, including associations with graph analytic measures of participation coefficient, modularity and segregation, and BOLD signal dimensionality's relationship to whole brain RSFC are reported in Supplemental Material (Supplemental Table 1, Supplemental Figures 4 & 5)

Gradients & Manifold Eccentricity

Cortical gradients were computed using functions from the BrainSpace toolbox (https://github.com/MICA-MNI/BrainSpace; Vos de Wael et al., 2020), as implemented in MATLAB. For each participant, the 400 x 400 GPIP functional connectivity matrix was thresholded row-wise to the upper 10% of connections to retain only the strongest positive connections (Hong et al., 2019; Margulies et al., 2016). Cosine similarity was computed on the sparse matrix to input to the diffusion map embedding algorithm employed below, generating a

matrix that captures similarity in whole-brain connectivity patterns between vertices (Hong et al., 2019; Margulies et al., 2016).

We then applied diffusion map embedding, a non-linear dimensionality manifold learning technique from the family of graph Laplacians (Coifman et al., 2005), to identify gradient components at the individual participant level. Each gradient represents a low-dimensional embedding estimated from a high-dimensional similarity matrix. In the embedding space, vertices that feature greater similarity in their whole-brain functional connectivity patterns appear closer together, whereas vertices that are dissimilar are farther apart. Each embedding axis can thus be interpreted as an axis of variance based on connectivity pattern similarity/dissimilarity. Euclidean distance in the embedded space is equivalent to the diffusion distance between probability distributions centered at those points, each of which is equivalent to a *difference in gradient* score. The algorithm is controlled by a single parameter α, which controls the influence of density of sampling points on the manifold (Margulies et al, 2016). We used $\alpha = 0.5$ in this study, which differentiates diffusion map embedding from Laplacian eigenmaps, and allows the inclusion of both global and local relationships in the estimation of the embedded space. An iterative Procrustes rotation was performed to align participant-specific gradient components to a young-old group average template and enable group comparisons. Group contrasts were conducted using surface-based linear models, as implemented in Surfstat (Worsley et al., 2009; http://www.math.mcgill.ca/keith/surfstat/) controlling for sex, education, site and eWBV.

We calculated a metric of manifold eccentricity to quantify the diffusivity of vertices in gradient space. More diffuse vertices within a network indicates more variable and dedifferentiated functional connectivity profiles. Following Bethlehem et al. (2020) and Park et al. (2020), we summed the squared Euclidean distance of each vertex from the whole-brain median in a 2-dimensional gradient space for each participant. Mean manifold eccentricity was then compared across age groups. Statistical significance was determined with spin-test permutation testing, which overcomes biases in the test statistic due to the spatial autocorrelation inherent to BOLD data (Alexander-Bloch et al., 2018). An ANCOVA on manifold eccentricity was also conducted controlling for sex, education, site and eWBV.

Edge-Level Connectomics

Inter-regional functional connectivity group differences were tested with PLS. PLS is a multivariate method that determines the association between two sets of variables by identifying linear combinations of variables in both sets that maximally covary together (McIntosh and Lobaugh, 2004; McIntosh and Misic, 2013). In our analyses, one set of variables was individual RSFC matrices, while the other set represented group assignment or individual difference metrics (e.g., BOLD dimensionality; see Supplemental Material).

Functional connectivity was assessed at the whole-brain level using the Schaefer atlas (Schaefer et al., 2018; Yeo et al., 2011; 400 x 400 matrix; 200 x 200 matrix as supplementary analysis, Supplemental Figure 6). Motivated by prior work (e.g., Grady et al., 2016; Sullivan et al., 2019; Spreng et al., 2016), we also examined RSFC among sub-networks of the default, frontoparietal control, and dorsal attention networks. For the sub-network analysis, we first reassigned each of the 400 parcels to the corresponding network of the Yeo 17-network solution following the mapping based on Schaefer et al. (2018). Next, we created a matrix for the pairwise connections between 8 sub-networks: dorsal attention (DAN-A, DAN-B), frontoparietal control (CONT-A, CONT-B, CONT-C), and default (DN-A, DN-B, DN-C), resulting in a 192x192 parcel matrix. The full 17-network characterization of the 400x400 parcel results, along with the 17-network and sub-network characterizations of the 200x200 matrix, can be found in Supplemental Figures 7, 8, and 9. At each level, a data matrix **X** was created using all participants' parcellated functional connectivity matrices. The **X** matrix was organized such that each row corresponded to an observation (each participant, nested in age groups), and the cells in each column corresponded to the unique connections from each participant's connectivity matrix (the lower triangle of the matrix). The column means within each group were calculated, and the data in **X** were mean-centered. The mean-centered data were then submitted to singular value decomposition (SVD) to provide mutually orthogonal latent variables. Each latent variable represents a specific relationship (e.g. RSFC x Group) and consists of three elements: (1) a left singular vector consisting of the weighted connectivity pattern that optimally expresses the covariance, (2) a right singular vector, which represents the weights of the study design variables and can be interpreted as data-driven contrast weights between groups, and (3) a scalar singular value, which represents the covariance strength between the design variables (Group) and RSFC accounted for by each latent variable. Brain connectivity scores were calculated by taking the dot product of the left singular vector and each participant's RSFC matrix. A brain connectivity score, therefore, represents a single measure

of the degree to which a participant expresses the connectivity pattern captured by a given latent variable.

All PLS latent variables were statistically evaluated using permutation testing. Rows of **X** were randomly reordered and subjected to SVD iteratively, as described above. This was done 1,000 times to create a distribution of singular values under the null hypothesis of no existing relationships between X and Y for the corresponding PLS analysis: that there is no group difference in whole-brain (or sub-network) RSFC. A *p*-value was computed for each latent variable as the proportion of permuted singular values greater than or equal to the original singular value. Critically, permutation tests involve the entire multivariate pattern and are performed in a single analytic step, so correction for multiple comparisons is not required (McIntosh and Lobaugh, 2004).

Bootstrap resampling was used to estimate the reliability of weights for each RSFC edge. Participants were randomly resampled (rows in **X**) with replacement while respecting group membership. The matrix was subjected to SVD and the process was repeated 1,000 times, generating a sampling distribution for the weights in the singular vectors. To identify individual connections that made a statistically significant contribution to the overall connectivity pattern, we calculated the ratio between each weight in the singular vector and its bootstrap-estimated standard error. Bootstrap ratios are equivalent to z-scores if the bootstrap distribution is approximately unit normal (Efron and Tibshirani, 1986). Bootstrap ratios were, therefore, thresholded at values of ±1.96, corresponding to the 95% CI.

Network-Level Contributions

PLS analyses identified inter-regional connectivity patterns that differed by group and/or covaried with individual difference metrics. For each of these analyses, network-level effects were also examined. To quantify the network-level contributions to the PLS-derived functional connectivity pattern, two separate weighted adjacency matrices were constructed from positive and negative RSFC weights. For both matrices, nodes represent parcels defined by the individual parcellation, while edges correspond to the thresholded bootstrap ratio of each pairwise connection. Network-level functional connectivity contributions were quantified by assigning each parcel according to the network assignment reported by Yeo et al. (2011), and taking the average of all connection weights in a given network, thereby generating a 7 x 7 matrix (17 x 17 matrix for

the 17-network solution; and an 8 x 8 matrix when examining the default, frontoparietal control, and dorsal attention sub-networks). The significance of mean within- and between- network connectivity was computed by permutation testing. During each permutation, network labels for each node were randomly reordered and the mean within- and between- network connectivity were recalculated. This process was repeated 1000 times to generate an empirical null sampling distribution that indicates no relationship between network assignment and connectivity pattern (Shafiei et al., 2019). The significance of the pairwise connections to the network matrix was determined by estimating the proportion of times the value of the sampling distribution was greater than or equal to the original value.

Spring-Embedded Plots

Spring-embedded plots were rendered from group average matrices of RSFC data using Pajek software (Mrvar and Batagelj, 2016). Sparse matrices containing the top 5% of positive connections were entered into Pajek. A partition was assigned based on the Yeo 7- or 17-network solution (Yeo et al., 2011) to optimize community (i.e., network) structure for visualization.

Results

To interrogate the intrinsic functional architecture of the aging brain, we implemented a multifaceted, multiscale data acquisition and analysis protocol in younger and older healthy adults (see Figure 1 and Methods). To identify global patterns of network dedifferentiation with age, we first assessed age differences in the dimensionality of the ME-fMRI BOLD signal as output from ME-ICA. Next, we examined network-specific dedifferentiation patterns, contrasting macroscale gradients and edge-level network connectomics between younger and older adults. At each turn, we examined associations between network organization and cognitive functioning for younger and older adults. Brain and behavior associations for each analysis are reported in Supplemental Materials (Supplemental Tables 2, 3 and 4; Supplemental Figures 10 and 12). All results are reported with covariates of site, sex, education, and eWBV where appropriate.

BOLD Dimensionality

Two 10-minute runs of resting-state ME-fMRI were collected. BOLD dimensionality, the number of independent BOLD components in ME-fMRI signal, was stable across runs ($r(299) = .79$, $p < .001$ [.75, .83]; Figure 2A). Younger adults showed greater BOLD dimensionality than older adults ($t(299)=15.38$, $p < .001$; Cohen's $d= 1.81$; Figure 2B). This remained true when covariates of site, sex, education, and eWBV were included ($F(1,281)= 97.07$, $p < .001$; $\eta_p^2 = .26$). In the context of lifespan development, which included an additional sample aged 8-46 (Kundu et al., 2018), a power function provided a suitable fit between age and BOLD dimensionality ($R^2=.547$; Figure 2C). BOLD dimensionality associations with cognition are in Supplemental Tables 2, 3 and 4 and Supplemental Figure 10A.

Figure 2

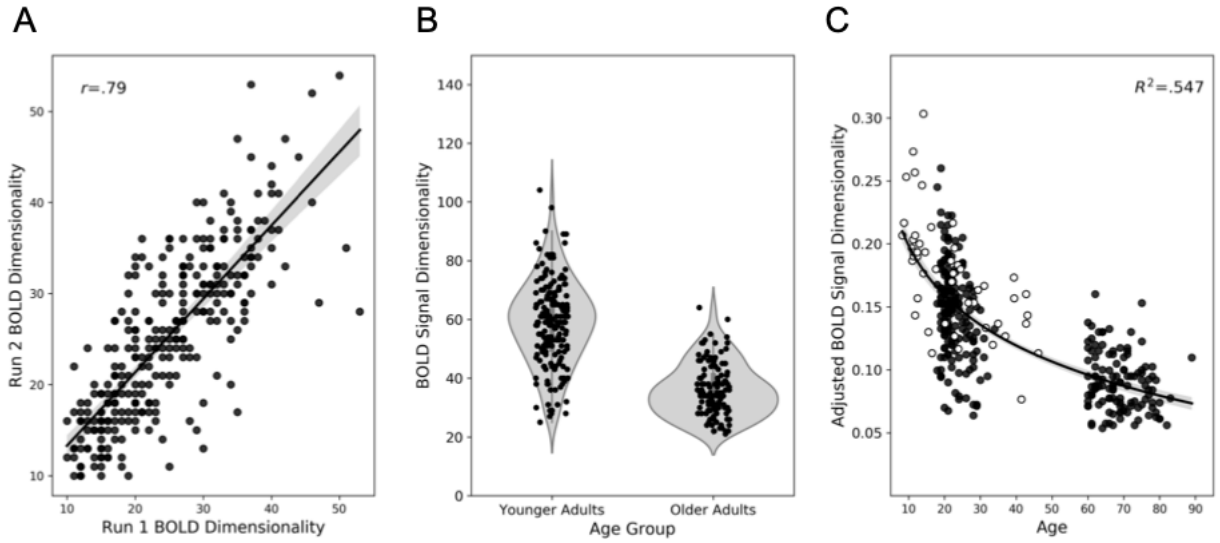

Figure 2 Caption: BOLD signal dimensionality. (A) High test-retest reliability across two ME-fMRI runs. (B) Violin plots show distributions of total BOLD signal components across runs in younger and older adults. (C) Scatter plot showing BOLD signal dimensionality by age with a power distribution and 95% confidence intervals overlaid. Points in white were contributed by Kundu and colleagues (2018). Adjusted BOLD signal dimensionality = Total number of accepted BOLD components / number of time points acquired.

Gradient Analyses

We next characterized macroscale gradients of functional connectivity in younger and older adults (e.g., Hong et al., 2019; Margulies et al., 2016). In both groups, the principal gradient spanned from unimodal regions to transmodal regions (Figure 3A), suggesting that macroscale functional organization of the cortex is generally preserved with age. However, several age differences emerged. A whole-brain age group comparison on the principal gradient revealed higher gradient values in the right superior parietal lobule and somatosensory cortex for older adults (FWE $p < .05$; cluster defining threshold $p < .01$; Figure 3A). This suggests that these regions exhibited a pattern of functional connectivity that is less similar to unimodal cortices, and more similar to heteromodal cortex, in older versus younger adults. In contrast, older adult connectivity profiles for occipital and ventral temporal regions were more similar to unimodal than heteromodal cortices.

The second gradient displayed a continuum of functional connectivity profiles spanning visual cortex on one end to somatomotor and auditory cortices on the other (Figure 3B). Whole-

brain group comparisons revealed that temporoparietal junction connectivity patterns are less similar to those of visual regions for older adults. Additionally, whole brain connectivity patterns for a segment of the superior parietal lobule/intraparietal sulcus (ventral to the region in the first gradient) are less similar to the connectivity profiles of somatomotor regions, and more similar to visual cortical regions, for older compared to younger adults.

Finally, we rendered principal-second gradient manifold scatterplots in a 2D gradient embedding space in younger and older adults (Figure 3C). Older adults showed more diffuse, and thus dedifferentiated vertices. We quantified this diffusivity by calculating manifold eccentricity– the sum of Euclidean distance across all vertices from the median– for each participant and compared across groups. Results revealed significantly greater manifold eccentricity in older adults ($t(299) = -10.74$, $p_{SPIN} < 0.01$, Cohen's $d = 1.26$; $F(1,281)= 47.18$, $p < .001$, $\eta_p^2 = .14$ with site, sex, education, and eWBV covariates included). See Supplemental Tables 2, 3 and 4 and Supplemental Figure 10B for associations with behavior.

As BOLD dimensionality and manifold eccentricity both demonstrated significant age group differences, we conducted post-hoc product-moment correlations to test whether these global measures of brain organization were reliably associated. Negative correlations were observed in both younger ($r(179)= -.575$, $p < .001$, [-.66, -.47]) and older adults ($r(118)= -.255$, $p < .005$, [-.42, -.08]), such that higher BOLD dimensionality was related to less diffuse, more compact vertices in the manifold. In computing a partial correlation controlling for age, the relationship remained when performed on the full sample ($pr(298)= -.391$, $p < .001$, [-.48, -.29]). Non-overlapping 95% confidence intervals indicated a significantly more negative correlation in younger adults. Results were similar when repeated with covariates (young: $pr(161)= -.45$, $p < .001$, [-.53, -.36]; old: $pr(113)= -.23$, $p < .05$, [-.35, -.11]; full sample: $pr(280)= -.34$, $p < .001$, [-.44, -.23]), although confidence intervals overlapped between groups. Supplemental Figure 11 illustrates the relationship in each age group.

Figure 3

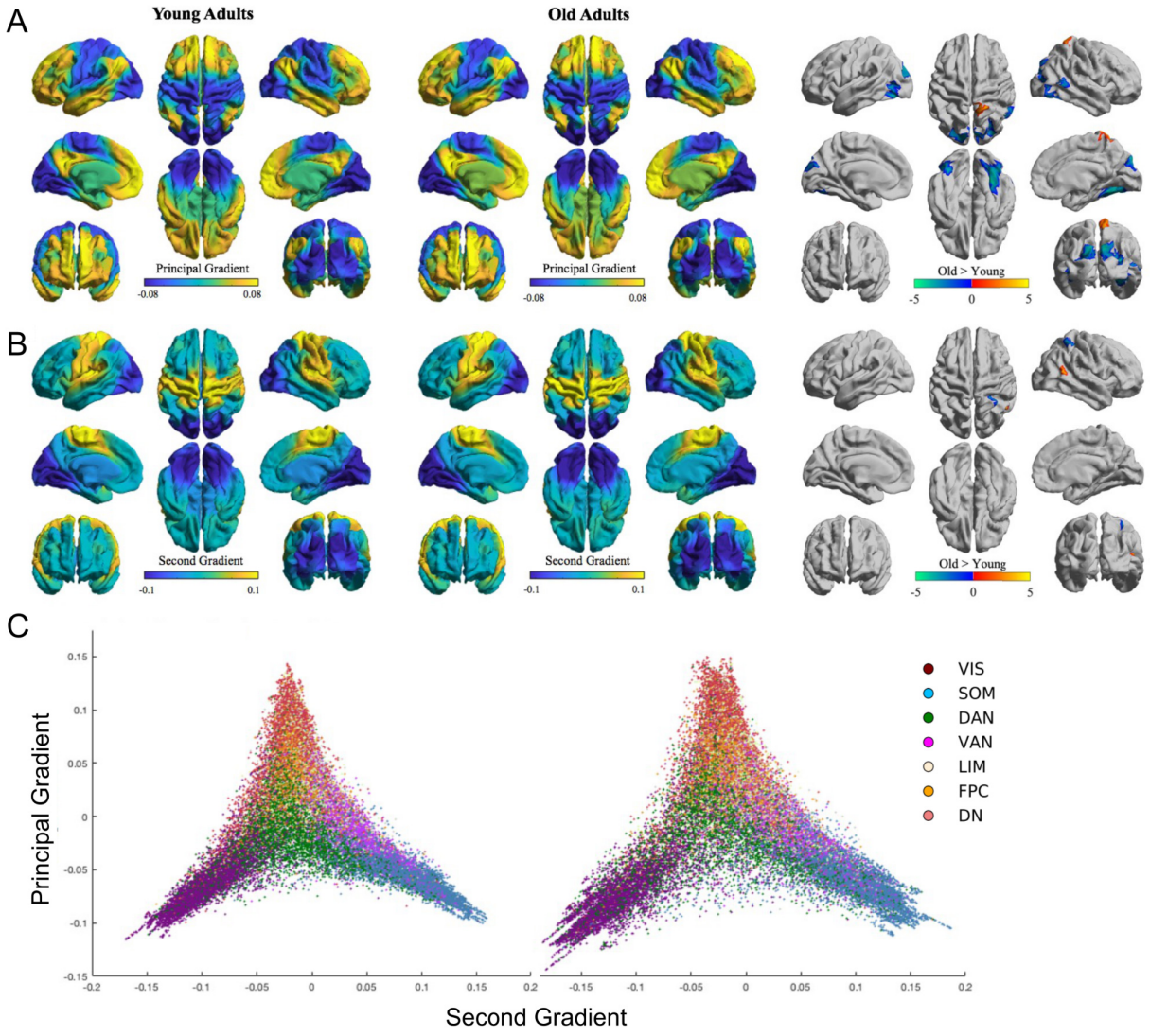

Figure 3 Caption: Gradients of cortical connectivity in younger and older adults. (A) The mean principal gradient for younger (left) and older (center) adults, representing an axis of functional connectivity similarity variance that ranged lowest to highest from unimodal to transmodal cortex. (B) The mean second gradient for younger (left) and older (center) adults, representing an axis of functional connectivity similarity variance that ranged lowest to highest from visual to somatomotor cortex. Older adults > younger adults contrasts revealing statistically significant clusters at FWE $p < 0.05$, cluster defining threshold $p < 0.01$ (A & B right). (C) Scatterplots representing the principal-second gradient manifold for younger (left) and older (right) adults. Scatterplot colors indicate functional networks as per the 7-network solution by Yeo et al. (2011). VIS = visual, SOM= somatomotor, DAN= dorsal attention, VAN = ventral attention, LIM = limbic, FPC= frontoparietal control, DN= default.

Edge-Level Connectomics

We next examined edge-level, interregional functional connectivity differences between younger and older adults. Group mean connectivity matrices are in Figure 4A-B. Qualitative differences in the top 5% of positive connections between groups can be observed with a spring-embedded layout arranged by their network membership (Figure 4C-D). The spring-embedded plot displays stronger integration of the dorsal attention and frontoparietal control networks in older adults.

PLS (whole brain)

Age-related differences in the 79800 interregional connections (i.e., the lower triangle of the 400x400 functional connectivity matrix) were quantitatively assessed with PLS. A significant latent variable (permuted $p = 0.0001$) revealed a pattern of age differences in RSFC, with increases and decreases observed across the connectome (Figure 4E). Network contribution analysis of within- and between- network edges revealed significant age effects. Older adults demonstrated lower within-network connectivity across all seven networks, and lower connectivity between limbic, frontoparietal control and default networks (Figure 4F). Older adults showed greater between-network connectivity across systems for the visual and somatomotor networks (Figure 4G). The overall pattern of age-related differences was similar when examined with a 200 parcellation scheme (Supplementary Figure 6). Brain connectivity scores' association with cognition are reported in Supplemental Table 2, 3, and 4, and Supplemental Figure 12.

Figure 4

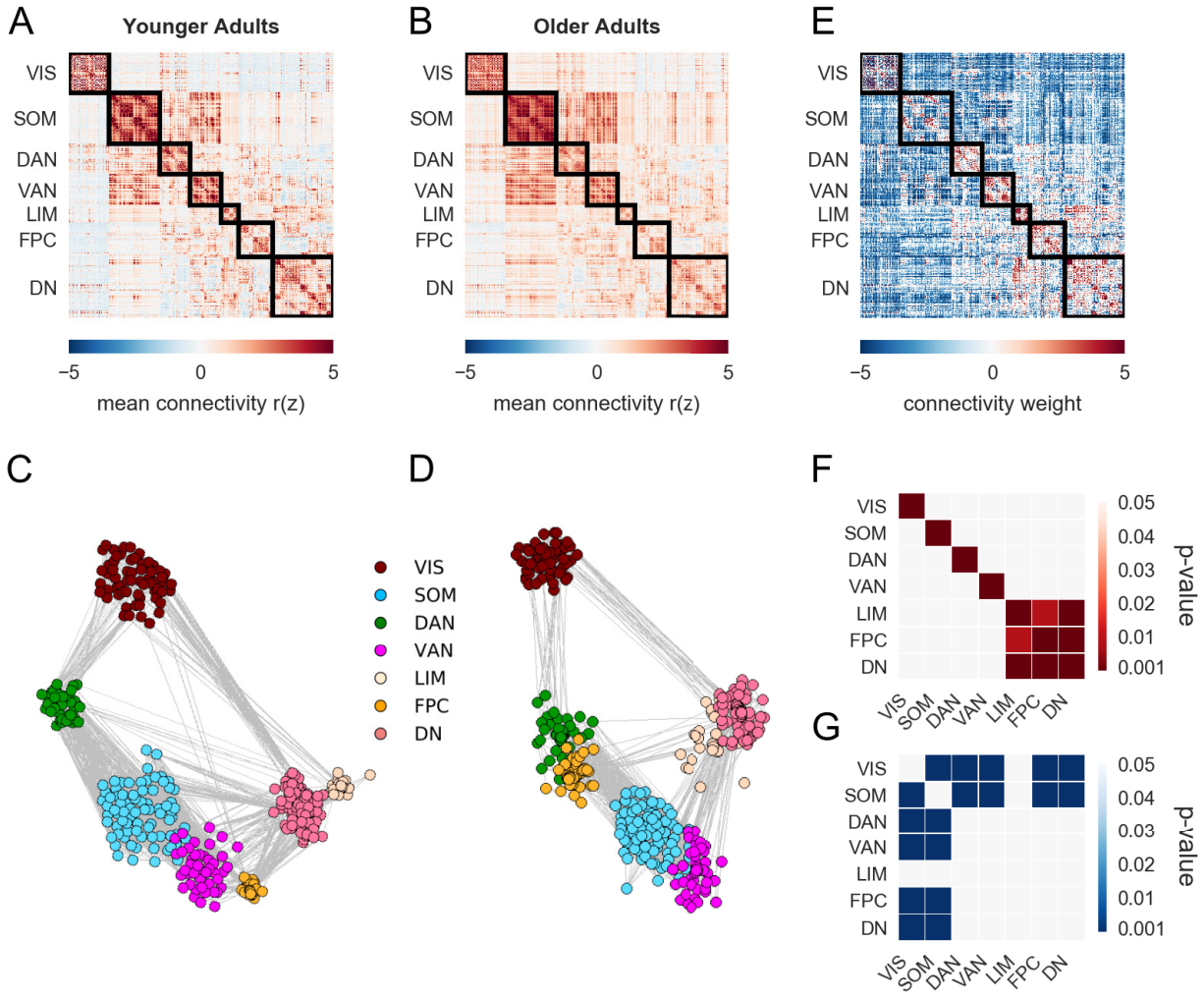

Figure 4 Caption: Functional connectomics in younger and older adults. Mean RSFC for the 400-parcellated data in (A) younger and (B) older adults. Spring-embedded plots with a 7-network solution (5% edge density) of the mean correlation matrices for (C) younger and (D) older adults. (E) Multivariate PLS analysis was used to identify age-related differences in RSFC between younger and older adults. Red color indicates significantly greater RSFC in younger adults, and blue color indicates significantly greater RSFC in older adults. (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. The mean positive and negative bootstrap ratios within and between networks are expressed as a *p*-value for each z-score relative to a permuted null model. Higher z-scores indicate greater connectivity than predicted by the null distribution. VIS = visual, SOM = somatomotor, DAN = dorsal attention, VAN = ventral attention, LIM = limbic, FPC = frontoparietal control, DN = default.

PLS (sub-network)

In an *a priori*, targeted sub-network analysis we examined age-group differences in functional connectivity among sub-networks of the dorsal attention, frontoparietal control and default networks. The mean age-group sub-network matrices are shown in Figure 5A-B. The spring-embedded representation of the top 5% of positive connections in each group (Figure 5C-D) suggests that older adults show more integration of the default network (DN-A) and frontoparietal control network (CONT-C).

Quantitative comparison with PLS of the inter-regional functional connectivity revealed a distinct pattern of age differences (permuted $p < 0.0001$; Figure 5E). Younger adults (Figure 5F) showed more within-network connectivity. Between subnetwork connections were also seen in the young for CONT-A and CONT-B, and between DN-A to DN-B and DN-C. Between network connections in the young were also observed for CONT-B and DN-B. Older adults (Figure 5G) showed greater between-network connectivity of the dorsal attention network with frontoparietal control and default networks (DAN-A to CONT-B and CONT-C; DAN-B to CONT-B, CONT-C, DN-A, and DN-B), as well as greater frontoparietal control connectivity with the default network (CONT-A to DN-A; CONT-B to DN-C; CONT-C to DN-B). Older adults also showed greater connectivity among frontoparietal control subnetworks (CONT-A to CONT-C; CONT-B to CONT-C). A similar pattern of connectivity was observed with a 200 parcellation scheme (Supplemental Figure 9). Sub-network brain connectivity scores' associations with cognition are reported in Supplemental Tables 2, 3, and 4, and Supplemental Figure 12.

Figure 5

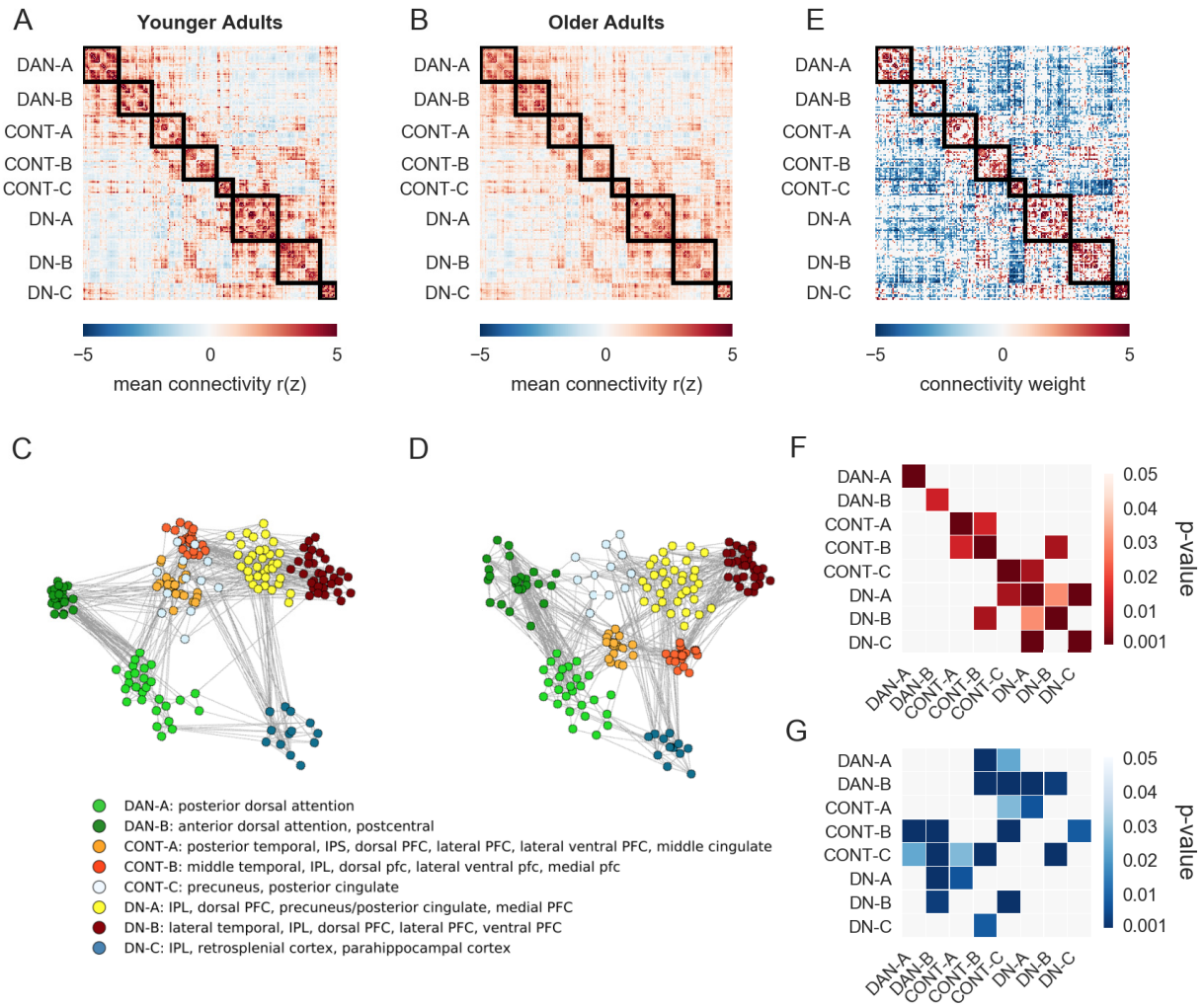

Figure 5 Caption: Functional connectivity of the dorsal attention (DAN), frontoparietal control (CONT), and default (DN) sub-networks following the Yeo 17-network solution. Mean group connectivity in (A) younger and (B) older adults. Spring-embedded plots (5% edge density) of the mean correlation matrices for (C) younger and (D) older adults. (E) Differences in RSFC between younger and older adults among DAN, CONT, and DN. (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. DAN = dorsal attention, FPC = frontoparietal control, DN = default.

Connectomics Site Replication

To verify that our edge-level results are robust and replicable, and not confounded by potential overfitting of the PLS model, the full and sub-network PLS analyses were conducted only on the Ithaca sample. Brain connectivity scores were then computed from the Ithaca sample-derived weights and the Toronto sample individual-subject RSFC matrices, and compared between groups. Age group differences were replicated in the held out Toronto sample ($t(61)= 6.42$, $p < .001$, Cohen's $d= 1.63$; $F(1,57)= 21.13$, $p < .001$, $\eta_p^2= .27$ with sex, education, and eWBV covariates included). In the sub-network analysis, age group differences were also replicated in the held out Toronto sample ($t(61)= 7.01$, $p < .001$, Cohen's $d= 1.79$; $F(1,58)= 24.16$, $p < .001$, $\eta_p^2 =.29$ with sex, education, and eWBV covariates included). These site replication analyses (Supplemental Figure 13) demonstrate that the PLS results are robust to potential issues of model overfitting and that the edge-level effects of functional brain aging observed in the Ithaca sample were also observed at the Toronto site.

Cognition

Overall, predicted age-group differences in cognition were observed. Younger adults performed better on indices of episodic memory ($t(281)= 17.51$ $p < .001$; Cohen's $d = 2.11$), executive function ($t(281)= 12.67$, $p <.001$; Cohen's $d = 1.52$), and processing speed ($t(281)= 15.03$, $p < .001$; Cohen's $d = 1.81$). Older adults had higher semantic memory index scores ($t(281)= 9.18$, $p < .001$; Cohen's $d = 1.10$; see Table 1). Effects remained when testing for age group differences with ANCOVAs controlling for site, sex, education, and eWBV (Episodic: $F(1,277)= 194.07$, $p < .001$, $\eta_p^2 = .41$; Semantic: $F(1,277)= 37.55$, $p < .001$, $\eta_p^2 = .12$; Executive Function: $F(1,277)= 132.70$, $p < .001$, $\eta_p^2 = .32$; Processing speed: $F(1,277)= 97.21$, $p < .001$, $\eta_p^2 = .26$).

Associations between cognition and BOLD signal dimensionality, manifold eccentricity, and brain connectivity scores from the whole brain and sub-network analyses were examined (See Supplemental Tables 2, 3, and 4, and Supplemental Figures 10, 12 and 14). While several significant brain-behavior associations were observed, all of these fell below statistical significance thresholds after site was added as a covariate in the models.

Discussion

Brain aging is marked by dedifferentiation in patterns of brain activity and functional connectivity. Here we adopted a comprehensive, multi-method approach to examine patterns of

intrinsic network dedifferentiation across multiple spatial scales. Specifically, we applied novel methods to identify global, macroscale gradient, and edge-level differences in RSFC between younger and older adults. BOLD dimensionality, the number of BOLD (i.e., non-noise) components in the fMRI signal, was lower for older adults signaling a global shift towards dedifferentiated brain networks in older age. In contrast, the organization of macroscale connectivity gradients was largely preserved with age. However regional differences in connectivity gradients did emerge. The most prominent of these revealed that the whole-brain connectivity profiles of visual processing regions more closely resembled those of other unimodal cortices in older versus younger adults. Edge-level, multivariate analyses with partial least squares also revealed regional and network-specific patterns of dedifferentiation in older adulthood. Across the full cortical connectome, visual and somatomotor regions were more functionally integrated with other large-scale networks for older versus younger adults. In a targeted, sub-network analysis including default, frontoparietal and dorsal attention networks, older adults showed greater default-executive coupling and reduced anticorrelation between default and dorsal attention networks. By examining age differences in the functional connectome across multiple spatial scales, we revealed that the intrinsic network architecture of the aging brain is marked by both global as well as topographically-discrete, network-specific patterns of functional dedifferentiation. These findings offer a comprehensive account of functional brain aging, and identify putative shifts in the intrinsic functional architecture of the aging brain that may underpin both domain-general and domain-specific cognitive changes that occur over the course of late life development.

BOLD Signal Dimensionality and Global Network Dedifferentiation

Dimensionality in the BOLD signal was significantly lower for older versus younger adults, reflecting a generalized pattern of network dedifferentiation continuing into later life. This finding builds upon an earlier report of cross-sectional dimensionality reductions from adolescence to early and middle adulthood (Kundu et al., 2018; Figure 2). Reductions in dimensionality in early adult development, largely attributable to functional integration among prefrontal and other transmodal cortices, reflects the transition from local connectivity to longer-range connections and the formation of spatially distributed yet intrinsically coherent brain networks (Kundu et al., 2018). The shift in functional brain organization parallels cognitive development over this period, which

is marked by the emergence of more integrative and complex cognitive functions (Zelazo and Carlson, 2012), and is also evident within the structural connectome (Park et al., 2020).

Declines in the dimensionality of the BOLD signal, which begin in adolescence, continue unabated throughout adulthood and into later life. In younger adults, lower dimensionality reflects greater functional integration and the emergence of large-scale brain networks (Kundu et al., 2018). However, our observation of continued reductions in BOLD signal dimensionality into older adulthood suggests that network integration may reach an inflection point in middle age (Zonneveld et al., 2019). After this point, continued reductions in dimensionality may no longer be driven by network integration, but rather global network disintegration, and associated loss of coherent network components in the BOLD signal. Critically, our findings using this novel metric of BOLD signal dimensionality are consistent with earlier reports of age-related decreases in network modularity (Geerligs et al., 2015) and network segregation (Chan et al., 2014). Indeed these measures are reliably and positively correlated with dimensionality in our sample (see Supplemental Table S1). However, unlike these two global measures of network organization, BOLD signal dimensionality is agnostic with respect to the selection of cortical parcellation schemes, network definitions or specific network metrics. As such, we suggest that dimensionality may serve as a useful, data-driven marker of functional brain health in later life. An important next step in this regard will be to improve our mechanistic understanding of dimensionality reductions with age. Such global shifts may result from systemic structural, neurophysiological, metabolic or cerebrovascular changes known to occur with advancing age (e.g., Tsvetanov et al., 2020).

Finally, as a novel metric applied to a healthy aging sample, we acknowledge that there are important future directions to more fully interrogate the validity and applicability of BOLD signal dimensionality as an informative measure or marker of functional brain aging. While beyond the scope of the current review, work is underway in our laboratory to conduct a comprehensive validation of this metric, following the roadmap outlined by the original validation studies in younger and middle-aged adults (Kundu et al., 2013, 2017, 2018). However, as a physical property of T2* signal decay, the TE-dependence of BOLD signal (the fundamental component of ME-ICA BOLD signal denoising) should be largely robust to age differences. Directly testing this assumption will be an important direction for future research. Taken together, the TE-dependence of the BOLD signal as well as the comprehensive validation studies conducted in healthy younger

samples, give us confidence in BOLD signal dimensionality as a reliable, informative marker of brain aging.

Gradients and Macroscale Connectomics

Reductions in BOLD signal dimensionality into older age suggest a global shift towards a dedifferentiated network architecture. We investigated whether this global shift may comprise more precise topographical patterns, reflected as greater similarity in connectivity profiles among brain regions. We tested this hypothesis by examining macroscale connectivity gradients in younger and older adults. While this is the first report of gradient analyses using ME-fMRI and individualized parcellation methods, our findings largely recapitulate connectivity gradients observed in young adults (Margulies et al., 2016). Coherent transitions in functional connectivity patterns were observed from unimodal to transmodal association cortices (principal gradient) and from visual to somatomotor cortices (second gradient). This gradient architecture was similar for young and old, suggesting the macroscale organization of the gradients is preserved with age, as has been observed previously (Bethlehem et al., 2020). However, specific age-related regional differences did emerge in both gradient maps.

For the first gradient, visual processing regions showed connectivity profiles that were more similar to the unimodal gradient anchor for older versus younger adults. This finding appears incongruent with our edge-level results (discussed below) which show greater age-related integration of visual and somatomotor cortices with heteromodal association regions. Importantly, gradients do not index functional connectivity strengths per se, but rather patterns of connectivity between specific regions and the rest of the brain. Thus, the shift in connectivity profiles for visual regions towards greater similarity with other unimodal cortices does not address functional integration of these regions. Instead, we suggest that thresholding the connectivity matrices before gradient mapping may have contributed to the age-related shift of visual cortices towards the unimodal anchor of the first gradient. While speculative, we suspect that matrix thresholding may have biased the suprathreshold connections towards an over representation of stronger local versus weaker long-range functional connections. This would be consistent with relative age-related reductions in volume and integrity of long-association fiber pathways versus local connections in primary sensory regions (Kochunov et al., 2012; Raz et al., 2005). These age-related structural differences would, in turn, bias functional connectivity profiles towards more local processing,

yielding an age-related shift in the gradient map towards the unimodal anchor. Nevertheless, these findings highlight the importance and potential impact of thresholding decisions, a point we return to in our discussion of edge-level connectivity below.

Age-related difference clusters across both gradients included regions within somatomotor and attentional networks. Of note, changes within these clusters all indicate a movement towards zero along the gradient and therefore suggest a reduction in differentiation with respect to their corresponding gradient anchor (unimodal or transmodal in the case of the principal gradient, somatomotor or visual in the case of the second gradient). Specifically, both the superior parietal lobule, a node of the dorsal attention network implicated in externally-directed attention and visuomotor control processes, and somatomotor regions showed greater similarity in connectivity profiles to transmodal regions. This is consistent with earlier reports, and patterns observed in the present edge-level analysis, of reduced anticorrelation between the dorsal attention and default networks in later life (Spreng et al., 2016).

It is important to note that we applied diffusion map embedding, a non-linear dimensionality manifold learning technique from the family of graph Laplacians (Coifman et al., 2005). This approach is among the most widely cited in the literature. However, given the novelty of gradient mapping in older adult populations, a direction for future research will be to critically evaluate the full range of approaches, including incorporation of repulsion properties in the gradient analysis. This emerging technique could yield greater clarity into the segregation of discrete networks and changes with age (Böhm et al. 2021).

Edge-level Connectomics

To more precisely investigate edge-level connectivity patterns, we adopted a multivariate analytical approach. As PLS uses singular value decomposition to test age differences across all edges in a single analytical step, we report RSFC differences across the full functional connectome, eliminating the need to apply functional connectivity strength or density thresholds. Visual inspection of the full connectomes for younger and older adults (Figure 4, Panels A-D) reveals a global pattern of network dedifferentiation for older adults, consistent with our dimensionality findings and previous reports (Betzel et al., 2014; Chan et al., 2014; Geerligs et al., 2015; Malagurski et al., 2020; Stumme et al., 2020). These qualitative differences were statistically validated in the group analysis (Figure 4, Panel E) and aggregate network matrices (Figure 4,

Panels F-G). As predicted, younger adults showed a robust pattern of within-network connectivity, as well as connectivity between transmodal networks (Bullmore and Sporns, 2009; Gratton et al., 2012).

Despite preserved macroscale gradients, edge-level analyses revealed striking age differences in network-specific connectivity patterns. First, within-network connectivity was lower for older adults across the seven canonical networks investigated here. Reduced within-network functional connectivity is a hallmark of normative aging (Damoiseaux, 2017 for a review). As such, we speculate that degraded within-network coherence is likely a key determinant of reduced BOLD signal dimensionality, and global network dedifferentiation, in older adulthood. In addition to lower within-network coherence, edge-level analyses also revealed three distinct, network-specific dedifferentiation patterns. The most striking of these revealed greater integration of visual and somatomotor regions with all other networks for older adults (Figure 4, Panel G). Functional integration of visual and somatosensory regions has been observed previously. Chan and colleagues (2014) reported reduced segregation of visual cortices from other brain networks, although this was not explicitly quantified in their analyses. Similarly, age-related increases in node participation, a graph analytic marker of functional integration, were limited to visual and somatosensory networks in a large study of age differences in RSFC (Geerligs et al., 2015). Further, Stumme and colleagues (2020) reported that age differences in RSFC were most prominent in visual and somatosensory cortices. While previous studies reported patterns of sensorimotor integration with age, these have not gained prominence as a central feature of functional brain aging. As discussed above with regards to the gradient analysis results, statistical thresholding of the gradient matrices might significantly impact these findings. Threshold-based approaches highlight age-related differences among the most robust connections, often associated with heteromodal cortices, potentially obscuring less robust age differences in other networks. This is particularly evident in our findings, where somatomotor and visual networks show small age differences relative to those observed for association networks in the thresholded, spring-embedded plots (Figure 4, panels C-D). In contrast, analysis of the unthresholded matrices revealed integration of sensorimotor networks to be among the most striking features of the aging connectome (Figure 4, panels E-G).

Our findings of greater visual network integration parallel task-based studies identifying greater top-down modulation of visual association cortices by transmodal regions as a central

feature of functional brain aging. Greater activation of transmodal cortices, in the context of age-related declines in the fidelity of sensory signaling, has been interpreted as increased demand for top-down modulation of early sensory processing (Clapp et al., 2011; Li and Rieckmann, 2014; Payer et al., 2006; Spreng and Turner, 2019b). Indeed, sensory declines and motor slowing account for much of the individual variability in cognitive functioning among older adults (Baltes and Lindenberger, 1997; Salthouse, 1996). This suggests that greater modulation of these primary sensorimotor regions (and visual attention and visuomotor control regions of the superior parietal lobule, see 'Gradient analyses' above) may be necessary to sustain complex thought and action in later life. While beyond the scope of the current study, we speculate that such task-driven demands for greater cross-talk between transmodal and sensorimotor cortices may, in turn, shape the intrinsic functional architecture of these networks in older adulthood (Stevens and Spreng, 2014).

We also conducted a targeted analysis of edge-level age differences in the frontoparietal control, dorsal attention, and default networks. Previous work has demonstrated that these networks interact during goal-directed cognitive tasks (Spreng et al., 2010; Dixon et al., 2018; Murphy et al., 2020), show similar connectivity profiles during both task and rest (Spreng et al., 2013) and undergo significant changes into older adulthood (Grady et al., 2016; Sullivan et al., 2019; Ng, et al., 2016). For this *a priori* analysis, we adopted the sub-network topography for the three networks derived from the 17-network solution (Yeo et al., 2011). This enabled us to investigate age-related changes with greater precision. Importantly, as we observed for the full connectome analysis, the thresholded spring-embedded plots (Figure 5, panels C-D) failed to reveal the robust age-differences in connectivity among default, control and dorsal attention regions that emerged from the edge-level analyses (Figure 5, panels E-G). While the predicted pattern of reduced within-network connectivity was recapitulated across the sub-networks, we observed two additional network-specific dedifferentiation patterns in this sub-network analysis. As predicted, there was greater age-related coupling of default and frontal brain regions, a pattern we have described as the Default to Executive Coupling Hypothesis of Aging (DECHA; Turner and Spreng, 2015; Spreng and Turner, 2019a). This pattern did not emerge in the seven network analysis (Figure 4). However, when applied to the edge-level sub-network matrices (Figure 5, panels E-G) a clear DECHA pattern emerged for CONT-A to DN-A, CONT-B to DN-C, and CONT-C to DN-B sub-networks (Figure 5, panel G). We have posited that this dedifferentiation pattern may reflect the shifting architecture of cognition in later life (Turner and Spreng, 2015;

Spreng et al., 2018) with both adaptive and maladaptive consequences for cognitive aging (Spreng and Turner, 2019a).

A second dedifferentiation pattern emerged in this sub-network analysis. Older adults showed greater connectivity between the dorsal attention and the two other association networks. This pattern was particularly pronounced for the DAN-B sub-network which includes the superior parietal lobule. Previous reports have shown reduced anti-correlation between dorsal attention and default networks (Keller et al., 2015; Spreng et al., 2016) in older adulthood. These edge-level findings also converge with our gradient analyses where the superior parietal lobule, a node of DAN-B, showed an age difference in connectivity gradient, with a functional connectivity profile more similar to that of other transmodal regions. The DAN-B sub-network encompasses regions of the putative frontal eye fields and precentral gyrus implicated in top-down, or goal-directed, attentional control. This is again consistent with a neuromodulatory account of neurocognitive aging, wherein greater allocation of attentional resources may be engaged to sharpen perceptual representations in later life (Li et al., 2006; Li and Rieckmann, 2014).

Cognitive Function

Our findings suggest that both global and network-specific dedifferentiation are core features of the functional aging connectome. In a final series of analyses we investigated whether these network changes were associated with cognitive functioning. We observed significant behavioral correlations with BOLD signal dimensionality and edge-level connectivity. Intriguingly however, all observed associations fell below statistical significance thresholds when site was included as a covariate in the statistical models. This was the case even though both brain and behavioral age effects replicated across both sites (see Supplemental Figure 13 and Supplemental Table 5). As a result we do not interpret the brain and behavior associations further here and report all uncorrected and partial correlations in Supplemental Tables 2, 3 and 4 (see site-specific scatter plots Supplemental Figure 14). While we took extraordinary care to match data collection protocols and core demographics, study site encompases many additional moderating factors that may have influenced brain and behavioral associations across the two sites (e.g., socioeconomic status, see Chan et al., 2018). While increases in statistical power enabled by multi-site investigations permit greater sensitivity to detect brain-behavior associations, it also comes at

the potential cost of structured noise related to population differences. Understanding these differences will be an important direction for future research.

Conclusion

We employed an innovative, multi-method data acquisition and analysis protocol to study functional brain aging across multiple spatial scales, with a specific emphasis on age-related patterns of intrinsic network dedifferentiation. Reduced BOLD signal dimensionality suggested a global, age-related shift towards dedifferentiated network organization in older versus younger adults. Limitations of a cross sectional study design restrict interpretations with respect to lifespan shifts in brain function. However, we speculate that network integration across the adult lifespan may include an inflection point in middle adulthood, beyond which network integration in early adulthood shifts to a pattern of network dedifferentiation, and the dissolution of a segmented and modular network architecture.

The methodological and analytical innovations adopted here were selected to, at least in part, overcome several of the most enduring and pervasive challenges in lifespan network neuroscience. These include age-related variability in noise profiles within the BOLD signal, as well as distortions introduced by group-wise spatial alignment to standardized templates. Of course the methods implemented here cannot address the totality of confounds that complicate RSFC analyses. Among the most critical of these, and an important direction for future research, is resolving, or at least accurately modeling, age differences in neurovascular coupling. Altered neurovascular coupling with age can introduce spurious RSFC differences that are difficult to detect with standard imaging protocols (Tsvetanov et al., 2020). While ME-ICA methods, which separate neural from non-neural sources in the BOLD signal, are a significant advance, implementation of multimodal methods such as simultaneous arterial spin labeling and echo-planar imaging may be necessary to resolve this issue (Tsvetanov et al., 2020). Additionally, residual motion-related noise was still observed in the BOLD signal, which could be attributable to respiration (e.g. Power et al., 2018; Lynch et al., 2020). While this noise did not confound our age effects, its persistence requires additional consideration and points to a need for further advances to improve signal-to-noise with ME-fMRI data. Despite these limitations, we suggest that the multifaceted approach adopted here offers a comprehensive account of age differences in the functional network architecture of the brain, including both novel and previously observed

patterns of network dedifferentiation and integration. Taken together, these findings add further clarity and precision to current understanding of how functional networks are formed, shaped, and shifted into older adulthood.

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Bridge to Chapter 3

Findings from Study 1 suggested that dedifferentiation in healthy aging is characterized both by global and network-specific properties. BOLD dimensionality systematically decreased across the lifespan, marking a non-specific property of global brain function. Dimensionality decreases from adolescence through middle adulthood are thought to reflect the formation of long-range connections that help to establish coherent, large-scale brain networks (Kundu et al., 2018). Indeed, younger adults had more modular, segregated networks compared to older adults. Further integration in older age, as indicated by reduced BOLD dimensionality, was reflected in reduced connectivity within networks and widespread integration of visual, somatomotor, and dorsal attention networks. Network integration may therefore contain an inflection point in middle adulthood where network differentiation transitions to dedifferentiation. Prior work has implicated age-related dedifferentiation, particularly of association networks, with declining episodic memory and processing speed (Chan et al., 2014; Malagurski et al., 2020). Although further replication is needed, we found initial evidence to suggest that specific between-network increases observed may support older adult complex cognition.

In a set of more targeted studies, we ask whether functional and structural differences may support domain-specific cognition. Autobiographical memory is an ideal lens through which to test this as it measures episodic and semantic aspects of recollection, which follow age-related cognitive trends of losses and gains (Levine et al., 2002). Autobiographical memory is also associated with the default network (Svoboda et al., 2006; Benoit & Schacter, 2015), a set of regions particularly vulnerable in aging. In Study 2 we focus our inquiry on two regions of the default network that are well-studied in healthy aging and disease, the hippocampus and temporal pole. We examine how structural differences in these regions may differentially impact structure-cognition relationships in younger and older adults. Results from this study will inform whether local brain-behavior relationships may be rooted in structure.

Chapter 3: Anterior hippocampus and temporal pole volumes are associated with episodic autobiographical memory in healthy older adults

Adapted from: Setton, R., Sheldon, S., Turner, G.R., & Spreng, R.N. (*Under Revision*). Anterior hippocampus and temporal pole volumes are associated with episodic autobiographical memory in healthy older adults. *Hippocampus*.

Abstract

Autobiographical recollection differs for younger and older adults. Older individuals recall fewer episodic details and convey more semantic information than young. Here we examine how neuroanatomical differences in temporal lobe grey matter volumes are related to recollection in older versus younger adults. The present study obtained grey matter volume measurements for the hippocampus and temporal poles– regions integral to episodic and semantic autobiographical memory– as predictors of memory differences in healthy younger (n=158) and older (n=105) adults. The hippocampus was segmented into anterior and posterior regions with an automated pipeline to test for regionally specific effects. Temporal pole volumes were extracted from FreeSurfer. The Autobiographical Interview was administered to measure episodic and semantic autobiographical memory. As predicted, older adults recalled fewer episodic details. Posterior hippocampal volumes were smaller for older compared to younger adults. No age-related volume differences were observed for the anterior hippocampus or temporal poles, yet both of these volumes were related to more episodic autobiographical recall in older adults. Temporal pole volumes were positively associated with episodic recollection, whereas the association with anterior hippocampus volumes depended on sex. Episodic recollection was positively associated with anterior hippocampus volumes in older females, but negatively in older males. These findings provide a novel account for the involvement of anterior hippocampus and temporal poles in episodic autobiographical memory later in life.

Introduction

Autobiographical memory (AM) changes with age, often presenting as a shift from highly episodic to semantic-laden recollections (e.g., Levine et al., 2002). This shift in AM co-occurs with age-related brain changes to temporal lobe structures implicated in episodic and semantic memory function, namely the hippocampus and temporal pole. However, there is considerable variation in the extent to which older adults express changes in AM recollection (e.g., Wilson et al., 2002) and regional grey matter volumes of these regions (e.g., Sele et al., 2020). Here we leverage a large sample of healthy younger and older adults with AM data to test for age group differences in hippocampal and temporal pole volume relationships to episodic and semantic AM. In doing so, we determine how individual differences in grey matter volume in select regions relate to episodic and semantic AM differences in younger and older.

The hippocampus plays a central role in AM retrieval (Svoboda et al., 2006), binding together information across a number of cortical systems (e.g., Moscovitch et al., 2016) and invoking a sense of re-experiencing (e.g., Thakral et al., 2020). Mounting evidence suggests that the hippocampus, rather than being a uniform structure, exhibits functional specialization along the longitudinal axis (Poppenk et al., 2013; Strange et al., 2014; Brunec et al., 2018). Anterior and posterior portions of the hippocampus have also been functionally related to different aspects of the autobiographical retrieval process (Moscovitch et al., 2016; Sheldon & Levine, 2016). Anterior hippocampus is associated with generalized or gist-based representations of past events (semantic AM) while the posterior hippocampus is associated with more fine-grained recollections (episodic AM; see Sheldon et al., 2019).

Long-axis specialization is also reflected in structure. Larger posterior and smaller anterior volumes have been related to better recollection and spatial memory in healthy adults (Poppenk & Moscovitch, 2011; Maguire et al., 2006; Brunec et al., 2019). It is likely that age-related vulnerability to the hippocampus alters these selective relationships to memory. However, mixed evidence on age-related volume change within the hippocampus renders it difficult to draw conclusions about continued specialization into older age (see Ta et al., 2011 and Bettio et al., 2017 for reviews). Cross-sectional findings comparing younger and older adults have found smaller volumes in both anterior (e.g., Rajah et al., 2010) and posterior (e.g., Driscoll et al., 2003; Malykhin et al., 2008; Stark et al., 2021) portions of the hippocampus. Mixed findings have also been observed with age-volume relationships in adult lifespan samples, with

age sometimes imparting a stronger effect on anterior volumes (e.g., Jack, 1997; Hackert et al., 2002; Gordon et al., 2013), and at other times a stronger effect on posterior volumes (e.g., Kalpouzos et al., 2009). Longitudinal findings in older samples are more unified around greater volume loss in the anterior hippocampus with age (e.g., Chen et al., 2010). It has also been suggested that variability in hippocampal volumes does not differ across age groups and that volume loss may be a heritable trait (Lupien et al., 2006). This overall disparity suggests that findings on age-related volume differences in the hippocampus highly depend on the sample under study and the individuals, or group of individuals, carrying the variance (Buckner, 2004). Within-subject volume loss is undoubtedly of interest to some researchers, but cohort studies may be useful to determine how volume-behavior relationships differ. Indeed, hippocampal volume relationships to memory in healthy aging are still unclear (Van Petten, 2004).

The temporal poles are also implicated in AM (Svoboda et al., 2006; Renoult et al., 2019), particularly in the processing and retrieval of schematic and personal semantic information (Graham et al., 2003; Renoult et al., 2012). Individuals with semantic dementia, which often presents with lesion to the temporal poles (e.g., Chan et al., 2001), show impairments to both semantic and episodic AM (Irish et al., 2012). Semantic processes may therefore be necessary for AM, shaping and constraining information encoded and subsequently retrieved. Young adults show similar activation patterns within the anterior temporal region while viewing video clips with shared prior knowledge, suggesting that amodal conceptual representations may be involved during encoding of naturalistic scenes (Raykov et al., 2021; Murphy et al., 2017; Patterson et al., 2007; Binder & Desai, 2011). Memory integration during associative inference paradigms is also enhanced with prior knowledge (Miller-Goldwater et al., 2021). Since preservation of semantic memory is a hallmark of healthy aging (e.g., Park & Reuter-Lorenz, 2009), it has been put forward that prior knowledge may facilitate better recollection particularly for older adults (Umanath & Marsh, 2014; Spreng & Turner, 2019). As a semantic memory hub (Lambon Ralph et al., 2017), the temporal pole may therefore associate with AM differently in younger and older adults, but a direct relationship between temporal pole volume and AM has not been directly tested.

Unlike the hippocampus, both cross-sectional and longitudinal findings are mixed with regard to age-associated change to temporal pole volumes. Across two healthy adult lifespan samples, one study found the temporal pole to be reliably stable with increasing age (Bergfield et

al., 2010). In a separate investigation of 116 older adults split into younger and older groups, the younger elderly participants had larger temporal pole volumes (Resnick et al., 2000). Longitudinal studies examining one year regional volume change have found significant reductions (Fjell et al., 2009) and no significant reductions (Resnick et al., 2000) in the temporal pole. One study with a larger sample and additional timepoints resolves some of these findings (Sele et al., 2020). Temporal pole volumes demonstrated accelerated decline with advancing age over a four-year period relative to other regional volumes, but the extent of temporal pole volume decline was highly variable across participants.

Sex is an important consideration in volumetry, particularly with respect to the hippocampus. Males and females tend to have comparable hippocampal volumes after adjusting for total brain volume (Tan et al., 2016). Young adult females, however, have shown larger posterior hippocampal volumes than males in association with unique patterns of structural covariance with the rest of the brain (Persson et al., 2014). Rates of age-related hippocampal atrophy are steeper in females, which may contribute to an increased susceptibility to Alzheimer's disease (e.g., Fisher et al., 2018). Sex differences have also been reported in temporal pole volume (Lotze et al., 2019). We therefore explore whether sex impacts grey matter volume relationships to AM in both the hippocampus and temporal poles.

Volume measurements were obtained for anterior hippocampus, posterior hippocampus, and the temporal pole, and associated with AM in a well-powered sample of healthy younger and older adults. The aim of our study was to determine how individual differences in episodic and semantic AM in younger and older adults relate to grey matter volumes of these key temporal lobe regions, and how these associations differ between younger and older adults. A secondary aim was to explore possible sex effects on the interactions between age and AM on volume in each of the regions under study.

Methods

Participants

Participants were 158 younger (91 female) and 105 older (57 female) healthy adults from Ithaca, New York and Toronto, Canada (Table 1). Behavioral and functional neuroimaging data from these participants have been reported elsewhere (Setton & Mwilambwe-Tshilobo, *Under*

Revision; Setton et al., 2021; Spreng et al., *Under Revision*) and are summarized briefly below. This study was carried out in accordance with the Institutional Review Board at Cornell University and the Research Ethics Board at York University.

Standard inclusion and exclusion criteria were carried out to ensure that all participants were healthy and without evidence of neurological, psychiatric, or other medical illness known to impact cognition. Specifically, participants were asked about acute or chronic psychiatric illness, current or recent treatment with psychotropic medication, and significant changes to health status within three months of the eligibility interview. Individuals with the presence of any one of these were not eligible to continue.

Further exclusions were made post data collection on the basis of cognitive status and depressive symptoms. Participants with scores below 27/30 on the Mini-Mental State Examination (Folstein et al., 1975) and an age-adjusted national percentile of 25 on the NIH Fluid Cognition measure (Gershon et al., 2013) were excluded. Of the 214 participants who completed either the Beck Depression Inventory (Beck et al., 1996) or the Geriatric Depression Scale (Yesavage et al., 1982), participants with scores at or above the cutoff for "moderate depression" were not included.

Assessments of physical and mental health status were also collected as part of the battery. We include these data to rule out other potential differences that could influence the results reported here. The Health Buffer Questionnaire had participants rate how difficult it was to engage in day-to-day activities due to physical and emotional problems with a 5-point Likert scale ("Interference", n = 250), check off any current experiences with physical health conditions (including migraines and persistent back pain; "Physical Symptoms," n = 230), and list how many times a doctor had been visited for a health concern in the last four months. Separately, Physical Activity Level was a single question asking participants to choose one response that best described their usual pattern of daily activities (n = 188). Responses ranged from "Level 1: Inactive or little activity other than usual daily activities" to "Level 5: Participate in aerobic exercises such as brisk walking, jogging or running at a comfortable pace or other activities require similar levels of exertion for over 3 hours per week."

Composite measures of episodic and semantic memory were derived from laboratory-based tasks to characterize the sample (Supplementary Methods). Statistics and tests for differences across groups are presented in Table 1.

Table 1

Sample Demographics

	Descriptive Statistics		Inferential Statistics				
	Younger Adults	Older Adults	*T*	dof	*p*	95% CI	Cohen's *d*
N							
Ithaca	131 (74 female)	83 (47 female)					
Toronto	27 (17 female)	22 (11 female)					
Age (years)							
Range	18 - 34	60 - 89					
M	22.59	68.19					
SD	3.33	6.29					
Education (years)*							
Range	12.00 - 24.00	12.00 - 24.00	-7.32	261	< .001	[-2.78, -1.60]	0.92
M	15.18	17.37					
SD	1.94	2.90					
MMSE*			3.69	261	< .001	[.28, .90]	0.47
Range	22.00 - 30.00	25.00 - 30.00					
M	29.08	28.500					
SD	1.23	1.29					
Depressive Symptoms (z-score)							
Range	-.88 - 3.65	-.97 - 4.41	0.05	212	0.96	[-.26, .28]	0.01
M	0.01	0.00					
SD	1.01	1.00					
Health Buffer Questionnaire: Interference*							
Range	4 - 19	4 - 20	6.55	248	< .001	[2.08, 3.86]	0.85
M	9.42	6.45					
SD	3.81	2.98					
Health Buffer Questionnaire: Physical Symptoms			-0.36	228	0.72	[-.36, .25]	0.05
Range	0 - 5	0 - 4					
M	0.87	0.92					
SD	1.18	1.09					
Physical Activity Level							
Range	1 - 5	1 - 5	1.04	186	0.3	[-.17, .55]	0.15
M	3.43	3.24					
SD	1.21	1.27					
NIH Fluid Cognition (unadjusted score)*							
Range	88.74 - 153.37	78.21 - 122.79	18.36	255	< .001	[22.75, 28.21]	2.33
M	119.63	94.16					
SD	12.92	6.86					
Episodic Memory*			15.98	255	< .001	[1.08, 1.36]	2.22
Range	-1.71 - 1.41	-2.11 - 0.65					
M	0.48	-0.72					
SD	0.47	0.69					
Semantic Memory*							
Range	-2.78 - 1.42	-1.21 - 1.94	-8.9	255	< .001	[-1.02, -.65]	1.13
M	-0.34	0.51					
SD	0.77	0.69					

Note. Depressive Symptoms refers to z-scores on the Beck Depression Inventory and Geriatric Depression Scale. Age group differences were tested in 214 participants. The Health Buffering Questionnaire Interference refers to frequency that physical and emotional difficulties interrupted daily function while Physical Symptoms refers to the number of health conditions reported by participants. Age group differences were tested in 250 and 30 participants, respectively. Episodic Memory and Semantic Memory reflect composite scores. Age group differences in NIH fluid cognition, episodic memory, and semantic memory were tested in 257 participants. Positive T values reflect higher scores in younger adults, negative values reflect higher scores in older adults. Statistical tests are nearly identical when including sex, education, site, and eWBV as covariates in an ANCOVA.

Neuroimaging

T1-weighted volumetric magnetization prepared rapid gradient echo sequences were acquired at the Cornell Magnetic Resonance Imaging Facility (TR=2530ms; TE=3.4ms; 7° flip angle; 1mm isotropic voxels, 176 slices, 5m25s) with 2x acceleration and sensitivity encoding, and at the York University Neuroimaging Center (TR=1900ms; TE=2.52ms; 9° flip angle; 1mm isotropic voxels, 192 slices, 4m26s) with 2x acceleration and generalized auto calibrating partially parallel acquisition (GRAPPA) encoding at an iPAT acceleration factor of 2.

Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevitch et al., 2015) segmented each participant's hippocampus along the longitudinal axis in native space. ASHS uses multi-atlas label fusion to segment the medial temporal lobes into subfields, and has been well-validated among manual and other automated approaches (Bussy et al., 2021). ASHS was run with the ASHS-PMC-T1 atlas (Xie et al., 2016) in all participants. Given the relatively low resolution of T1-weighted images, we limited our inspection to anterior (head) and posterior (body and tail) regions of the hippocampus (Wisse et al., 2020). All ASHS outputs were visually inspected for gross errors and to confirm the presence or absence of the uncal apex in anterior and posterior segments, respectively (Poppenk et al., 2013; see Figure 2A). No errors were observed (see Supplementary Figure 1 for examples).

Temporal pole volumes were extracted from cortical reconstruction and volumetric segmentation performed in FreeSurfer version 6.0.1 (Fischl et al., 2002; Reuter et al., 2012). Whole hippocampal volume was also extracted. Measurements of estimated total intracranial volume (eTIV), grey matter, and white matter volume were used for volumetric adjustment. Specifically, the residuals of a linear regression between each volume and eTIV were used to calculate an adjusted volume (Jack et al., 1989; Buckner et al., 2004; Stark et al., 2021). Compared to volumes as a proportion of eTIV (Voevodskaya et al., 2014), this approach removes the influence of head size on regional volumes, an important consideration when examining structural changes in healthy aging where age becomes a confounding variable

All regional volumes were adjusted for head size prior to analysis (Tables S1-S2). Two younger and two older adults were excluded for outlying volume measurements after adjustment. Whole brain tissue volume is known to decrease in older age with the expansion of cerebrospinal fluid volume, even without marked change to total intracranial volume (Matsumae et al., 1996). Estimated whole brain volume (eWBV) was calculated as (grey matter + white matter)/(eTIV)

and included as a covariate where indicated to narrow in on regionally specific effects (see similar approach in Schmitz et al., 2016).

Autobiographical Interview

The Autobiographical Interview (AI; Levine et al., 2002) served as our measure of AM to examine relationships to brain volume. Participants completed the interview as part of a larger set of cognitive assessments during a separate experimental session. Trained research assistants conducted the interviews, providing thorough instructions and ensuring comprehension prior to the start of each interview. Participants were asked to describe a specific episode from each of three (younger adults) or five (older adults) time periods: childhood, teenage years, young adulthood, middle adulthood, and late adulthood. For each memory, participants first described the episode in as much detail as possible (free recall). When recollection came to a natural end, participants were lightly prompted to recall any additional details (general probe). After memories were recalled from all time periods, participants went through each memory once more and were questioned with specific cues to encourage further episodic remembering (specific probe). Self-reported ratings of vividness, emotional change, significance at the time, significance now, and rehearsal were also collected for each memory. All interviews were recorded and transcribed prior to scoring.

In brief, scoring involved categorizing text into episodic-like (internal) and non-episodic (external) details. Internal details included those involving the sequence of events, location, time, sensory information, emotions, and thoughts related to the event chosen. External details included specific information about unrelated events, semantic information (general and personal), repetitions, and other non-scorable verbiage. Updated scoring protocols have recently been published (e.g., Strikwerda-Brown et al., 2017), but scoring on our high volume of interviews commenced prior to their publication. For the purpose of this study, we consider only scores from free recall and general probe cueing stages of the interview, which reflect spontaneous recollection tendencies.

The transcribed interviews were scored by two trained researchers (Inter-rater reliability internal: $r(261)=.91$, $p < .001$; external: $r(261)=.82$, $p < .001$). Counts of internal and external details were averaged across memories to provide stable measures of episodic and semantic memory. Notably, we divided detail counts by total word count to control for verbal output,

which may arbitrarily underestimate or inflate detail counts if not considered. Word count was not different across groups: ($F(1,257)= 1.03$, $p=.310$ controlling for site, sex, and education), suggesting verbosity did not confound density scores. Internal and external density scores were therefore our AM metrics of interest (Spreng et al., 2018; Lockrow et al., In Preparation).

Analyses

Our aim was to determine how individual differences in AM within younger and older cohorts relate to grey matter volume in the anterior and posterior hippocampus and temporal poles. In other words, we tested for an interaction between age group, AI detail density, and regional volume. Analyses proceeded in three parts to test for: 1) age group differences in detail density as an initial replication of prior work; 2) age group differences in hippocampal volumes and associations with detail density on the AI; 3) age group differences in temporal pole volumes and associations with detail density on the AI.

ANCOVAs were used to examine age group differences and Generalized Estimating Equations (GEE) were used to explore interactions with AM. GEEs are a semi-parametric version of the general linear model which can accommodate correlated repeated measurements (e.g., left and right volumes, anterior and posterior segments) by modeling the within-subject covariance structure and treating it as a nuisance variable (Liang & Zeger, 1986). GEEs, modeled as normal positive (gamma) distributions with exchangeable correlation matrices, were conducted with volume as the predicted variable to test for effects of age group, hemisphere, segment (anterior/posterior in the hippocampus only), detail density (internal and external separately), and their interaction (see Supplementary Results for GEEs with laboratory-based composites of episodic and semantic memory). Follow-up GEEs were carried out within age group or hemisphere subsets of the data for marginal and significant age group interactions. Finally, general linear models (GLM) were used to detect simple effects of detail density on each regional volume. Sex, site, education, and eWBV were included in each model.

Software

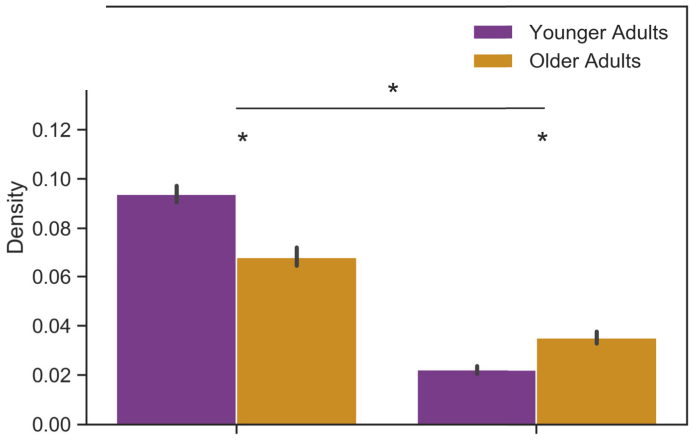
Statistical analyses were carried out in python 3.6.3 and R version 3.3.3. In python, descriptive statistics were tabulated with pandas and visualizations were created with seaborn.

Statsmodels was used to model GEEs and GLMs. In R, ANCOVAs were run with lme4 and nlme, and emmeans was used for post-hoc paired t-tests with a Tukey HSD adjustment.

Results

Age Group Differences in Internal/External Density of Recollections from the Autobiographical Interview

We first tested for age group differences on the AI to replicate established findings. Age group, detail category (internal, external), sex, and the interaction between them were entered into a mixed ANCOVA on density scores. Education and site were included as covariates. Significant main effects of age group ($F(1,258)=10.22$, $p < .005$, $\eta_p^2=.02$) and detail category ($F(1,261)=1463.17$, $p < .001$, $\eta_p^2=.74$) were qualified by a significant interaction ($F(1,261)=167.57$, $p < .001$, $\eta_p^2=.24$). Compared to younger adults, older adults recalled a lower density of internal details ($t(258)=11.06$, $p < .001$, Cohen's $d=1.38$) and a higher density of external details ($t(258)=6.32$, $p < .001$, Cohen's $d=.79$), corroborating prior work (Levine et al., 2002; Figure 1). A main effect of sex was also observed ($F(1,258)=3.98$, $p < .05$, $\eta_p^2 = .01$), such that females had more internally and externally dense recollections than males overall.



gure 1. Age Group Differences in ernal/External Density of Recollections m the Autobiographical Interview. Mean ernal and external detail density on the AI tted by age group. Compared to younger ılts, older adults recalled a lower density of ernal details and a higher density of external ails. Sex was included in the model. Site and ıcation were included as covariates. Density = ail count / word count. * denotes significant

To rule out the possibility that older adults' density scores were disproportionately influenced by recall of temporally distant events (e.g., Linton, 1975; Rubin & Wenzel, 1996; Wagenaar, 1986), additional ANCOVAs were run testing for the influence of temporal distance on internal or external density. Age group, temporal distance (recent, remote), sex, and the interaction between them were modeled with sex and education as covariates. Recent memories were defined as the last memory recalled for each group: young adulthood for younger adults and late adulthood for older adults. Remote memories were defined as childhood memories for younger adults and young adulthood memories for older adults to equate temporal distance across groups. As above, age group differences were present for both internal ($F(1,258)= 50.10$, $p < .001$, $\eta_p^2 = .12$) and external density ($F(1,258)= 66.19$, $p < .001$, $\eta_p^2 = .14$). No interactions with temporal distance were observed. This suggests that internal and external density are stable individual difference measures with distinct age-related patterns.

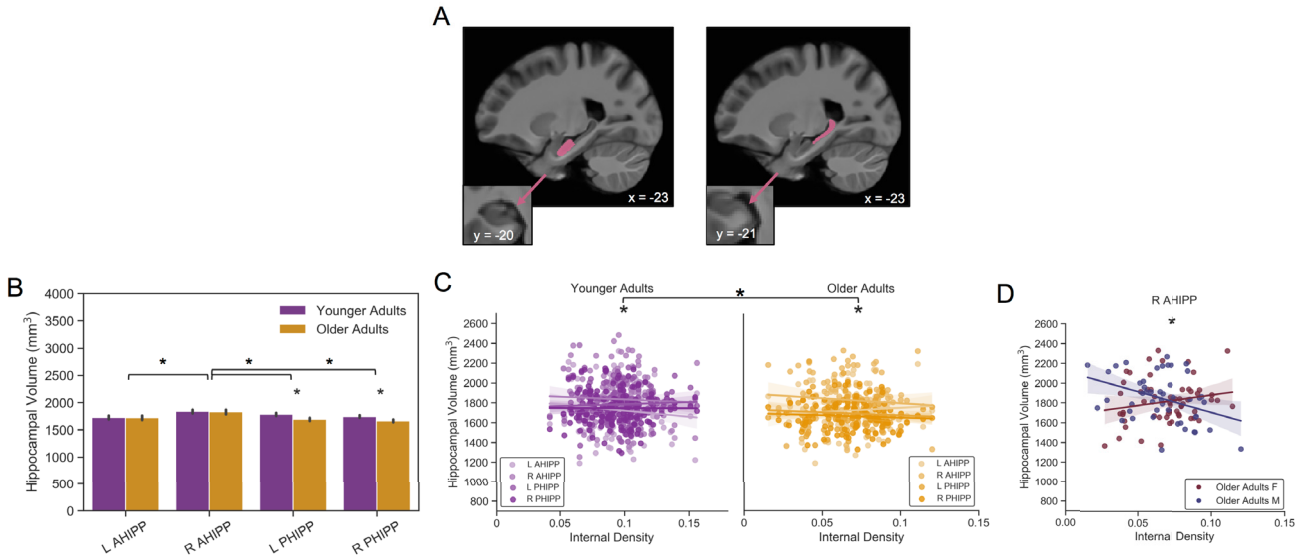
Age Group Differences in Hippocampal Volumes and Associations with Internal/External Density

Next, we tested for age group differences in hippocampal volume. Older adults were found to have smaller posterior hippocampus volumes than younger adults. Specifically, main effects of age group ($F(1,258)=4.65$, $p < .05$, $\eta p2=.01$), hemisphere ($F(1,782)=16.18$, $p < .001$, $\eta p2=.01$), and segment ($F(1,782)=27.66$, $p < .001$, $\eta p2=.03$) on volume were observed. These were qualified by a number of significant interactions. A hemisphere by segment interaction ($F(1,782)=59.21$, $p < .001$, $\eta p2=.07$) showed that right anterior segments were larger than right posterior segments ($t(782)=9.78$, $p < .001$, Cohen's $d=.70$), left anterior segments ($t(782)=8.09$, $p < .001$, Cohen's $d=.58$), and left posterior segments ($t(782)=7.32$, $p < .001$, Cohen's $d=.52$). A sex by segment interaction ($F(1,782)=11.91$, $p < .01$, $\eta p2=.01$) indicated that males had larger anterior compared to posterior segments ($t(782)=6.50$, $p < .001$, Cohen's $d=.46$). Segments were comparable in females. Critically, an age group by segment interaction ($F(1,782)=16.97$, $p < .001$, $\eta p2=.02$) showed that older adults had smaller posterior, but not anterior, hippocampus volumes compared to younger adults ($t(258)=3.71$ $p < .005$, Cohen's $d=.46$; Figure 2B), leaving older adults with larger anterior compared to posterior segments ($t(782)=6.79$, $p < .001$, Cohen's $d=.49$). Converging results were obtained when testing for differences in the ratio of posterior to anterior hippocampus volumes (see Supplemental Results). We determined that this result was

not driven by the oldest of the older cohort as the same pattern was found when splitting older adults into 60-69 and 70+ age categories (Supplementary Figure 2).

In order to examine age group differences in the relationship between density scores and hippocampal volumes, we ran GEEs on hippocampal volumes modeling age group, hemisphere, segment, density score, and their interaction. Sex interaction terms with density and segment were included based on the above ANCOVAs.

The GEE with internal density yielded a significant interaction between age group, hemisphere, segment, and internal density (Wald $\chi 2$ (1)=8.53, $p < .005$; Figure 2C; Table S3). This suggested that the difference in hippocampal volume relationships to internal density differed as a function of age group. To decompose the interaction, follow-up models within each age group indicated hemisphere by segment by internal density interactions in both younger (Wald $\chi 2$ (1)=3.84, $p = .05$) and older (Wald $\chi 2$ (1)=4.94, $p <.05$) adults. This result suggested that there was an overall difference in slope between internal density and each of the volumes in both younger (purple in Figure 2C) and older (yellow in Figure 2C) adults. In younger adults, follow-up GLMs on each of the four hippocampal volumes showed that internal density was not significantly related to any volume (Supplementary Figure 3). In older adults, a sex by internal density interaction (Wald $\chi 2$ (1)=12.78, $p <.001$) was observed in the right anterior hippocampus (Figure 2D). Internally dense recollections were associated with smaller volumes in older males ($b= -2.60$, $SE=.81$, $p < .005$). A trending association with larger volumes was present in older females ($b=1.27$, $SE=.71$, $p = .075$). Complementary results were obtained when the ratio of posterior to anterior hippocampus volumes was replaced as the dependent variable (see Supplemental Results & Supplementary Figure 5). Here, internal density was associated with a smaller volume ratio across sexes in the left hemisphere, but was dependent on sex in the right hemisphere.



in views illustrate the presence and absence of the uncal apex in each segment. (B) Mean volumes of anterior and posterior hippocampal segments plotted by hemisphere and age group. Older adults had smaller posterior, but not anterior, hippocampus volumes than younger adults. (C) Scatterplots demonstrating a significant interaction between internal detail density and age group on hippocampal volumes. Slopes were significantly different in younger and older adults. Within each age group, relationships between internal density and hippocampal volumes (L AHIPP, R AHIPP, L PHIPP, R PHIPP) were also significantly different from one another. (D) Scatterplot demonstrating a crossover interaction in older adults between sex and internal density in the right anterior hippocampus. Older males with larger right anterior

The GEE on external density in the hippocampus showed a marginal main effect of detail density (Wald χ^2 (1)=3.77, *b*= -2.05, *SE*=1.06, *p* = .05; Supplementary Figure 6A), such that greater volume across all hippocampal segments was associated with less externally dense memories in all participants (see Table S4 for full results). A sex by density interaction (Wald χ^2 (1)=4.36, $p < .05$) indicated that the negative association between external density and hippocampal volumes was driven by females (*b*=-3.02, *SE*=1.55, *p* = .052; Supplementary Figure 6B). External density was not related to any of the four hippocampal volumes in males. External density was not a significant predictor of volume ratio scores (see Supplementary Results).

Age Group Differences in Temporal Pole Volumes and Associations with Internal/External Density

Turning to the temporal pole, we found that volumes were similar across age groups (Figure 3B), but males had larger volumes than females ($F(1,258)=4.18$, $p < .05$, $\eta p2=.01$).

The GEE with internal density revealed a significant main effect of internal density (Wald $\chi 2$ (1)=6.18, $p < .05$) and an age group by internal density interaction (Wald $\chi 2$ (1)=4.56, $p < .05$; see Table S5). In older adults, more internally dense recollections were related to larger temporal pole volumes bilaterally (Wald $\chi 2$ (1)=5.54, b=2.12, SE=.90, $p < .05$; Figure 3C). Internal density was not related to temporal pole volumes in younger adults.

The GEE with external density on temporal pole volume showed a marginal main effect of density (Wald $\chi 2$ (1)=3.42, b= -3.02, SE=1.633, $p = .065$) and a significant age group by density interaction (Wald $\chi 2$ (1)=7.91, $p < .005$; Table S6). Figure 3D illustrates volume-density slopes going in opposite directions for each age group. Although external density was not a significant predictor of volume within each age group alone, the slope in younger adults was highly similar to that between semantic index from laboratory-based measures and temporal pole volume (Supplementary Figure 7).

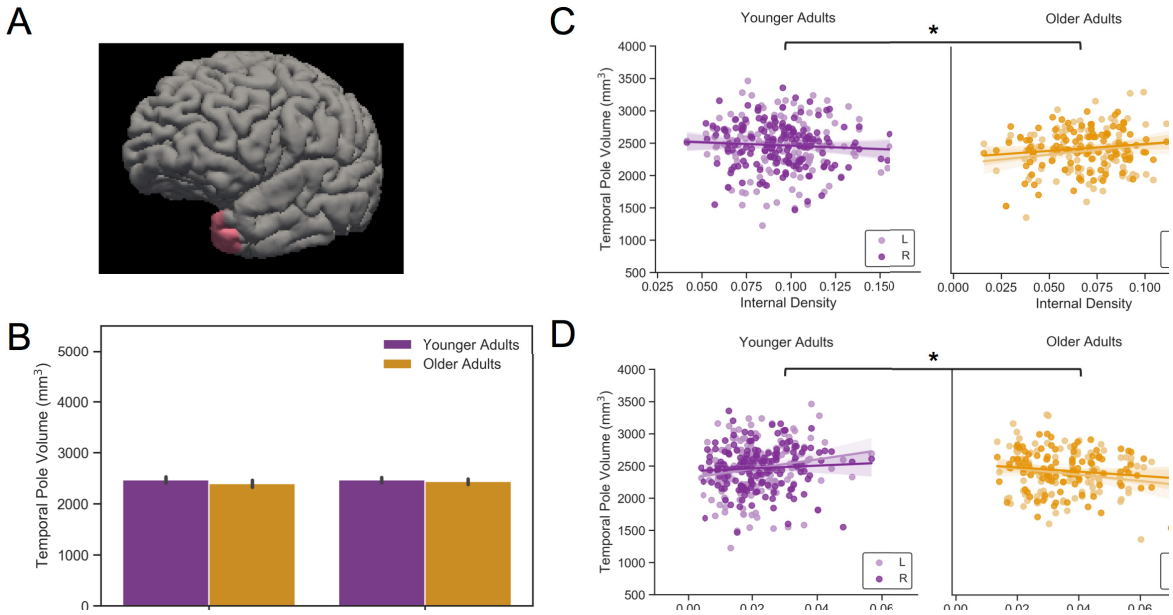


Figure 3. Age Group Interaction with Density in the Temporal Poles. (A) A surface rendering of the left temporal pole from FreeSurfer. (B) Mean volumes of left and right temporal poles plotted by age group depict no differences. (C) Scatterplots demonstrating contrasting relationships between internal detail density and volume (top) as well as between external detail density and volume (bottom) across age groups. Older adults with more internally dense recollections had larger temporal pole volumes. All volumes were adjusted for eTIV. Sex was included in the model. Site, education, and estimated whole brain volume were included as effects of no interest in each model. * denote

Discussion

We investigated age group differences in AM, hippocampus and temporal pole volumes, and AM-volume associations in a large sample of healthy younger and older adults with Autobiographical Interviews. We replicated the long-standing finding that younger adult recollections contain more episodic (internal) information while older adult recollections contain more semantic (external) information. Posterior hippocampus volumes were smaller in older, compared to younger, adults (Figure 2A). Temporal pole volumes, which were comparable in size across groups, were positively associated with episodic AM only in older adults (Figure 3C). In contrast, temporal pole volumes were more strongly related to laboratory-based semantic abilities in younger adults (Supplementary Figure 7). We speculate that in the face of posterior

hippocampal volume atrophy, episodicity of AM becomes more reliant on the temporal pole in older adulthood.

Younger and Older Adult Recollections Systematically Vary in Episodic and Semantic Detail Recollection

As previously reported (e.g., Levine et al., 2002), older adults included fewer episodic and more semantic details when recalling past events on the AI. Studies using the AI typically report detail counts, whereas here we report on detail density, a metric that controls for the overall verbal output of recollections. We have previously introduced density scores as a novel dependent variable from the AI (Spreng et al., 2018), and have recently found that they are more sensitive to age effects than detail counts, and provide more reliable and valid estimates of individual differences in AM (Lockrow et al., *In Preparation*). In controlling for verbal output, density scores, to some extent, reflect the efficiency that one conveys episodic or semantic detail. Arguably, this more accurately captures the recollective process, which involves top-down control mechanisms to retrieve relevant details and hold them in mind (Piolino et al., 2010). Indeed, density scores, but not counts, associate with performance-based laboratory tasks of episodic memory and executive function (Lockrow et al., *In Preparation*). As the AI was administered to the present sample without an imposed time constraint, density scores are also less influenced by narrative length. Critical to the findings reported here, density scores for both episodic and semantic detail had significantly different distributions in younger and older adults. This suggests that the overall differences in episodic and semantic information generated during recollection cannot be explained by individual differences in recollective style, and reflects a shift as a function of older age.

Hippocampus Volumes Differ by Age Group but Show Little Association with AM

Older adults had smaller posterior hippocampal volumes, in line with recent longitudinal work from healthy adult lifespan samples showing greater microstructural change to the posterior hippocampus in older age (Langnes et al., 2020). Significant age-related reductions in older adults have also been observed in nearby parahippocampal white matter, which includes axons of the perforant pathway (Stoub et al., 2012). In terms of macrostructure, both anterior and posterior grey matter volumes shrink with age, but show slightly different trajectories, with the posterior

region showing an earlier inflection point and steeper decline thereafter (Langnes et al., 2020; Chauveau et al., 2021). Different trajectories of atrophy may partially explain why other longitudinal findings have demonstrated more robust anterior hippocampal volume change over time in older age (Chen et al., 2010); the years sampled may disproportionately impact the rate of change observed. Similarly, the results reported here are situated among other cross-sectional studies with both converging and diverging results. While we cannot rule out that our findings reflect cohort effects, we contend that they serve as a necessary backdrop for comparing volume-AM associations across age groups.

Neither anterior nor posterior hippocampal volumes were related to AM in younger adults. Our study is not the first to report null relationships between hippocampal grey matter volume and hippocampal-dependent tasks including AM, imagery, and navigation in larger samples of healthy young adults (Clark et al., 2020; Weisberg et al., 2019). Using higher resolution scans to examine hippocampal subfields, such as CA2,3/DG and subiculum, may be more appropriate to capture specific relationships to hippocampal-dependent processes, such as AM (Palombo et al., 2018; Barry & Maguire, 2019). It is also possible that more extreme conditions, such as expertise (Clark et al., 2020) or pathology (Van Petten, 2004) are needed to detect associations.

Older adults' smaller posterior hippocampus volumes could speak to their recollection of fewer specific, episodic details, but no association between posterior hippocampus volumes and episodic AM was observed. According to one framework, tasks which require the recollection of specific episodic details—like the AI—recruit the posterior hippocampus to generate context and recreate the remembered scene (see Sheldon & Levine, 2016 and Sheldon et al., 2019 for reviews). Smaller volumes may impair these abilities, as suggested by findings that age-related atrophy to parahippocampal white matter volume predicts episodic memory performance in older adults (Stoub et al., 2014). Yet, our results suggest that typical aging may not sufficiently alter hippocampal volumes to detect relationships with hippocampal-dependent tasks. Indeed, strong positive associations with episodic memory scores have been observed for individuals with mild cognitive impairment and Alzheimer's disease, who often have more pronounced atrophy to the hippocampus than cognitively healthy older adults (Chauveau et al., 2021).

An association between anterior hippocampus volumes and episodic AM was detected in older adults. The anterior hippocampus has been widely observed to play a role in the construction, compared to elaboration, of both past and future autobiographical events (e.g., Benoit & Schacter, 2015). Forming part of a network of regions that has been referred to as the dorsomedial subsystem of the default network (Andrews-Hanna et al., 2014), anterior temporal memory network (Ranganath & Ritchey, 2012), or semantic memory network (Chapleau et al., 2019), the anterior hippocampus is thought to play a role in retrieval of AMs more generally, and the conceptual components on which more specific details later build (Sheldon & Levine, 2016). In the current study, older adults reported more semantic recollections and had better laboratory-tested semantic memory abilities, in agreement with the relative preservation of semantic knowledge in older age (Parker & Reuter-Lorenz, 2009). Anterior hippocampus activity has also been implicated in silent elaboration of AMs in older adults (Addis et al., 2011). Given the implicit nature of the task, the authors speculated that this finding was related to more semanticized AMs in older participants. However, anterior hippocampal volumes were associated with episodic, rather than semantic, AM in our sample of older adults.

Unexpectedly, the relationship between anterior hippocampus volumes and episodic AM was qualified by an interaction with sex in older adults. Larger right anterior hippocampus volumes were associated with less episodic AM in males and the opposite pattern in females. Younger adult females have previously been found to have larger posterior hippocampal volumes than younger males, along with unique patterns of structural covariance with the anterior hippocampus (Persson et al., 2014). Sex differences are also robustly observed in verbal versus spatial memory abilities (e.g., Weiss et al., 2003), which draw on anterior and posterior hippocampus respectively (Poppenk et al., 2013). It is conceivable that age amplifies sex differences in cognition and/or brain structure. However, we refrain from interpreting this sex interaction in older adults as it is likely underpowered and should be replicated in a larger sample. The ability to detect these interactions in healthy aging samples presents an exciting future direction given that older females are inordinately vulnerable to Alzheimer's disease (see Fisher et al., 2018 for review).

Temporal Pole Volumes Relate to Episodic AM in Older Adults

Our final set of analyses tested for age group differences in temporal pole volumes and corresponding associations with AM. We specifically targeted the temporal pole as this region serves as a semantic processing hub (e.g., Hoffman & Morcom, 2018; Lambon Ralph, 2017) associated with prior knowledge during encoding of naturalistic stimuli (Raykov et al., 2021). Differential relationships with cognition emerged across age groups despite no discernible volume difference. Younger adult volumes were positively related to laboratory-tested semantic memory abilities, whereas older adults showed no such relationship. Rather, temporal pole volumes in older adults were positively related to episodic AM. A meta-analysis of age-related functional brain change has demonstrated that older adults recruit the anterior temporal region more than younger adults across a number of cognitive domains including memory retrieval (Spreng et al., 2010). In fact, older adults showed coactivation of the temporal pole with anterior hippocampus during an in-scanner AM task (Addis et al., 2011). The magnitude of anterior temporal activity in older adults was positively related to episodic details recalled from a separate session.

We speculate that age-related volume differences in posterior hippocampus, a region implicated in specific detail generation (Sheldon & Levine, 2016), may result in additional recruitment of intact areas such as the anterior hippocampus and temporal poles. The anterior hippocampus forms preferential connections to the temporal pole (Kahn et al., 2008) via the uncinate fasciculus (Kier et al., 2004), laying the groundwork for greater functional connectivity at rest (Honey et al., 2009) and during semantic processing (e.g., Hoffman & Morcom, 2018). Indeed, patients with semantic dementia often demonstrate damage and altered intrinsic functional connectivity to both of these regions (e.g., Chan et al., 2001; Schwab et al., 2020). If these regions are recruited to support episodic AM recollection in older adults, memories might necessarily be "semanticized," or imbued with more semantic information (Spreng et al., 2018). While speculative, this view emphasizes the significance of regional integrity and supports frameworks of neurocognitive aging that describe functional reorganization in relation to structural change as a form of adaptive scaffolding (Park & Reuter-Lorenz, 2009; Spreng & Turner, 2019; Andrews-Hanna et al., 2019). Further longitudinal inquiry involving both functional and structure measures is needed to test these claims. Future work would also benefit from inspecting other lateral temporal regions, which show increased involvement during older adult cognition (Spreng et al., 2010).

Concluding Remarks

Here we report on hippocampal and temporal pole grey matter volume relationships to AM in a well-powered sample of healthy younger and older adults. Older adults had smaller posterior hippocampus volumes, yet stable anterior hippocampus and temporal pole volumes, which may support better episodic AM in older age. Mixed findings of age-related grey matter vulnerability within the hippocampus across cross-sectional and longitudinal studies may not be entirely incompatible, with cross-sectional findings likely capturing different snapshots along the aging trajectory. While it is prudent to consider cohort effects when comparing younger and older adults, within-group brain-behavior relationships offer important insight into how age-related brain change—including atrophy—may support cognition in later life. Our findings also underscore the importance of considering sex differences in lifespan developmental research. Mapping out the complex interplay of structural, functional, and cognitive change in late life will be imperative to better understanding the brain mechanisms that continue to support complex cognition like AM.

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Bridge to Chapter 4

In Study 2, we first replicated findings that older adults recount past experiences with less episodic and more semantic detail. Older adults also had smaller posterior hippocampus, but not anterior hippocampus nor temporal pole volumes. Leading frameworks of autobiographical memory posit that posterior hippocampus plays a role in retrieval of specific, episodic autobiographical details (Sheldon et al., 2019). Smaller posterior hippocampus volumes in older adults could therefore be linked to less episodic recollection. However, we found no evidence that this was the case. Anterior hippocampus and temporal pole volumes were associated with older adults' episodic recollections, whereas temporal pole volumes were related to domain-general semantic abilities in younger adults. These results tentatively suggest that structures once associated with semantic processing become associated with episodic processing in the transition from younger to older adulthood. Reduced structural specialization of these regions may represent an adaptive change to preserve access to episodic memory as it declines in older age.

Study 3 examined whether age-related functional connectivity differences of the hippocampus and temporal pole establish differences engrained in structure-cognition relationships. We also investigate whether local structural differences observed in the posterior hippocampus contribute to functional connectivity changes in older adults. Results from Study 3 will inform how local brain functional and structural change intersect to support cognitive gains and losses in older adulthood.

Chapter 4: Age effects and individual differences in episodic and semantic autobiographical memory relate to resting-state functional connectivity of the hippocampus and temporal pole with the default network

Adapted from: Setton, R., Mwilambwe-Tshilobo, L., Sheldon, S., Turner, G.R., & Spreng, R.N. (*In Preparation)*. Age effects and individual differences in episodic and semantic autobiographical memory relate to resting-state functional connectivity of the hippocampus and temporal pole with the default network. *Current Biology*.

Abstract

Recollection of one's personal past, or autobiographical memory (AM), involves the retrieval of both episodic and semantic details and is thought to be supported by the default network. Here we take an individual differences approach to examine resting-state functional connectivity of the anterior hippocampus, posterior hippocampus, and temporal pole with the default network and test for associations with episodic and semantic AM. T1-weighted anatomical images, 20 minutes of multi-echo resting-state fMRI, and Autobiographical Interviews were collected for 263 healthy adult participants (158 younger, 105 older). We first examined resting-state functional connectivity profiles for each region of interest across all participants. Multivariate partial least squares was then used to test for age-group differences. Finally, behavior partial least squares was used to test for individual difference associations between resting-state functional connectivity and AM (episodic and semantic) across groups. Compared to younger adults, older adults had lower connectivity within anterior hippocampus, posterior hippocampus, and temporal pole, but greater connectivity across distributed regions of the default network. This pattern was positively related to posterior hippocampal volumes in older adults, which were smaller compared to those of younger adults. Behavior PLS examining associations between functional connectivity and AM identified two significant patterns. The first was an age-invariant dissociation of connectivity related to episodic versus semantic AM. Episodic AM was related to anterior hippocampus and temporal pole connectivity with orbitofrontal cortex as well as connectivity within posterior hippocampus. Semantic AM was related to temporal pole connectivity with regions across lateral temporal cortex. This association was stronger in older adults, who recalled more semantic information in their AMs compared to younger adults. In the second pattern, younger, but not

older, adults displayed a pattern of connectivity related to both episodic and semantic AM, as reflected in temporal pole connectivity with regions throughout the default network. Our findings add precision to age-related differences in the functional organization of the default network and provide strong evidence for discrete network ensembles that scale with systematic variation in episodic and semantic AM across the healthy adult lifespan.

Introduction

The recollection and re-telling of personal past experiences varies across individuals and changes over the lifespan (Palombo et al., 2018; Levine et al., 2002). Some recall the rich spatiotemporal context of a prior experience, while others remember relatively few specific details. Similarly, some individuals recount experiences within a deeper semantic context, while others provide little background information. This autobiographical form of recollection systematically shifts with advancing age, as the episodic quality of memory diminishes and semantic features become more prominent (Levine et al., 2002). Neuropsychological studies have identified the hippocampus and temporal pole as necessary for episodic and semantic aspects of autobiographical memory (AM; e.g., Eslinger, 1998; Herfurth et al., 2010; see also Irish & Piguet, 2013). Meanwhile, task activation studies have found AM to involve a more distributed set of brain regions within the default network (Svoboda et al., 2006; Spreng et al., 2009; Rugg & Vilberg, 2013; Benoit & Schacter, 2015). Little is known about how the hippocampus and temporal pole specifically interact with the default network and whether these interactions relate to individual differences in AM recollective styles.

The hippocampus and temporal pole form part of the default network (Buckner et al., 2008). The default network can be broken down into a core set of regions and two-subnetworks, each of which loosely maps onto the anterior temporal and posterior medial cortical systems that support different forms of memory-guided behavior (Andrews-Hanna et al., 2014; Ranganath & Ritchey, 2012). The dorsal medial default network, corresponding to the anterior temporal system, is made up of regions functionally affiliated with the dorsomedial prefrontal cortex, including the temporal pole (Andrews-Hanna et al., 2014). This sub-network is implicated in semantic-like tasks such as abstract processing, mentalizing, and language comprehension (Andrews-Hanna et al., 2019). The medial temporal default network, corresponding to the posterior medial system, is comprised of regions functionally affiliated with the medial temporal lobe, including the hippocampus (Andrews-Hanna et al., 2014). This sub-network is associated with more episodic abilities such as mental simulation, future thinking, scene construction, and situating items within a spatial context (Andrews-Hanna et al., 2019). The functional architecture of hippocampus and temporal pole with these discrete network ensembles is not well-characterized. It also remains to be determined whether variability within these ensembles scales with variability in AM across people.

An age-related shift in the quality of AM recollection coincides with robust changes to the functional integrity of the default network. Specifically, connectivity within the default network is reduced in older adults, and more integrated with other large-scale networks (see Damoiseaux, 2017 for a review). Compared to younger adults, older adults show specific reductions within core regions and the dorsal medial sub-network, but relative preservation of connectivity within the medial temporal sub-network (Campbell et al., 2013). An open question is whether the shift to semantic-laden AMs in older age is related to functional reorganization of the default network. Here, we determine whether individual differences and age effects in one's tendency to recall more detailed AMs is related to functional ensembles that comprise the default network.

One approach to answering this question is to examine how resting-state functional connectivity (RSFC) of this circuit covaries with AM. RSFC reflects a combination of genetic and experience-dependent changes to functional interactions (e.g., Stevens & Spreng, 2014). Individual differences in these functional dynamics may map onto individual differences in behavior, including the propensity to retrieve certain details when describing past experiences. Indeed, self-reported appraisals to recall one's personal past with more episodic detail has been associated with RSFC between the hippocampus and posterior visual regions, a pattern similar to functional connectivity during visual episodic memory tasks (Sheldon et al., 2016; Petrican et al., 2018). Self-reported semantic-based remembering has been associated with hippocampus RSFC to prefrontal cortex (Sheldon et al., 2016). A distinction between these ensembles in relation to objective AM performance has yet to be made.

We first characterized anterior hippocampus (AHIPP), posterior hippocampus (PHIPP), and temporal pole (TP) RSFC with the extended default network (see Table 1 for affiliations and abbreviations) in healthy younger and older adults. Second, we applied multivariate partial least squares to test for age group differences in RSFC. We predicted that younger adults would show more differentiated default sub-networks than older adults, reflected in stronger RSFC between the temporal pole and the dorsal medial sub-network and between hippocampus and the medial temporal sub-network. We also predicted relative de-differentiation of sub-networks in older adults. Finally, we used behavioral partial least squares to examine how these RSFC profiles related to individual differences in episodic and semantic AM, and whether these associations differed between younger and older adults. We predicted that episodic AM would associate with

RSFC between regions of the hippocampus and the medial temporal sub-network. Conversely, we predicted that semantic AM would relate to temporal pole RSFC with the dorsal medial sub-network. Evidence for this dissociation across all participants would fit into a broader framework of separable distributed network ensembles (or "process-specific assemblies"; Moscovitch et al., 2016), discernible at rest, configured to support different dimensions of AM (Ranganath & Ritchey, 2012; Cooper & Ritchey, 2019). We also hypothesized that RSFC associations with episodic and semantic AM may differ by age group, reasoning that RSFC differences may underlie the age-related shift in episodic and semantic detail generation. The overarching goal was to link RSFC of an AM circuit with variability in AM performance across individuals.

Figure 1

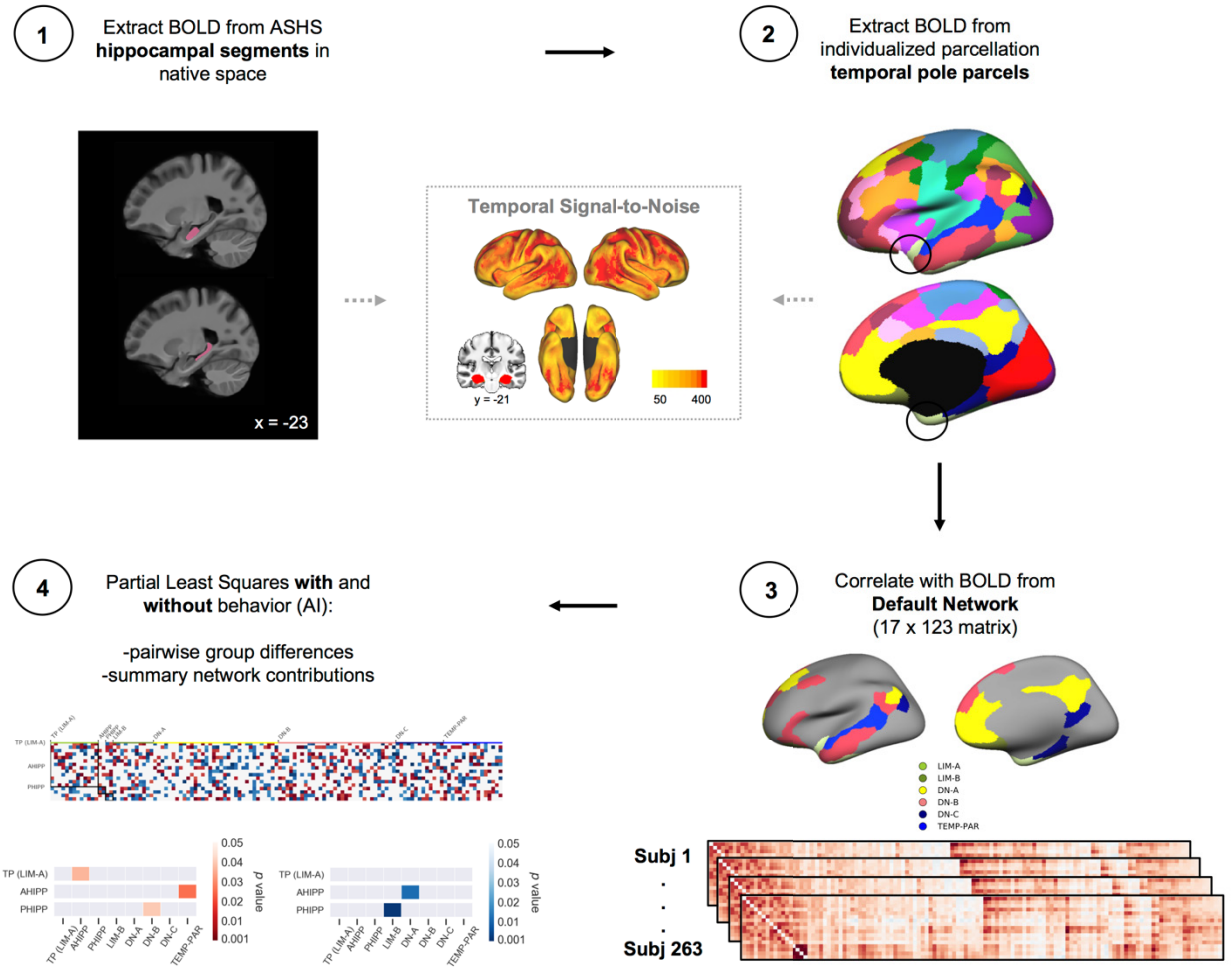

Figure 1. Schematic of Functional Connectivity Analytical Workflow. (1) BOLD data were extracted from left and right anterior and posterior hippocampal segments, as output from Automatic Segmentation of Hippocampal Subfields (ASHS). (2) BOLD data were extracted from temporal pole parcels, as defined by each participant's individual-specific parcellation solution. Inset shows temporal signal-to-noise map, thresholded to 50-400 for visualization purposes. The group temporal signal-to-noise ratio map was masked with the right and left hippocampus probability maps using the Harvard-Oxford Subcortical Structural Atlas in FSL for display only. Temporal signal-to-noise values were sufficiently high to examine RSFC within all regions included in the present analysis. (3) Functional connectivity between temporal pole, anterior hippocampus, and posterior hippocampus parcels and limbic, default, and temporoparietal sub-network parcels were constructed for each participant, resulting in a 17 x 123 rectangular matrix. (4) Matrices were submitted to Partial Least Squares to examine patterns of maximal covariance with group assignment or AI detail density. The resultant matrix of regional pairwise connections was summarized by network contribution plots illustrating the most reliable within- and between-network connections.

Table 1

Regions of the Default Network and Sub-network Affiliations

Sub-network	Regions
AHIPP	Left and right anterior hippocampus
PHIPP	Left and right posterior hippocampus
LIM-A	Temporal poles (TP)
LIM-B	Orbitofrontal cortex (OFC)
DN-A (core)	Inferior parietal lobule (IPL), dorsal prefrontal cortex (dPFC), medial prefrontal cortex (mPFC), precuneus and posterior cingulate cortex (Prec/PCC), and right inferior temporal cortex (iT)
DN-B (dorsal medial sub-network)	Lateral temporal cortex (lT), anterior temporal cortex (aT), anterior inferior parietal lobule (aIPL), dorsal medial prefrontal cortex (dmPFC), lateral prefrontal cortex (lPFC), and ventral prefrontal cortex (vPFC)
DN-C (medial temporal sub-network)	Posterior inferior parietal lobule (pIPL), retrosplenial cortex (RSC), and parahippocampal cortex (PHC)
TEMP-PAR	Temporal parietal cortex

Note. Sub-network is used to refer to bilateral hippocampal regions as well as sub-networks from the Yeo 17-network solution (2011).

Results

In the largest sample of AM and RSFC reported to date, we examined hippocampus and temporal pole RSFC with the default network and its relationship to episodic and semantic AM (Figure 1). We collected multi-echo resting-state fMRI from a cohort of healthy younger and older adults, and applied individualized cortical parcellations to test network and region-specific connectivity patterns. These innovations boost fMRI signal-to-noise ratios (Kundu et al., 2017; Raimondo et al., 2021), reduce age confounds associated with spatial normalization to a standard template (Setton & Mwilambwe-Tshilobo et al., *Under Revision*), and account for individual variability in default network sub-networks (e.g., Braga & Buckner, 2017). We implemented a hippocampal segmentation protocol, optimized for use in older adult brains, to investigate the separable contributions of anterior and posterior hippocampus to AM (Moscovitch et al., 2016; Sheldon & Levine, 2016; Sheldon et al., 2019) while accounting for age-related variability in this region. Finally, the Autobiographical Interview (Levine et al., 2002; Lockrow et al., *In Preparation*) was administered as a gold standard measure of episodic and semantic AM. Combined, these steps enhanced our power to detect how RSFC of the anterior hippocampus, posterior hippocampus, and temporal pole with the default sub-networks (see Table 1) associated with individual differences in AM. Our analysis proceeded in three steps: characterizing RSFC of the circuit, testing for age group differences, and identifying associations with episodic and semantic AM as a function of age group. At each turn, regional effects are summarized by network-level effects, reflecting the most reliable within- and between-network connections.

RSFC of AHIPP, PHIPP, and TP with the DN

We first established how each region of interest was functionally connected with regions across the extended DN. A surface representation of each region's RSFC pattern across all participants is shown in Figure 2A. TP showed strong positive connections with itself and lateral temporal cortex. AHIPP and PHIPP showed strong positive midline connections to anterior and posterior structures respectively. Weak negative connections were also observed between ventral PFC and AHIPP and PHIPP.

Average RSFC matrices in younger and older adults provide more detail at the parcel and hemisphere level (Figure 2B). Patterns were similar across groups. All three regions of interest showed broad correspondence to their sub-networks: TP showed strong positive connection to

lateral temporal regions within DN-B and TEMP-PAR; AHIPP/PHIPP showed positive connection to midline regions including OFC and mPFC, as well as regions within DN-C. Of these, ipsilateral connections were often stronger than contralateral.

Age Group Differences in RSFC

Quantitative comparison of the 2091 pairwise connections revealed a pattern of connectivity that distinguished younger and older adult RSFC (permuted $p < .001$; Figure 3A,C). Network contribution analyses summarize the significant contributions of within- and between-network edges to this pattern (Figure 3B). Significant regional connectivity differences are discussed in the context of network-level effects.

Younger adults showed greater connectivity within TP, AHIPP, and PHIPP, reflected in connections across hemispheres within each region. Younger adults expressed stronger connectivity along the longitudinal axis of the hippocampus, showing both ipsilateral and contralateral connections between AHIPP and PHIPP. Although intra-TP connectivity was most reliable, TP connectivity with regions throughout DN-B and temporoparietal cortex in both hemispheres was more prominent in younger adults. Anterior medial TP parcels, specifically, also showed selective connection to DN-A and DN-C regions in younger compared to older adults. Greater AHIPP— TP connectivity was observed via bilateral AHIPP connections to anterior medial TP parcels. Greater AHIPP—DN-C connections were reflected in bilateral AHIPP connectivity to PHC and right posterior IPL. PHC, as part of DN-C, is more often associated with PHIPP as part of a posterior medial temporal lobe pathway (Kahn et al., 2008). PHIPP connectivity to PHC was also observed, but to a lesser extent. Greater PHIPP—OFC connections reliably contributed to the overall pattern, although AHIPP—OFC connections were also observed with different parcels.

Older adults had a distinct pattern of greater between-network RSFC compared to younger adults. The first of these was higher TP connectivity, marked by TP —DN-A and TP —DN-C at the network-level. At the regional level, this result emerged as bilateral TP connectivity with precuneus/PCC, right dorsal PFC and RSC. The most reliable AHIPP RSFC differences in older compared to younger adults were with prefrontal DN-B regions including dorsal medial and lateral PFC. Similar connections were observed with PHIPP. Similarly greater AHIPP and PHIPP connectivity were observed with left precuneus/PCC. Overall, older adults showed

greater hippocampal connectivity across regions within DN-A and DN-B, whereas younger adults had stronger hippocampal connections with DN-C. Hippocampus may therefore bind posterior cortex to the DN in younger age (e.g., Spreng et al., 2016) but not into older adulthood. Indeed, older adults showed a striking pattern of greater PHIPP—TEMP-PAR connectivity emerging from bilateral PHIPP connections to right temporal parietal cortex.

We next tested whether this pattern was influenced by grey matter volumes of the three regions of interest. As seen in Figure 3C, larger PHIPP volumes in both hemispheres were associated with higher brain connectivity scores in older adults only (Left: pr(100)=.28, p < .005, [.09, .45]); Right: pr(100)=.21, p < .05, [.02, .39]). Older adults with larger PHIPP volumes had a pattern of RSFC more similar to that expressed by younger adults. This relationship was statistically attenuated when site was included as a covariate (Left: pr(99)=.14, p = .155, [-.05, .32]; Right: pr(99)=.060, p = .546, [-.13, .25]). AHIPP and TP volumes were not related to RSFC (all p's > .05).

Figure 2

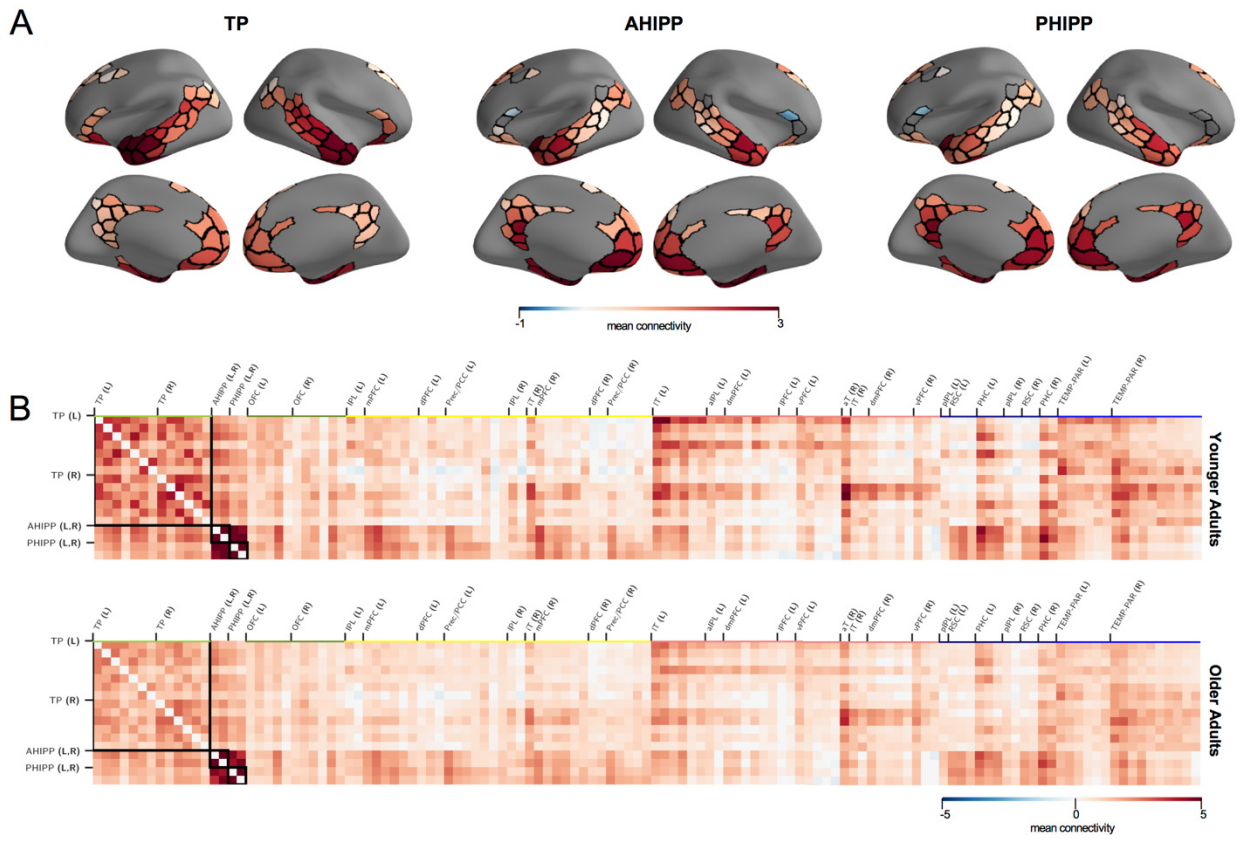

Figure 2. RSFC of AHIPP, PHIPP, and TP with the DN. (A) RSFC for each region of interest across the extended default network, collapsed across younger and older adults. For each region, BOLD data were averaged across parcels from both hemispheres to construct a new 1 x 109 RSFC matrix. Z values were averaged across all participants. The significance of each cell was determined with a one-sample t-test. P values below .05 were masked out. Hippocampal regions are not shown on the surface. For visualization purposes, all TP parcels on the TP surface were assigned the maximum value in the matrix to indicate self-connection. (B) Average RSFC in younger (top) and older (bottom) adults shown in full. Bootstrap resampling (resampling rate=10,000) was implemented to obtain a 95% confidence interval and determine reliable connections. Connections whose confidence intervals crossed zero were masked out. TP = temporal pole; AHIPP = anterior hippocampus; PHIPP = posterior hippocampus; OFC = orbitofrontal cortex; IPL = inferior parietal lobule; aIPL = anterior inferior parietal lobule; pIPL = posterior inferior parietal lobule; dPFC = dorsal prefrontal cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; lPFC = lateral prefrontal cortex; vPFC = ventral prefrontal cortex; Prec = precuneus; PCC = posterior cingulate cortex; iT = inferior temporal; lT = lateral temporal; aT = anterior temporal; RSC = retrosplenial cortex; PHC = parahippocampal cortex.

Figure 3

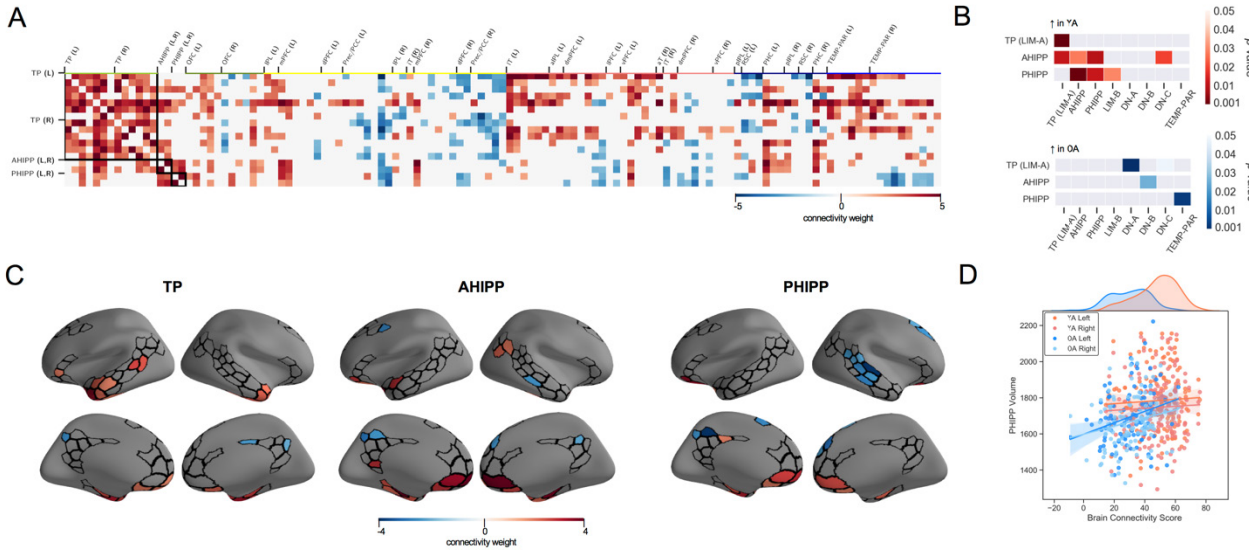

Figure 3. Age Group Differences in RSFC. (A) One pattern distinguished pairwise connectivity expressed more by younger adults, shown in warmer colors, from pairwise connectivity expressed more by older adults, shown in cooler colors. The matrix was thresholded at a bootstrap ratio = 1.96, representative of a 95% confidence interval. (B) Network contributions summarizing network-level differences. (C) A surface representation of (A). For each region of interest, unthresholded results were averaged across parcels in the left and right hemispheres and then thresholded to an average bootstrap ratio of 1.96. Hippocampal regions are not shown on the surface. (D) Brain connectivity scores from (A) plotted as a function of PHIPP volume in younger and older adults. In older adults, higher brain connectivity scores were related to larger bilateral PHIPP volumes. YA = younger adults; OA = older adults; TP = temporal pole; AHIPP = anterior hippocampus; PHIPP = posterior hippocampus; OFC = orbitofrontal cortex; IPL = inferior parietal lobule; aIPL = anterior inferior parietal lobule; pIPL = posterior inferior parietal lobule; dPFC = dorsal prefrontal cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; lPFC = lateral prefrontal cortex; vPFC = ventral prefrontal cortex; Prec = precuneus; PCC = posterior cingulate cortex; iT = inferior temporal; lT = lateral temporal; aT = anterior temporal; RSC = retrosplenial cortex; PHC = parahippocampal cortex.

RSFC Associations with AM

Autobiographical memory was tested with the Autobiographical Interview (Levine et al., 2002). As part of the interview, participants chose a single memory, specific in time and place, to describe in detail for a series of different time periods (e.g., childhood). Descriptions were scored for episodic-like "internal" details (i.e., order of events, location, time information, sensory descriptions, emotions, thoughts) and semantic-like "external" details (i.e., general semantic information about oneself and the world, repetitions, metacognitive statements, specific details about unrelated memories). A full subcategory listing is detailed in Tables S1-2. The number of internal and external details are typically tallied and averaged across events. Work from our laboratory has shown that measures controlling for verbosity, which we refer to as internal and external density scores, are more reliable and valid metrics of episodic and semantic AM (Lockrow et al., *In Preparation*).

We have previously examined how internal and external density scores in this sample were associated with grey matter volumes of AHIPP, PHIPP, and TP (Setton et al., *Under Revision*). We reported that older adults had less internally dense and more externally dense recollections than younger adults (Internal density: M_{young}: .09, SD_{young}: .02; M_{old}: .07, SD_{old}: .02; $t(258)=11.06$, $p < .001$, Cohen's $d=1.38$; External density: M_{young}: .02, SD_{young}: .01; M_{old}: .04, SD_{old}: .01; ($t(258)=6.32$, $p < .001$, Cohen's $d=.79$; Setton et al., *Under Revision*).

Here we test for RSFC patterns associated with internal and external density. To do so we used behavior PLS to identify patterns of RSFC in younger and older adults that covaried with internal and external density scores. PLS was carried out in the same 2091 pairwise connections between our three regions of interest—TP, AHIPP, and PHIPP—and regions of the extended DN. Two significant latent variables emerged.

An Age Invariant Pattern of RSFC Dissociates Internal from External Density

The first pattern revealed a main effect of detail density, separating RSFC associated with internal versus external density in both younger and older adults (18.77% covariance explained, permuted $p < .001$; Figure 4A). In both age groups, greater internal density of AM recollection was associated with higher RSFC between a number of regions (Figure 4A, warmer colors). First, internal density was positively associated with greater TP—LIM-B, AHIPP—LIM-B, and

bilateral PHIPP RSFC. Widespread TP connectivity was observed at the regional level, with left-lateralized connections throughout the extended DN and right TP connections to medial PFC regions including OFC, mPFC, and dmPFC, as well as temporoparietal cortex. Bilateral AHIPP connections to OFC were most reliable, although AHIPP connections across hemispheres and to right mPFC were also observed. Internal density was also associated with RSFC between right PHIPP and PHC.

In both younger and older adults, more externally dense memories were related to higher TP —TEMP-PAR connectivity. This included contralateral connections between TP and temporoparietal cortex. Contralateral connections were also observed between right TP and left DN-B regions including lT, lPFC, and vPFC.

RSFC associations with density scores were highly similar when controlling for sex, education, eWBV, and site, although the association with external density in younger adults was attenuated (p = .296; Table S2).

We conducted a *post hoc* analysis to explore which categories of internal and external details most contributed to the RSFC-density associations in each age group. RSFC associations with internal density were driven by internal event details in younger adults, and internal event, perceptual, and emotion/thought details in older adults (see Table S1). RSFC associations with external density were driven by external place, semantic, repetition, and other details in younger adults, and external event, place, time, perceptual, and emotion/thought details in older adults. Sex, education, and eWBV were included as covariates. Including site as an additional covariate reduced the magnitude of RSFC associations with external density, but results remained qualitatively similar (see Table S2).

A Specific Pattern of RSFC Younger Adults for Internal and External Density

The second pattern was an association with RSFC where internal and external density covaried together in younger adults (1.97% covariance explained, permuted $p < .05$; Figure 4C). Older adults did not reliably contribute to this pattern. Internal and external density in younger adults were positively associated with TP —LIM-B, TP—DN-C, and AHIPP—TEMP-PAR connections at the network level (Figure 4C, warmer colors). Regionally, left TP showed both ipsi- and contralateral connections to OFC, RSC, and PHC. Left AHIPP was connected to

temporoparietal cortex both ipsi- and contralaterally, while right AHIPP connectivity to temporoparietal cortex remained ipsilateral. AM in younger adults is thus associated with left intra- and interhemispheric RSFC within an extended DN. Internal and external density in younger adults were negatively associated with TP connectivity to DN-B. Specifically, younger adult AM was associated with less connectivity between left-lateralized TP connectivity to aIPL, dmPFC, lPFC, and vPFC (Figure 4C, cooler colors). Notably, internal and external density in younger adults was also negatively associated with hippocampal connectivity to anterior midline regions including OFC and mPFC, as well as right PHIPP connectivity throughout the extended DN. RSFC associations with density scores were nearly identical when controlling for sex, education, eWBV, and site.

Post hoc associations with AI subcategories were again conducted to determine which details contributed to the shared density association with RSFC in younger adults. Internal event, place, and time details along with external event, place, time, perceptual, repetition, and other details drove the RSFC-density association (see Table S1). When site was included as a covariate, RSFC associations with internal detail categories were nearly identical. Only external event and emotion/thought detail categories significantly contributed to the pattern (see Table S2).

Figure 4

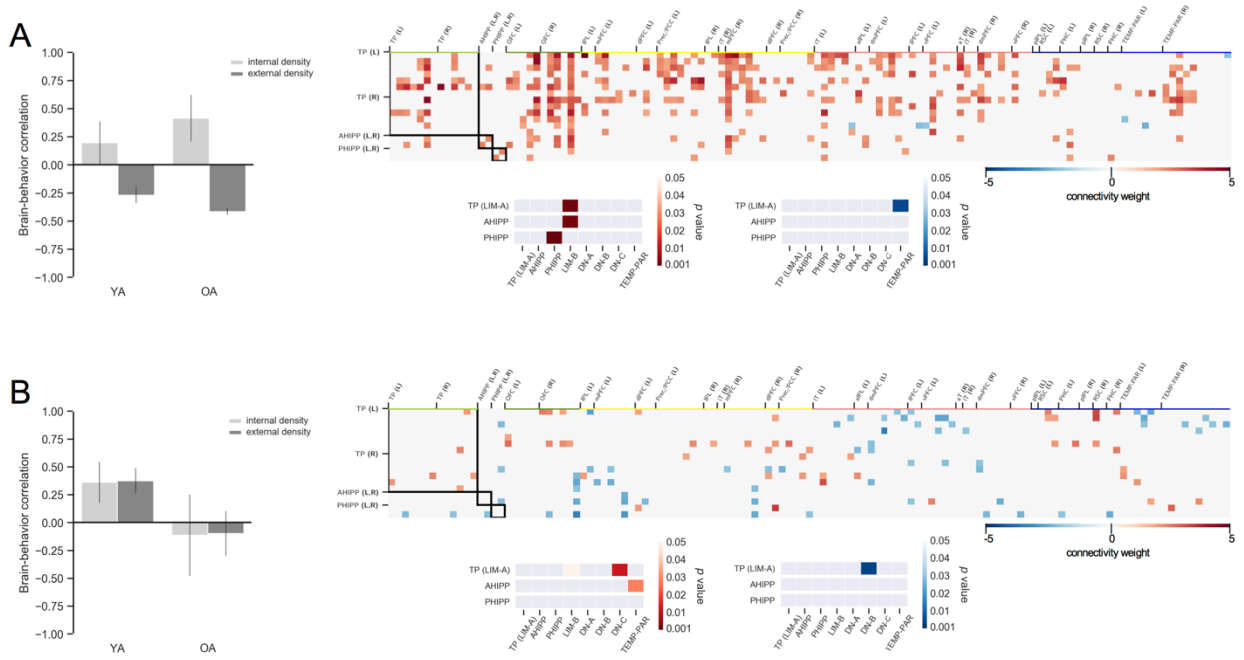

Figure 4. Individual Differences in Internal and External Density Related to RSFC. Two significant patterns of functional connectivity associated with internal and external density as a function of age group were identified by Behavior Partial Least Squares analysis. (A) A main effect of detail density distinguished pairwise connections related to internal (warmer colors) and external (cooler colors) density in both younger and older adults. (B) A main effect of age group shows pairwise connections associated with both internal and external density in younger adults (warmer colors). Cooler colors reflect pairwise connections negatively associated with density in younger adults. Network contribution plots characterize network-level effects. YA = younger adults; OA = older adults; TP = temporal pole; AHIPP = anterior hippocampus; PHIPP = posterior hippocampus; OFC = orbitofrontal cortex; IPL = inferior parietal lobule; aIPL = anterior inferior parietal lobule; pIPL = posterior inferior parietal lobule; dPFC = dorsal prefrontal cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; lPFC = lateral prefrontal cortex; vPFC = ventral prefrontal cortex; Prec = precuneus; PCC = posterior cingulate cortex; iT = inferior temporal; lT = lateral temporal; aT = anterior temporal; RSC = retrosplenial cortex; PHC = parahippocampal cortex.

Discussion

The present study established the functional architecture of AHIPP, PHIPP, and TP with the DN, differences between younger and older adults, and associations with episodic and semantic AM. Across participants, TP was strongly connected to lateral temporal regions in correspondence with a dorsal medial DN sub-network. AHIPP and PHIPP were strongly connected to regions of the medial temporal DN sub-network, including orbitofrontal cortex. Compared to older adults, younger adults had greater RSFC between both hippocampal regions and orbitofrontal cortex. As predicted, older adults had lower RSFC within AHIPP, PHIPP, and TP, but greater RSFC with distributed regions of the DN. This pattern of higher and lower RSFC was associated with PHIPP volumes in older adults, suggestive of a link between local structural and distributed functional differences with age. Across age groups, individual differences in episodic (internal density) and semantic (external density) AM were dissociated in their relationship to RSFC, indicating a maintained degree of distinctiveness between recollection of these types of details. More episodic AM was associated with greater AHIPP and TP connectivity to orbitofrontal cortex, and intra-PHIPP connectivity. More semantic AM was associated with higher TP connectivity to regions across lateral temporal and temporoparietal cortex. Relative to older adults, younger adults had a unique pattern of AM related to RSFC for both episodic and semantic AM. In this younger adult pattern, greater AM detail overall was associated with greater TP connectivity to orbitofrontal cortex and retrosplenial cortex, greater AHIPP connectivity to temporoparietal cortex, and lower connectivity TP connectivity to prefrontal cortex. Our findings provide a high-resolution map of RSFC between temporal lobe structures and regions throughout the DN as well as differences with age. They also serve as novel evidence that RSFC of AHIPP, PHIPP, and TP with the DN is related to individual differences in AM.

Age Group Differences in RSFC of AHIPP, PHIPP, and TP

A multivariate comparison of RSFC between age groups revealed that older adults had less connectivity within TP, AHIPP, and PHIPP, as well as less connectivity between AHIPP and PHIPP, largely consistent with prior work (Salami et al., 2016; Stark et al., 2021; Damoiseaux et al., 2016). This pattern recapitulates a pattern of large-scale network dedifferentiation across the healthy aging connectome (Setton & Mwilambwe-Tshilobo et al., *Under Revision*; Chan et al.,

2014; Geerligs et al., 2015; Wig, 2017). Reduced connectivity within AHIPP and within PHIPP suggests reduced specialization of the hippocampal longitudinal axis in older adults.

TP showed greater affiliation with lateral temporal and temporoparietal regions in younger adults, corresponding to a dorsal medial DN sub-network (Andrews-Hanna et al., 2010). Our analysis also revealed heterogeneity in TP RSFC in younger adults. Select anterior medial portions of TP were connected to core DN regions and parahippocampal cortex. AHIPP connectivity to this same TP region was among the most reliable connections in younger adults, along with AHIPP connectivity to parahippocampal cortex. Indeed, anterior medial TP may be more cytoarchitectonically similar to medial temporal polar cortex, which is homologous to ventral TP in nonhuman primates (Blaizot et al., 2010). As such, stronger RSFC of this TP region may be expected along the medial extent of the temporal lobe, including with parahippocampal cortex, and may thus show similarities to parahippocampal RSFC (Persichetti et al., 2021). Given its proximity and connection to AHIPP, this anterior medial TP region may be uniquely located to pivot between hippocampus and DN sub-networks. In older adults, TP was less functionally associated with dorsal medial DN regions, instead correlating more—and less selectively—with posterior core and medial temporal DN regions. This confirmed de-differentiation of a dorsal medial DN sub-network, as seen previously (Campbell et al., 2013). The more widespread connectivity between TP and posterior DN regions may also suggest decreased heterogeneity within the TP in older adulthood.

AHIPP and PHIPP RSFC in younger adults revealed a tighter correspondence to the medial temporal DN sub-network than older adults, as evidenced by greater connectivity to parahippocampal cortex, medial prefrontal cortex, and orbitofrontal cortex (Andrews-Hanna et al., 2010). This finding diverged from those identifying parahippocampal cortex as preferentially connected to PHIPP as part of a posterior medial network (Kahn et al., 2008; Ranganath & Ritchey, 2012). In older adults, greater hippocampal RSFC was most prominently observed between PHIPP and temporoparietal cortex. In fact, older adults had greater RSFC for both AHIPP and PHIPP with distributed regions throughout the DN. This was in contrast to prior work finding lower RSFC between PHIPP and core regions of the DN alongside increased connectivity within PHIPP in older adults (Damoiseaux et al., 2016; Salami et al., 2016; Stark et al., 2021). These inconsistencies may be due to differences in analysis choices, including the extent of regions tested for RSFC differences, functional boundary mapping (e.g., hippocampal

body as PHIPP instead of AHIPP; Zheng et al., 2021), smaller samples sizes, and poorer tSNR. The present work overcomes many of these methodological challenges to more fully characterize age differences in RSFC throughout the DN. The combination of techniques applied here—multi-echo fMRI for improved signal detection, hippocampal segmentation with an atlas optimized for use in older adults, and individualized parcellation for individual-specific demarcation of functional regions—provides unprecedented precision in characterizing this network.

RSFC differences across groups were related to PHIPP grey matter volume. We recently reported that older adults have smaller PHIPP grey matter volumes compared to younger adults, with no differences observed in AHIPP or TP (Setton et al., *Under Revision*). Here, larger PHIPP volumes in older adults were related to stronger expression of the "young-like" RSFC pattern. This finding suggests a link between local structural and distributed functional differences in older compared to younger adults (e.g., Park & Reuter-Lorenz, 2009). We speculate that the observed age differences in RSFC may be driven by grey matter atrophy to the posterior hippocampus. Including site as a covariate attenuated relationships, yet controlling for site may remove desirable demographic variability that may have even more pronounced effects on older adult brain structure and function (e.g., Chan et al., 2018). Replication in larger diverse samples will advance understanding of age differences in structure-function relationships within the temporal lobe, particularly where longitudinal data is lacking.

An Age-Invariant Pattern of RSFC Dissociates Episodic From Semantic Autobiographical Recollection

Despite age differences in the functional architecture of the AM circuit under examination, individual differences in episodic and semantic AM were dissociated in their patterns of RSFC across the full sample. This is consistent with task-related findings showing that younger and older adults engage similar regions during AM (e.g., Addis et al., 2011; Viard et al., 2007; Martinelli et al., 2013). However, task studies have also identified activity that differs between younger and older adults (Addis et al., 2011), interpreting differences as a consequence of the reduced episodic quality of memory in older age. Few studies have explicitly linked task activation to individual differences in AM. The advantage of the approach used here is that RSFC dissociated episodic and semantic aspects of recollection, providing evidence for

separable distributed network ensembles that may be configured to support different aspects of AM (Cooper & Ritchey, 2019; Ranganath & Ritchey, 2012), and may explain why individuals vary in how they recount the past.

Individuals with more episodically dense recollections had greater RSFC between AHIPP/TP and orbitofrontal cortex and within PHIPP. AHIPP, TP, and orbitofrontal cortex are anatomically and functionally connected as part of an anterior temporal network of regions. Together these regions are predicted to play a role in familiarity-based recognition, social and emotional processing, and semantic knowledge representation (Adnan et al., 2016; Kahn et al., 2008; Ranganath & Ritchey, 2012). Our results suggest that variation in RSFC among these regions may also scale with episodic processes. While self-reported episodic AM abilities in younger adults have been associated with RSFC between hippocampus and posterior medial regions (Sheldon et al., 2016; Petrican et al., 2018), a more distributed set of regions active during AM have been related to subjective ratings of imagined detail in younger and older adults (Addis et al., 2011). We expand on this with evidence for how the magnitude of connectivity among AHIPP, PHIPP, and TP relates specifically to episodic AM.

RSFC between AHIPP/TP and orbitofrontal cortex systematically increases through adolescence concurrent with development of complex cognitive function (Calabro et al., 2020; Murty et al., 2016). RSFC between these regions in association with episodic AM may reflect fluid aspects of everyday remembering. AHIPP is thought to support recollection of coarse or more generalized AM information, as would be expected in early stages of memory construction prompted by open-ended retrieval cues (Sheldon & Levine, 2016). Effective connectivity models have demonstrated interactions between AHIPP and frontotemporal regions during early AM retrieval that precede PHIPP interactions with posteriomedial regions during later elaboration (McCormick et al., 2015). Activity in ventromedial prefrontal cortex, which spans orbitofrontal cortex, is associated with temporarily binding schema representations from across cortex to form higher-order knowledge templates (Gilboa & Marlatte, 2017). When certain schemas are activated, orbitofrontal cortex can then bias information processing in a context-sensitive manner. Studies leveraging the higher temporal resolution of magnetoencephalography during AM have shown that ventromedial prefrontal cortex activity during construction drives hippocampal activity that is then sustained throughout elaboration (McCormick et al., 2020). TP is often associated with semantic processes and incorporating prior knowledge into encoded

representations (e.g., Lambon Ralph et al., 2017; Raykov et al., 2021). Functional interactions among AHIPP, TP, and orbitofrontal cortex could putatively reflect context-dependent retrieval that takes place in orbitofrontal cortex: representations of associated episodes in AHIPP arrive at orbitofrontal cortex, activate specific schemas that then call on relevant prior knowledge from TP, all to engage and retrieve context appropriate representations from PHIPP. The observed pattern of greater RSFC for more episodically dense AMs may therefore reflect connections forged as a result of repeated efficient context-dependent retrieval. As the ability for context-dependent retrieval, and episodic AM, wanes, this pattern of RSFC may diminish.

Our findings are the first to relate intrinsic functional connectivity between TP and lateral temporal and prefrontal regions to a greater propensity for semantic AM across individuals. This suggests that younger and older adults maintain RSFC patterns that may be recruited in similar ways to support semantic AM. A stronger association in older adults further suggests that this RSFC pattern may underlie recollection of more semantic information in older age. Lateral temporal, lateral prefrontal, and temporoparietal cortices are all predicted to communicate bidirectionally with anterior temporal regions including the TP during semantic cognition (Lambon Ralph et al., 2017). The observed interregional connections related to semantic AM underscores that variation in the functional connectivity across these specific regions at rest is sensitive to variation in semantic detail recollection. Although we did not have predictions about the laterality of effects, semantic AM was exclusively associated with contralateral TP connectivity. When examining the subcategory contributions to this RSFC pattern, we found that semantic details contributed most to the association in younger adults while unrelated specific details contributed most in older adults. This converges with the finding that older adults' recollections tend to be 'semanticized', whereby specific memories gradually lose their spatiotemporal context over time (Piolino et al., 2002). Thus, relevant episodic and semantic details may become more similar with age, and more distinct from irrelevant episodic details. The distinction between relevant and irrelevant episodic details in older adults is especially intriguing given age-related impairments to attention, stemming from a reduced ability to suppress irrelevant information (e.g., Gazzaley et al., 2005). AM studies tend to center on the episodic quality of recalling the past, yet it is clear that better characterization of semantic AM, especially in older age, can provide much needed insight into the neurocognitive contributions of shifts in narrative retelling.

A RSFC Pattern Associated with Autobiographical Recollection in Young Adults

A smaller, but significant, factor for individual differences in AM was age. Younger adults had a pattern of connectivity associated with AM distinct from older adults. In this pattern, episodic and semantic memory covaried together, revealing a network ensemble specific to younger adult recollection. More dense recollections were associated with greater RSFC between left TP (including anteromedial TP) and orbitofrontal cortex, precuneus/posterior cingulate cortex, retrosplenial cortex, and parahippocampal cortex. Less dense recollections were related greater left TP RSFC with prefrontalcortex and temporoparietal cortex. This pattern may represent a link between episodic and semantic AM that is deprecated in older adults. Leading models of AM posit that access to our repository of memories is hierarchical: specific episodic experiences are embedded within categories of more general events, which are in turn subsumed under lifetime periods (Conway & Pleydell-Pearce, 2000). Vivid recollections thus require aspects of both semantic and episodic memory: retrieval and reconstruction of an appropriate memory involves sifting through broader organizing categories to gain access to specific contextual details. At the level of the brain, networks associated with general semantic processing and episodic core recollection have substantial overlap (Renoult et al., 2019). Intact recollection may therefore require both. We speculate that the shared pattern of covariance in younger adults reflects access through nested levels of the AM hierarchy to more specific event complexes, the absence of which may explain limited access to episodic detail in older adult recollections. Anteromedial TP, which also showed greater RSFC to parahippocampal cortex in younger adults, may be a candidate region for a bridge between episodic and semantic AM.

Conclusions

The present study used novel acquisition methods to collect high quality resting-state fMRI data in the heretofore largest aging study of AM conducted with the AI. Leveraging multivariate methods, we were able to move beyond inferences made from silent in-scanner AM tasks to separately examine individual differences in episodic and semantic AM. We acknowledge that the brain-behavior associations presented convey an indirect characterization of age differences in brain function supporting AM (see Campbell & Schacter, 2016 and Finn, 2021 for similar commentary). Task activation studies are an effective means for identifying brain activity engaged

during cognition, but offer limited information about how activity varies across people. Using RSFC, here we identified specific network ensembles that systematically vary across individuals in predicting episodic and semantic AM. Interactions within and between these ensembles are likely key to understanding individual differences in recollection. These findings largely converge with recent work characterizing separable and combined roles of anterior temporal and posterior medial regions in AM and cognition more broadly (e.g., McCormick et al., 2015, 2020; Ranganath & Ritchey, 2012; Robin & Moscovitch, 2017; Sheldon & Levine, 2016), and provide testable hypotheses for future task fMRI studies (see also Geerligs & Tsvetanov, 2017). Continued advances in neuroimaging methods, such as real-time motion correction for audible in-scanner AM tasks (e.g., Gilmore et al., 2021), will be instrumental to further understand the different processes that underlie individual differences in AM.

We established the intrinsic functional architecture of regions implicated in AM, differences between younger and older adults, and associations with episodic and semantic AM. Across individuals, we found evidence for broad correspondence of hippocampus and temporal pole with default sub-networks. In line with more global patterns of age-related functional reorganization, older adults showed de-differentiation of these regions with their sub-networks compared to younger adults. This pattern was associated with posterior hippocampal volume in older adults, suggestive of a link between local structural and distributed functional differences in older age. Critically, episodic and semantic AM were differentially related to RSFC in an age-invariant fashion. Relative to older adults, younger adults also demonstrated a unique pattern of RSFC related to both episodic and semantic AM. Thus, individual differences in specific elements of this AM circuit scale with the tendency to recall one's personal past with a certain balance of episodic and semantic detail, but young adulthood bears a distinct signature of RSFC related to overall recollection. Our findings provide a high resolution map of RSFC between temporal lobe structures and regions throughout the DN, and strong evidence for how variance in this map is sensitive to individual differences in recollection across the lifespan.

STAR Methods

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
MATLAB R2018b	https://www.mathworks.com	RRID:SCR_001622
Python 2.7	https://www.python.org/	RRID:SCR_008394
FSL	https://www.fmrib.ox.ac.uk/fsl	RRID: SCR_002823
AFNI	https://afni.nimh.nih.gov/	RRID:SCR_005927
Freesurfer version 6	https://surfer.nmr.mgh.harvard.edu	RRID: SCR_001847
ASHS	https://www.nitrc.org/projects/ashs	
ME-ICA version 3.2 beta	https://github.com/ME-ICA/me-ica	
GPIP	Chong et al., 2017	
PLS	https://www.rotman-baycrest.on.ca/index.php?section=84	
Behavioral Data	https://osf.io/fzkm7/	
Neuroimaging Data	https://openneuro.org/datasets/ds003592	ds003592

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Roni Setton (roni.setton@mail.mcgill.ca).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Behavioral data have been deposited at the Open Science Framework and neuroimaging data have been deposited at OpenNeuro. Datasets are publicly available as of the date of publication. Access links and accession numbers are listed in the key resources table.

All original code and additional information required to reanalyze the data in this study are available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants were 263 healthy younger (N=158; 91 female; M_{age}=22.59, SD_{age}=3.33) and older (N=105; 57 female; M_{age}=68.19, SD_{age}=6.29) adults from Ithaca, New York and Toronto, Canada. We recently reported on this subset of participants to examine the link between AM and structural MRI (Setton et al., *Under Revision*). This subset comprised participants from a larger sample of participants with AM data (Lockrow et al., *In Preparation*) who also underwent MRI scanning. Briefly, all participants were screened for histories of neurological or psychiatric disorder, depressive symptomology (assessed with the Beck Depression Inventory or Geriatric Depression Scale; Beck et al., 1996; Yesavage et al., 1982), and mild cognitive impairment (using the Mini-Mental State Examination; Folstein et al., 1975).

METHOD DETAILS

Autobiographical Memory

AM was assessed with the Autobiographical Interview (Levine et al., 2002). Participants were asked to choose a memory from each of three (younger adults) or five (older adults) life stages: childhood, teenage years, early adulthood, middle adulthood, and older adulthood. Participants were instructed to only choose memories that were specific in time and place. Starting with the first memory, participants described the memory chosen in as much detail as possible until they reached a natural end (free recall). Participants were then asked if they remembered anything else about the memory (general probe) before moving onto the next life stage. After all memory descriptions, each memory was revisited and participants were probed with specific questions to cue episodic recollection (specific probe). Participants then rated the memory for vividness, emotional change, significance, and rehearsal of the memory on a 5-point Likert scale. Interviews were audio recorded and transcribed.

Interviews were scored according to the original protocol by trained researchers. According to this procedure, scorers identify the main event in each memory and subdivide the

text into internal details—episodic details related to the event—and external details—unrelated non-episodic details that often provide background. Internal details include information about the sequence of events, location, time, perceptual landscape, and the participant's emotions and thoughts. External details include semantic information, repetitions, metacognitive statements, and other details unrelated to the main event. A full listing of subcategories can be found in Tables S1-2. Tallies are then made for each detail type and for the broader internal and external categories. Text from specific probe was not considered in the present study. All interviews were double-scored and reached high inter-rater reliability (internal: $r(261)=.91$, $p < .001$; external: $r(261)=.82$, $p < .001$).

Work from our laboratory has shown that internal and external detail counts, which may serve as coarse approximations for episodic and semantic recollection, are positively associated with each other and overall word count (Lockrow et al., *In Preparation*). Dependent variables that control for verbosity have high reliability across memories, remove the positive association between internal and external details, and demonstrate convergent validity with other laboratory performance-based memory tasks. Here we use one such variable, a density score, which separately divides internal and external counts by a memory's overall word count. Internal and external density scores were averaged across memories to serve as stable measures of episodic and semantic recollection. Density scores for subcategories of internal and external details were also calculated.

Neuroimaging

Imaging data were acquired from both sites with similar scan protocols. Images in Ithaca were acquired with a 3T GE750 Discovery series MRI scanner fit with a 32-channel head coil at the Cornell Magnetic Resonance Imaging Facility. Data in Toronto were acquired on a 3T Siemens TimTrio MRI scanner with a 32-channel head coil at the York University Neuroimaging Center. These data are openly available as part of a recent cross-sectional healthy aging data release (Spreng et al., *Under Revision*).

T1-weighted volumetric magnetization prepared rapid gradient echo sequences at each site were as follows: on the GE750 Discovery (TR=2530ms; TE=3.4ms; 7° flip angle; 1mm isotropic voxels, 176 slices, 5m25s) with 2x acceleration with sensitivity encoding, and on the

Siemens TimTrio (TR=1900ms; TE=2.52ms; 9° flip angle; 1mm isotropic voxels, 192 slices, 4m26s) with 2x acceleration and generalized auto calibrating partially parallel acquisition (GRAPPA) encoding at an iPAT acceleration factor of 2.

Two ten-minute runs of eyes-open resting-state functional MRI were collected with a multi-echo (ME) EPI sequence: on the GE750 Discovery (TR=3000ms; TE_1=13.7ms, TE_2=30ms, TE_3=47ms; 83° flip angle; matrix size=72x72; field of view (FOV)=210mm; 46 axial slices; 3mm isotropic voxels; 204 volumes, 2.5x acceleration with sensitivity encoding), and on the Siemens TimTrio (TR=3000ms; TE_1=14ms, TE_2=29.96ms, TE_3=45.92ms; 83° flip angle; matrix size=64x64; FOV=216mm; 43 axial slices; 3.4x3.4x3mm voxels; 200 volumes, 3x acceleration and GRAPPA encoding).

QUANTIFICATION AND STATISTICAL ANALYSIS

Image Processing

Structure. T1-weighted images were submitted to FreeSurfer version 6.0.1 (Fischl et al., 2002; Reuter et al., 2012) for cortical reconstruction and volumetric segmentation. Values of estimated total intracranial volume (eTIV), grey matter volume, and white matter volume were extracted. Estimated whole brain volume (eWBV) was calculated as (grey matter + white matter)/eTIV) and used as covariate where indicated.

The medial temporal lobe was segmented with Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevitch et al., 2015), which employs multi-atlas label fusion to automatically delineate subfields in individual participants. ASHS was run with the ASHS-PMC-T1 atlas (Xie et al., 2016) in both younger and older participants. Outputs were visually inspected for gross errors. As our aim was to examine age differences in anterior/posterior hippocampus functional connectivity, we extracted regions of interest for anterior (head) and posterior (tail and body) portions of the hippocampus in each hemisphere (4 segments total; See Figure 1). The hippocampal body is sometimes considered separately (Zheng et al., 2021) or as part of the anterior segment (Zajac et al., 2020). We proceeded with the ASHS results, in line with preceding anatomical segmentations (Poppenk & Moscovitch, 2011; Sheldon et al., 2016).

Grey matter volumes were also extracted and adjusted for head size (Jack et al., 1989; Buckner et al., 2004).

Function. The functional data preprocessing and analysis here have been previously applied to a larger sample and detailed elsewhere (Setton & Mwilambwe-Tshilobo et al., *Under Revision*). We review them in brief below. A schematic of methodological steps is shown in Figure 1.

T1-weighted images were skull stripped in FSL BET (Smith, 2002) using default parameters. Skull-stripped anatomical and functional images were then submitted to ME Independent Components Analysis (Kundu et al., 2011; Kundu et al., 2013) for minimal pre-processing and denoising. Advantages of ME acquisitions include the ability to better approximate T2* in every voxel, derive a T2* map of the brain, and optimally combine echoes. The TE-dependence model of BOLD signal drives denoising by separating TE-dependent BOLD signal from TE-independent noise. Together, these provide a significant boost to BOLD signal detection, particularly in regions prone to signal drop-out, such as the TP and OFC (See Figure 1 inset). Denoised time series were quality checked to flag participants with unsuccessful coregistration, residual noise (framewise displacement > .50 and denoised time series with DVARS >1; Power et al., 2012), poor temporal signal to noise ratio (< 50), or fewer than 10 retained BOLD-like components. The denoised BOLD component coefficient sets in native space were then mapped to a common cortical surface (fsaverage5) in FreeSurfer and concatenated.

To examine age-related changes to functional brain network organization, we implemented a participant-specific functional parcellation approach with Group Prior Individual Parcellation (GPIP; Chong et al., 2017). This approach initializes with a pre-defined group atlas (Schaefer 400; Schaefer et al., 2018) and then refines participants' parcel boundaries by drawing on their resting-state fMRI data. GPIP has been shown to improve the homogeneity of BOLD signal within parcels, better demarcate functional regions (Chong et al., 2017), and enhance detection of brain-behavior associations (Kong et al., 2019; Mwilambwe-Tshilobo et al., 2019). The output of GPIP was a final optimal cortical parcellation for each participant from which BOLD coefficient sets were extracted.

In a separate analytical step, left and right anterior/posterior hippocampal regions of interest from ASHS were binarized and resampled to functional resolution in native space.

BOLD coefficient sets were subsequently extracted with AFNI 3dmaskave (Cox, 1996; Cox & Hyde, 1997; Gold et al., 1998) by run and concatenated.

Functional Connectivity

To assess RSFC, we conducted a variation on seed-voxel connectivity between our three regions of interest—anterior hippocampus (AHIPP), posterior hippocampus (PHIPP), and temporal pole (TP)—and an extended DN: limbic (LIM: LIM-A, LIM-B), default (DN-A, DN-B, DN-C), and temporal parietal (TEMP-PAR) sub-networks from the Yeo 17-network solution (Yeo et al., 2011). LIM-A and LIM-B were included for TP and OFC parcels. See Figure 1 for a surface rendering and legend of sub-networks. Table 1 includes a full description of regions belonging to each sub-network.

BOLD data were extracted from each participant's GPIP solution from only the parcels comprising these six sub-networks (119 parcels in total). Extracted BOLD data from anterior and posterior hippocampus were added at this step. Functional connectivity matrices were then created by computing the product-moment (*r*) correlation coefficient between each pair of regions. A canonical Fisher's r-to-z transformation was applied (as in Kundu et al., 2013) to simultaneously normalize the correlation values and account for varying degrees of freedom (i.e., number of BOLD coefficients) across participants. The matrix of Z values was then downsized to a rectangular 17 x 123 matrix to specifically examine how BOLD signal in TP, AHIPP, and PHIPP covaried with LIM, DN, and TEMP-PAR sub-networks.

Analysis

RSFC of AHIPP, PHIPP, and TP with the DN. Average RSFC was first calculated within each age group (Figure 2B). Bootstrap resampling (resampling rate=10,000) was used to calculate the 95% confidence interval around each pairwise z-value connection and determine reliability. Connections with confidence intervals crossing zero were masked out.

We performed a separate analysis to visualize the overall RSFC pattern of each region of interest with the extended DN across all participants (Figure 2C). For each region of interest, BOLD data were averaged across parcels from both hemispheres and RSFC matrices were recomputed, rendering three 1 x 109 matrices for each participant. Z values were averaged across

all participants and significance was determined with a one-sample t-test. P values below .05 were masked out. AHIPP and PHIPP are not shown on the surface. For visualization purposes, all TP parcels in TP RSFC were assigned the maximum value in the matrix to indicate auto-correlation.

Age Group Differences in RSFC and Relationships to AM. Partial Least Squares (PLS) was used to examine group differences in RSFC and behavior PLS was used to examine RSFC associations with AI density scores. PLS is a multivariate method that identifies patterns of maximal covariance between two sets of variables (McIntosh & Lobaugh, 2004; McIntosh & Misic, 2013). Here those variables were represented by participant RSFC matrices and either 1) age group or 2) AI density scores.

To run PLS, a data matrix **X** was created with all participants' rectangular connectivity matrices. Each row of **X** corresponded to a vector containing one participant's within-network (LIM-A—LIM-A, AHIPP—AHIPP, PHIPP—PHIPP) and between-network connections. Column-wise means are then calculated by age group. All data in **X** were then mean-centered and submitted to singular value decomposition to yield mutually orthogonal latent variables representing distinct relationships between the two variables mentioned above. Each latent variable consisted of: 1) a left singular vector containing the weighted connectivity pattern optimally expressing the covariance, 2) a right singular vector with the weights of the study design variables (i.e., age group or AI density scores), and 3) a scalar singular value with the covariance strength between the design variable and connectivity. For each pattern, a brain connectivity score can be calculated from the dot product of the left singular vector (1) and each participant's functional connectivity matrix. Stronger positive values reflect expression of the warmer colors while stronger negative values reflect expression of the cooler colors. Brain connectivity scores therefore represent the degree to which each participant expressed the pattern identified.

Permutation testing was used to statistically evaluate patterns identified and bootstrap resampling determined the reliability of pairwise connections (1000 permutations, 500 bootstraps). Connectivity weights were considered to significantly contribute to the overall pattern when bootstrap ratios (weight in the singular vector/bootstrap-estimated standard error) exceeded $\pm$ 1.96, corresponding to the 95% confidence interval.

For display purposes, PLS results for each region of interest were mapped to the surface by averaging unthresholded results across parcels in the left and right hemispheres and then thresholding to a bootstrap ratio of 1.96. AHIPP and PHIPP regions are not shown on the surface.

Partial correlations between brain connectivity scores and each region of interest volume (each hemisphere separately) were carried out to explore associations between volume and age group differences in RSFC. Covariates included sex, education, and eWBV. Associations were considered significant at $p < .05$. Site was not included as a covariate since participants across sites added desirable variability due to increased demographic diversity in the Toronto cohort. Instead, we ensured that any age group effects existed over and above site effects by conducting ANCOVAs on brain connectivity scores with site, sex, education, and eWBV as covariates ($F(1,257)= 138.86$, $p < .001$, $\eta_p^2= .35$). Correlations with site included as a covariate are also reported for completeness. We also report partial correlations between brain connectivity scores from Behavior PLS and density scores with sex, education, eWBV, and site as covariates with the corresponding results.

A final set of *post-hoc* correlations were conducted between brain connectivity scores from behavior PLS and more granular detail categories from the AI. The goal was to explore which specific detail types contributed to associations between RSFC and internal/external density (i.e., internal: event, place, time, perceptual, emotion/thought details; external: semantic, repetition, other, event, place, time, perceptual, emotion/thought). Partial correlations were run between brain connectivity scores and detail density from all detail categories with sex, education, and eWBV as covariates. Results with site as an additional covariate are also provided. Associations were considered significant at $p < .05$.

Network Contributions. PLS identifies inter-regional connectivity patterns that differ by group and/or covary with AI density. To examine network-level effects for each analysis, we calculated network contributions to each PLS-derived functional connectivity pattern (see Setton & Mwilambwe-Tshilobo et al., *Under Revision*; Mwilambwe-Tshilobo et al., 2019). Positive and negative weighted adjacency matrices were constructed from the PLS pattern: nodes represented parcels defined by either the individual parcellation or a unilateral segment of the hippocampus (i.e., left AHIPP), while edges represented the thresholded bootstrap ratio of each pairwise

connection. Network-level contributions were then quantified by 1) assigning each parcel according to the network assignment reported by Yeo et al. (2011) or to a hippocampal 'network' (left and right AHIPP, left and right PHIPP), 2) taking the average of all connection weights in a given network and calculating within- and between-network connectivity to yield a 3 x 8 matrix (LIM-A, AHIPP, PHIPP x LIM-A, LIM-B, DN-A, DN-B, DN-C, TEMP-PAR, AHIPP, PHIPP), and 3) permutation testing for significance. For each of 10,000 permutations, network labels were shuffled, and mean within-and between-network connectivity estimates were recalculated. After 10,000 iterations, an empirical null sampling distribution was created. Within- and between-network connections were deemed significant when the proportion of times the value of the sampling distribution was greater than or equal to the empirical value did not exceed .05 (See Figure 1 for example).

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Chapter 5: General Discussion

Across three studies, we found that older adult brains show global and local patterns of losses and gains. In Study 1, we quantified BOLD dimensionality as a metric of global network integration and found that dimensionality was lower in older adults, signaling greater integration. Global integration in older adults emerged as reduced large-scale network structure across the brain and increased between-network connectivity specific to visual, somatomotor, and dorsal attention networks. In Study 2, posterior hippocampus volumes were smaller in older adults but were not related to worse cognition. Rather, episodic autobiographical memory (AM) was related to anterior hippocampus and temporal pole volumes in older adults. Temporal pole volumes in younger adults were associated with general semantic memory abilities. Study 2 also revealed that sex differences in brain structure, present in younger adults, pronounced sex differences in brain-behavior relationships by older age. In Study 3, older adult resting-state functional connectivity between temporal lobe structures and the default network was marked by a distinct pattern of integration, and was linked to reduced posterior hippocampal volumes. An age-invariant pattern dissociated connectivity related to episodic from semantic AM across individuals. Variation in the balance of episodic and semantic details, which systematically shifts with age, impacted functional connectivity. Relative to older adults, younger adults exhibited a unique pattern of functional connectivity associated with recollection overall. In sum, we demonstrate that global properties of older brain reorganization, even if they emerge in specific network interactions, may not be sufficient to characterize, and thus evaluate, an impact on aging cognition. Local age-related brain differences in structure, linked to brain differences in function, were found to play a role in supporting cognition that gradually wanes over the lifespan. Yet, functional circuits related to AM were largely preserved. These findings suggest that older adult brains undergo robust functional reorganization at both global and local levels. They also offer preliminary evidence for adaptive structural change, as either an antecedent or byproduct of functional reorganization, that may sustain fluid cognitive function in older age.

Herein lies the new perspective. Aging is a form of plasticity that involves both gains and losses that need to be studied together to fully appreciate whether and how they offset one another. Adaptive plasticity is not a new concept, but inquiry into healthy aging needs to look beyond mechanisms of decline and toward sustained function. Doing so requires looking at the brain as a whole unit *and* zooming in to determine the particular vulnerability or resilience of

different areas. It also involves moving away from using younger adults as the reference point and appreciating the brain as a dynamical system, constantly updating and adjusting in the face of change. In this way, we may uncover new insights about how to leverage age-related plasticity and how to optimize quality of life in the elderly.

Adaptation is More Than a Response to Decline

Current accounts of adaptive plasticity explain brain aging as a normative response to 'challenge' and late life development (Park & Reuter-Lorenz, 2009; Fabiani, 2012). Specifically, STAC predicts that neural processing inefficiencies, more prominent in older age, may spark functional reorganization and contribute to dedifferentiation via scaffolding. Scaffolding, or integrating previously unassociated brain regions, is viewed as adaptive when it compensates for declining cognition. GOLDEN views age-related decreases to executive function, and associated functional change, as developmental continuity, or a shift in the distribution of individual processing capacity. Both STAC and GOLDEN's stance on age-related change is inherently one of adapting to inefficiency.

BOLD dimensionality, a novel metric of large-scale network differentiation, was found to systematically decrease across the lifespan. This was in line with prior work illustrating decreased network segregation with age (Chan et al., 2014). Functional integration thus appears to be a developmental trend that starts early and continues on into late life, in support of GOLDEN. However, we found no evidence to suggest that integration was related to worse cognition. In fact, functional integration in early adulthood is predicted to aid in the assembly and refinement of large-scale brain networks to support complex cognition (Kundu et al., 2018). We provided cursory results suggesting that reduced BOLD dimensionality was related to better executive function independent of age (but see Appendix A). Continuity of functional integration into older age therefore did not reflect a steady trajectory of cognitive decline. However, global patterns of brain function may be too far-removed to characterize their impact on cognitive function.

More targeted investigation of age differences in brain-behavior relationships in Studies 2 and 3 demonstrated that temporal pole functional connectivity is associated with episodic and semantic AM in both younger and older adults, yet temporal pole structure is uniquely associated with episodic AM in older adults. This occurred in the presence of posterior hippocampal grey

matter atrophy and reduced hippocampal functional differentiation in older adults. On the surface, these results support STAC: structural and functional integrity of the hippocampus may decline, requiring intact regions, such as the temporal pole, to support episodic function. However, posterior hippocampus volumes were not related to episodic AM in older adults, suggesting that hippocampal atrophy alone could not explain the temporal pole volume association. Age-related alterations to hippocampal functional connectivity cannot be ruled out as an impetus, but no evidence was found to suggest that such alterations represented deficiency. Moreover, temporal pole functional connectivity with regions throughout the distributed default network was associated with episodic AM independent of age. Together these results underscore the important role that the temporal pole plays in AM circuits, a role that may eventually be engrained in structure with repeated use over time. Aside from its involvement in semantic processing (e.g., Lambon Ralph et al., 2017), the temporal pole is also highly associated with social and affective processing (Olson et al., 2007; Herlin et al., 2021). While speculative, more prevalent brain-behavior relationships with the temporal pole in older adults may be linked to concomitant socio-motivational shifts toward prioritizing meaningful interactions (Carstensen, 2006). As AM is a fundamental part of human connection (Bluck & Alea, 2011), greater temporal pole involvement may be socially and emotionally reinforcing. The temporal pole grey matter volume association with episodic AM may specifically reflect a honed ability to navigate between internal mentation and an external social world to appropriately tailor AM recollections in social settings. This would suggest an adaptive role for age-related reorganization in response to other cognitive gains.

STAC and GOLDEN are comprehensive frameworks with empirical support for a number of age-related brain and cognition changes. However, adaptation may be more than a normative response to decline.

Functional Integration as a Principle of Adaptive Brain Reorganization in Healthy Aging

In Study 1, younger adult BOLD dimensionality was strongly related to modularity, suggesting that integration early on in life facilitates network structure. This association was not present in older adults. In fact, we observed broad dedifferentiation of visual, somatomotor, and dorsal attention networks with other networks in older adults. Thus, the organizing principle of functional integration may change across the lifespan.

The AM circuit is an appropriate example for why this integration may be viewed as adaptive. The notion of adaptive plasticity has been posed within the context of age-related cellular changes to the hippocampus (Gray & Barnes, 2015). For example, the cholinergic drive onto principal hippocampal neurons of aged compared to young rodents is impaired in dentate gyrus, CA3, and CA1. The expected consequence would be less excitable neurons. Aged rodents also have larger gap junctions between principal hippocampal neurons and dentate gyrus, CA3, and CA1, which would increase neuronal excitability. However, single-unit firing rates are preserved. These two opposing age-related changes may work in tandem to balance network excitability. Extrapolating outward, hippocampal grey matter loss in aging may impair episodic memory function (e.g., Driscoll et al., 2003). Reduced specialization of hippocampus may impair episodic memory function (e.g., Langnes et al., 2020). In the same way, reduced specialization of temporal pole may impair semantic memory function. As reported in the studies here, older adults had greater semantic AM and temporal pole volumes were associated with more episodic AM in older adults. Temporal pole was dedifferentiated from its corresponding sub-network in older adults, but functional connectivity in association with AM was largely comparable to younger adults.

Differentiation of regions and brain networks, then, may no longer be a relevant principle to older adult functional organization and how it supports ongoing cognitive abilities. A similar idea has been proposed by the default-executive coupling hypothesis of aging (DECHA; Turner & Spreng, 2015; Spreng & Turner, 2019), which relates findings of increased lateral prefrontal activity to reduced suppression of the default network (which includes the hippocampus) during externally-directed task fMRI. DECHA draws on evidence that the default network is more coupled with executive networks in older adults at rest. This effectively makes the default network ‘stickier’ and less likely to decouple from executive networks during task, interfering with and impairing task performance. Unlike other models of neurocognitive aging, DECHA predicts that this form of integration may benefit goal-directed cognition that calls on prior knowledge (crystallized cognition, see below), which is supported by the default network. In other words, dedifferentiation of brain networks may support cognitive gains in older age.

Crystallized Capacities as a Principle of Adaptive Cognitive Reorganization in Healthy Aging

The focus of the present thesis was to characterize brain-behavior relationships in the whole-brain and in a smaller system of regions related to AM. At each turn, we investigated relationships to semantic memory: a domain-general composite score of semantic processing in Study 1, and semantic AM in Studies 2 and 3. The motivation was to understand what global and specific age-related brain change may support a robust cognitive gain in older adulthood. Global brain change, as in Study 1, may be too coarse to inform semantic memory maintenance with age. However, in Study 3 we observed that functional connectivity between the temporal pole and regions of lateral temporal cortex were related to systematic variation in semantic AM across the lifespan. As older adults' recollections shift to contain more semantic detail, this pattern becomes more prominent. With respect to AM, the predominant view is that greater semantic recollection is a compensation for reduced access to episodic AM (e.g., Devitt et al., 2017). As such, age differences in brain-behavior relationships to semantic AM are less characterized. However, crystallized abilities continue to shape cognition in older adults. As with functional integration, a reliance on these cognitive gains may be adaptive, reflecting more than a response to fluid decline.

It has been suggested that memory is an adaptive constructive process (Schacter, 2012). Because memories are inherently reconstructive, recollections are colored by the views and beliefs we have as individuals when we recall them. Such impressions may occur as early as encoding, where attitudes in response to stimuli shape the subsequent information remembered (Bartlett, 1932). Errors and distortions are thus a natural consequence of an imperfect, dynamic system that adapts to a changing individual. In other words, memory is prone to error independent of age because our experiences and identities, malleable as they are, constrain how we remember. Development continues past the age of 65, a lifetime of experiences alters our outlook, and reduced cognitive demand refines the cognitive abilities needed for everyday function. By definition, memory should change with age. Yet, older adult memory is often evaluated against younger adult memory. It is possible that a shift toward greater reliance on semantic memory reflects an updated "working self" (Conway & Pleydell-Pearce, 2000). Several lines of empirical research suggest that the semanticized autobiographical recollections of older adults contain a distinct verbal cadence that expresses a set of discourse goals including personal

narrative, reminiscence, and identity establishment (Boden & Bielby, 1983, 1986; Coupland & Coupland, 1995). Semantic memory, which preserves decontextualized schemas to extract the most important parts of memories with fewer errors, is vital for communication. Indeed, a proposed function of AM is communication (Hayes et al., 2018). In light of a socioemotional shift toward nurturing meaningful relationships (Carstensen, 2006), the more semantic autobiographical recollections of older adults may serve an adaptive communicative function.

Crystallized abilities, more broadly, confer benefits beyond social cognition. Accumulated knowledge and experience over the lifespan improves decision-making by improving literacy and attenuating temporal discounting (Li et al., 2013). Strategies to improve these abilities in younger adults and neuropsychiatric populations is an active area of inquiry. For example, episodic future thinking has been proposed to reduce rates of temporal discounting in younger adults (Peters & Buchel, 2010; Benoit et al., 2011; Sasse et al., 2015). This form of episodic simulation appears to be less effective at improving discount rates in older adults, except for individuals with higher fluid abilities (Sasse et al., 2017). Although individual differences in fluid and crystallized abilities are important considerations, interventions that rest on fluid abilities may not be as relevant in older age. Indeed, semantic future thinking has been shown to reduce discounting in amnesics with lesions to the medial temporal lobe (Palombo et al., 2016). This may also be the case for older adults who experience significant functional and structural change to the temporal lobes. Crystallized cognitive gains may therefore be able to support fluid losses in older age.

Leveraging Functional Integration and Crystallized Capacities in the Aging Brain

Functional network integration and crystallized abilities may support fluid cognition in older age, suggesting that neurocognitive aging may, to some extent, reflect adaptive plasticity. Studies 2 and 3 demonstrated that temporal pole structure and function can support episodic AM. It is also conceivable that functional integration and crystallized cognition can together support fluid abilities. Accrued experience and updated beliefs shape perception, and necessarily, brain activity and intrinsic functional organization (Yeshurun et al., 2017; Stevens & Spreng, 2014). These cognitive shifts perhaps help to establish an integrated network architecture. A critical future direction will be to test adaptive plasticity and determine how these two gains may together support fluid processes.

DECHA provides a framework with which to test adaptive plasticity. Age-related increases in default-executive coupling may impede performance on a task in which these two networks are more efficiently anticorrelated, such as executive function tasks (Spreng et al., 2016). However, if default-executive coupling is beneficial for goal-directed cognition that draws on crystallized abilities, one exciting question is whether incorporating crystallized cognition (i.e., semantic memory) into an executive task can boost performance. Initial evidence suggests that doing so offers a small but significant advantage to younger adults (Spreng et al., 2014). As older adults exhibit declines to executive functioning and more default-executive coupling, one might predict a larger effect. Relatedly, crystallized cognition and default-executive coupling have been shown to benefit divergent thinking in older adults (Adnan et al., 2019). Such evidence would suggest that harnessing older adult brain integration may be the route to further plastic change, such as supporting fluid cognition losses. A valuable avenue for future research will also be to directly ask how age-related functional integration and crystallized abilities relate to real-world functioning. Understanding how these principles of brain reorganization shape and are shaped by an individual's changing goals and motivations will illuminate a putative functional role for these brain changes.

Changing motifs of brain organization over the lifespan would necessitate altering the approach to how we understand and evaluate the aging brain. Longitudinal research remains invaluable, especially to understand trajectories and mechanisms of age change. Cross-sectional studies may be limiting, but they also force us to examine relationships within older adults alone. Doing so has enabled us to glean that the brain structure and function that supports cognition in early adulthood may be fundamentally different by older adulthood. Moreover, it behooves the field of cognitive neuroscience to recognize the importance of the human brain as an entity steeped in a social world that reinforces and discourages behavior. Without considering how the aging brain navigates its changing social environment, we are bound to view it from the narrow lens of decline. In this view, we should re-evaluate whether young adults are the appropriate reference point to elucidate older adult neurocognition.

The Importance of Sex in Healthy Aging

A final consideration made clear by the findings presented here is the need for continued inquiry into how and why sex impacts brain-behavior relationships later in life. Sex differences

in brain and behavior are robustly present in younger adults. For example, males and females show diverging proclivities for spatial and verbal memory (e.g., Weiss et al., 2003), and sexual dimorphism in grey matter volume is evident throughout the brain (e.g., Kiesow et al., 2020). Although our findings require replication in a larger sample, in Study 2 we observed that brain-behavior associations are less different among the sexes in younger adulthood. One possibility is that sex differences become more pronounced with age, when distinct abilities and/or social roles are more established (e.g., Kiesow et al., 2020). Alternatively, it may be that older male and female brains respond differently to age-related change, yielding diverging brain-behavior relationships. This latter point is nontrivial given that older females tend to be more susceptible to Alzheimer's disease (e.g., Fisher et al., 2018). For this reason, it is imperative to distinguish whether such differences represent vulnerabilities (i.e., to dementia) or adaptations (i.e., fixed social roles). Yet much of the research remains inconclusive about whether any one sex harbors an advantage to buffer against age-related brain vulnerabilities (female advantage: Sangha et al., 2021; Canales-Rodriguez et al., 2021; male advantage: Cavedo et al., 2018). This is perhaps unsurprising given the vast number of health factors associated with age including hypertension, obesity, and APOE e4 carrier status, some of which afflict one sex more than another (Armstrong et al., 2019). Accordingly, sex differences also need to be investigated at multiple scales. The need to include sex and gender as factors of interest in cognitive neuroscience is increasingly being recognized, and is even more urgent within the domain of aging given the increasing complexity and implications for disease.

Limitations of Resting State Functional Connectivity

A series of novel acquisition methods were applied across the three studies to collect high quality anatomical and resting-state fMRI data from a large sample of healthy younger and older adults. Paired with an in-depth collection of cognitive assessments, we aimed to test for whole-brain and systems-level brain-behavior relationships. In Studies 1 and 3, we used resting state functional connectivity to establish the whole-brain and systems-level functional architecture in younger and older adults, and examine how variability in this architecture related to individual differences in cognition. Resting-state functional connectivity is thought to reflect experience-dependent changes in functional connections, formed from the repeated use and disuse of circuits (Stevens & Spreng, 2014). While the methods implemented here were designed to respect

individual variation in brain function and optimize sensitivity to brain-behavior relationships, one limitation of resting-state functional connectivity is that it is not able to directly inform mechanisms of cognition (e.g., Campbell & Schacter, 2016; Finn, 2021). Moreover, networks identified at rest are often considered part of an intrinsic architecture, yet increasing evidence suggests that rest may simply reflect another less-constrained, episodic task state (e.g., Buckner et al., 2013). Identifying population differences in network makeup during an unconstrained task nonetheless provides an excellent backdrop for more hypothesis-driven task studies by enabling researchers to survey differences in large systems across cortex (see also Geerligs & Tsvetanov, 2017). As demonstrated in Study 3, variation in connectivity at rest is associated with variation in cognition. This underscores that resting state functional connectivity remains an informative tool to ask how and why individuals vary from one person to the next. A combination of both task fMRI and resting state functional connectivity will ultimately help to disentangle trait (i.e., intrinsic) and state (i.e., task) differences in brain function (Geerligs et al., 2015).

Conclusions

The studies contained within this thesis set out to characterize age differences in brain function, structure, and cognition as well as the intersection between them. In line with an extant neurocognitive aging literature, network integration was a defining feature of older adult functional brain change. Here we extend these findings and demonstrate that age-related functional integration within a circumscribed circuit is rooted in concomitant structural differences that may support fluid cognition in older age. These findings provide preliminary evidence for adaptive neuroplasticity, calling for a new perspective on brain and cognitive change in late life development.

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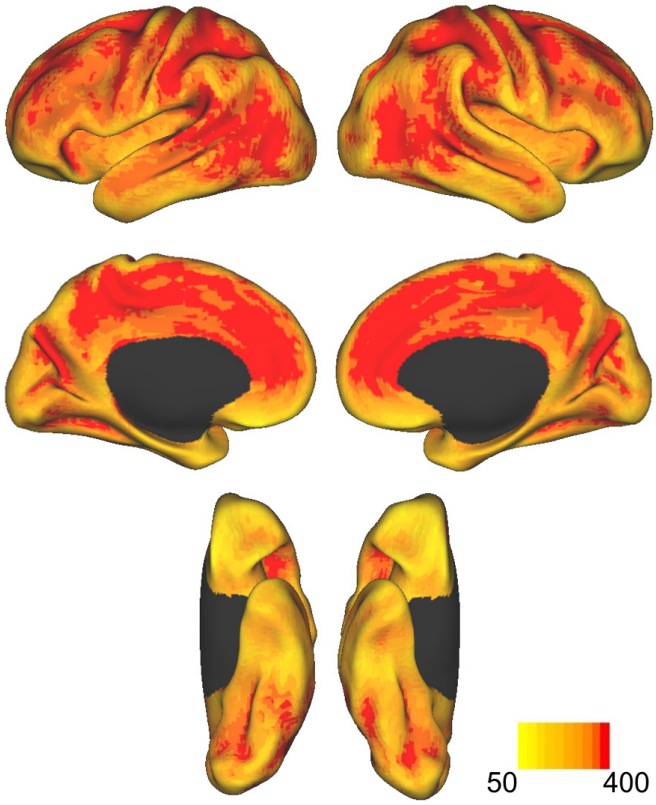
Appendix A: Supplementary Material to age differences in the functional architecture of the human brain

Supplemental Figure 1



Supplemental Figure 1 Caption: Temporal Signal to Noise. A temporal signal to noise ratio (tSNR) map was created for both runs of each participant's denoised data and averaged. The average group map (N=301) was projected onto an inflated surface, separated by left and right hemispheres. Maps were thresholded to demonstrate that the low end of tSNR values were well above 50. A maximum tSNR of 400 is shown here for visualization purposes.

Impact of Motion on RSFC

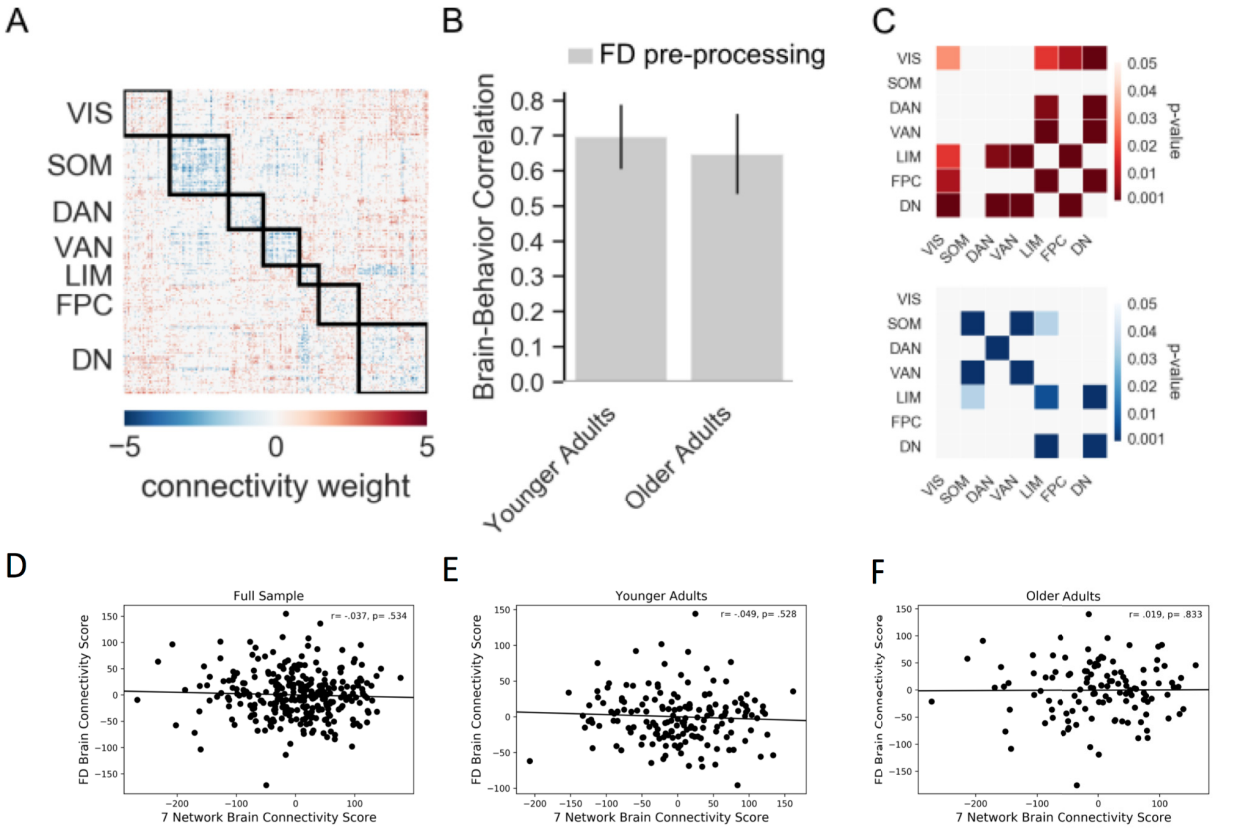
ME-ICA has been shown to effectively remove distant dependent motion effects in RSFC data (Power et al., 2018). To rule out the possibility that these residual motion effects confounded our main results, we conducted a behavior PLS analysis with raw framewise displacement (FD). This analysis yielded a significant pattern (59.21% covariance explained, permuted p = 0.004; Supplementary Figure 2A) representing the main effect of correlating functional connectivity with FD across younger and older adults (younger adults r = .70; older adults r = 0.65; Supplementary Figure 2B). While a motion-related connectivity pattern emerged (explaining 59.2% of the cross-block covariance), no significant group differences or age group interactions emerged. Network contribution plots expressing the mean positive and negative weights within and between networks are depicted in Supplementary Figure 2C. Higher FD was associated with greater within-VIS connectivity and LIM, FPC, and DN connectivity (warmer colors), as well as lower within-network connectivity of SOM, DAN, VAN, LIM, and DN (cooler colors).

As described in Methods, covariance in PLS can be specified as percent cross-block covariance, where the cross-block covariance is between the brain data and predictor variables. The sum of the percent cross-block covariance must sum to 100% over all latent variables (LVs). As such, the value of covariance explained for a given LV cannot be interpreted in isolation but must be weighed against the other LVs. This is demonstrated in the case of a single predictor variable, where the resultant LV will explain 100% of the cross-block covariance.

These findings suggest that ME-ICA patterns of RSFC are still impacted by motion. BOLD signal post-MEICA has been related to residual respiratory effects (Power et al., 2018), but to our knowledge there is no evidence to suggest that this residual noise would confound group comparisons. Rather, residual motion may reduce signal-to-noise in a similar manner across groups. Indeed, we find that motion effects are not confounded by group membership in our sample. A second LV accounting for 40.79% (p = .38) of the covariance dissociated age groups in their relationship to motion. Relative to the first LV, group specific motion effects on connectivity account for less covariance in the data. This LV, however, was not significant . If this LV was significant, then there would be evidence that motion differentially impacted connectivity by group, limiting the interpretation of the data. Because this interaction was not significant, our primary results, all of which compare groups, are not confounded by motion.

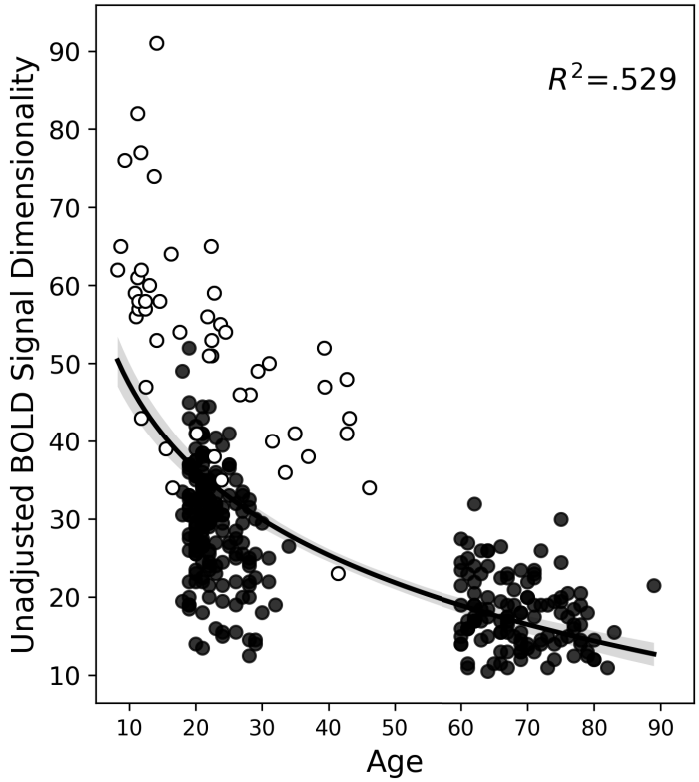
We empirically confirmed that the pattern of connectivity covarying with motion is not consistent with the age differences in RSFC reported in the main text. We determined this by assessing the correspondence between brain connectivity scores from the whole-brain age contrast (Figure 4) and from the motion-associated effects (Supplementary Figure 2A-C). Relationships are plotted in Supplementary Figure 2D-F. Partial correlations controlling for sex, education, eWBV, and site were as follows: Across the full sample, pr = -.037, p = .534; in younger adults: pr = -.049, p = .528; in older adults pr = .019, p = .833.

Supplemental Figure 2



Supplemental Figure 2 Caption: Behavioral PLS examining the relationship between functional connectivity with motion in younger and older adults. Framewise displacement (FD) was calculated on the middle echo prior to processing. (A) Functional connections that correlate with higher FD (warmer colors) and lower FD (cooler colors). (B) Correlations of FD with the functional connectivity pattern in younger and older adults. Error bars indicate the 95% confidence interval derived from the bootstrap estimation. (C) Network contributions of the mean positive and negative edge weights within and between networks. Scatterplots depicting age differences in brain connectivity scores on the x-axis and motion-related brain connectivity scores on the y-axis (D) across the full sample, (E) in younger adults, (F) in older adults. VIS = visual, SOM = somatomotor, DAN = dorsal attention, VAN = ventral attention, LIM = limbic, FPC = frontoparietal control, DN = default networks.

Supplemental Figure 3



Supplemental Figure 3 Caption: BOLD signal dimensionality. The scatter plot shows BOLD signal dimensionality by age with a power distribution and 95% confidence intervals overlaid. Points in white were contributed by Kundu and colleagues (2018). Here, BOLD dimensionality is not adjusted by the number of time points acquired. BOLD dimensionality was averaged across two runs for points in black.

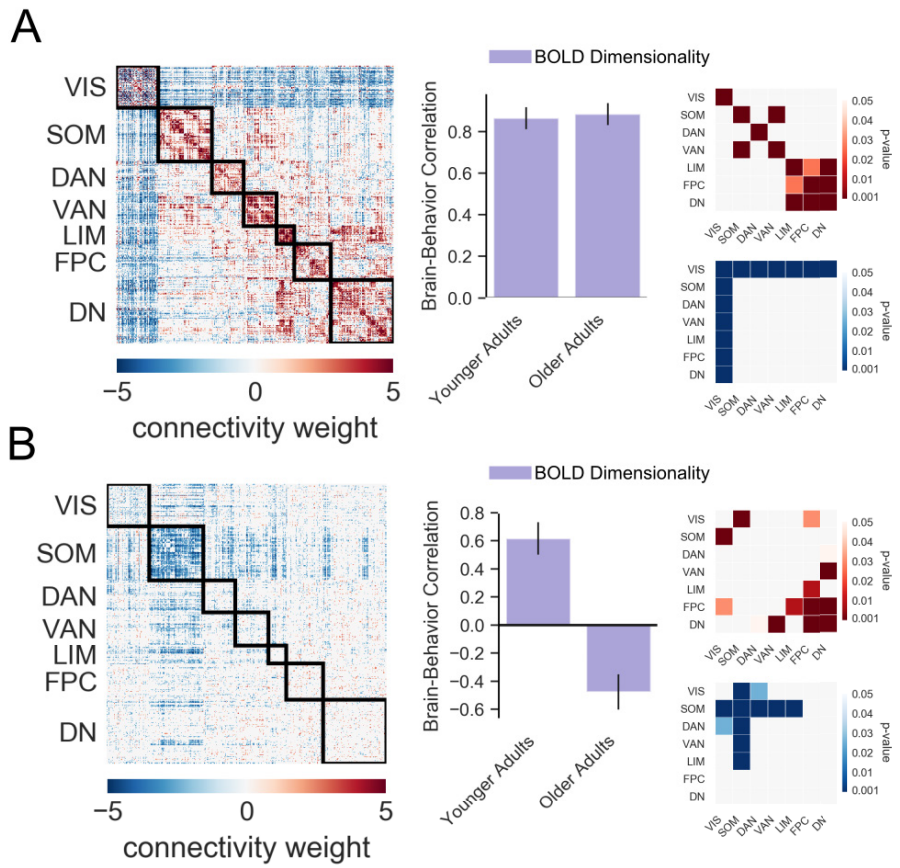
Characterizing BOLD Dimensionality

The present report leverages ME fMRI acquisition and processing to define a novel metric of BOLD dimensionality as a proxy for global functional integration. We further investigate the biological substrate of BOLD dimensionality by examining its most defining interregional connections and comparing it to similar summary statistics of global RSFC organization.

We first used behavior PLS to characterize the interregional connections associated with BOLD dimensionality. In brief, behavior PLS identifies functional connectivity patterns that optimally co-vary with a behavioral measure. Two significant patterns captured the association between functional connectivity and BOLD dimensionality in younger and older adults. The first pattern reflects a main effect of BOLD dimensionality across groups(69.69% variance explained, permuted $p < .001$; younger adults r = .86; older adults r = .88; Supplementary Figure 4A). Network contribution plots summarize the significant interregional associations. Higher BOLD dimensionality was related to more within-network connectivity (Supplementary Figure 4A, warmer colors). Higher BOLD dimensionality was also related to connectivity among heteromodal association networks LIM, FPC, and DN . Dimensionality was negatively related to VIS connectivity across the connectome (Supplementary Figure 4A, cooler colors).

The second pattern revealed an age group difference in the association between functional connectivity and BOLD dimensionality (30.31% variance explained, permuted $p < .001$; younger adults r = .62; older adults r = -.48). In younger adults, higher BOLD dimensionality was related to more connectivity within and between FPC and DN (Supplementary Figure 4B, warm colors). In contrast, higher BOLD dimensionality in older adults was related to more SOM connectivity with itself and with VIS, DAN, VAN, and LIM (Supplementary Figure 4B, cool colors).

Supplemental Figure 4



Supplemental Figure 4 Caption: Behavioral PLS of the relationship between functional connectivity and BOLD dimensionality in younger and older adults. Two significant latent variables were identified. (A) The first latent variable expresses an effect of the number of BOLD components on functional connectivity. From left to right: functional connections that correlate with a higher (warmer colors) and lower (cooler colors) number of BOLD components; Bar plots showing the correlations of BOLD dimensionality with the functional connectivity pattern in younger and older adults; Network contributions of the mean positive (warm colors) and negative (cool colors) edge weights within and between networks. (B) The second latent variable expresses age-related differences in the association between functional connectivity and BOLD dimensionality. From left to right: Functional connections that correlate with a higher number of BOLD components in younger (warm colors) and older adults (cool colors); Bar plots showing the correlation between BOLD dimensionality and the functional connectivity pattern; Network contributions of the mean positive (warm colors) and negative (cool colors) edge weights within and between networks. Error bars for the brain-behavior barplots indicate 95% confidence intervals derived from the bootstrap estimation. VIS = visual, SOM = somatomotor, DAN = dorsal attention, VAN = ventral attention, LIM = limbic, FPC = frontoparietal control, DN = default.

We then compared BOLD dimensionality to a series of graph theoretic measures to determine whether it provides unique information about global integration. Participation coefficient, and modularity were computed as implemented in the Brain Connectivity Toolbox (Rubinov & Sporns, 2011). Segregation was also calculated (Chan et al., 2014). Measures were calculated on each individual's z-scored functional connectivity matrix. Self-connections and negative weights were set to zero. Product-moment correlations were computed within each age group and on the full sample controlling for age, as shown in Supplemental Table 1 and Supplementary Figure 5. BOLD dimensionality was negatively associated with participation coefficient and positively associated with modularity and segregation in younger adults. In older adults, BOLD dimensionality was associated with segregation. In the full sample controlling for age, all graph metrics showed a significant relationship to BOLD dimensionality. The observed negative association between BOLD dimensionality and participation coefficient is consistent with a prior report of a negative association in a lifespan sample from children to middle-aged adults (Kundu et al., 2018). The positive association with modularity only in young adults reinforces that BOLD dimensionality highlights an inflection point in network organization across the lifespan: More dimensionality in young supports an established community structure; more dimensionality in older adults may support segregation as community structure devolves.

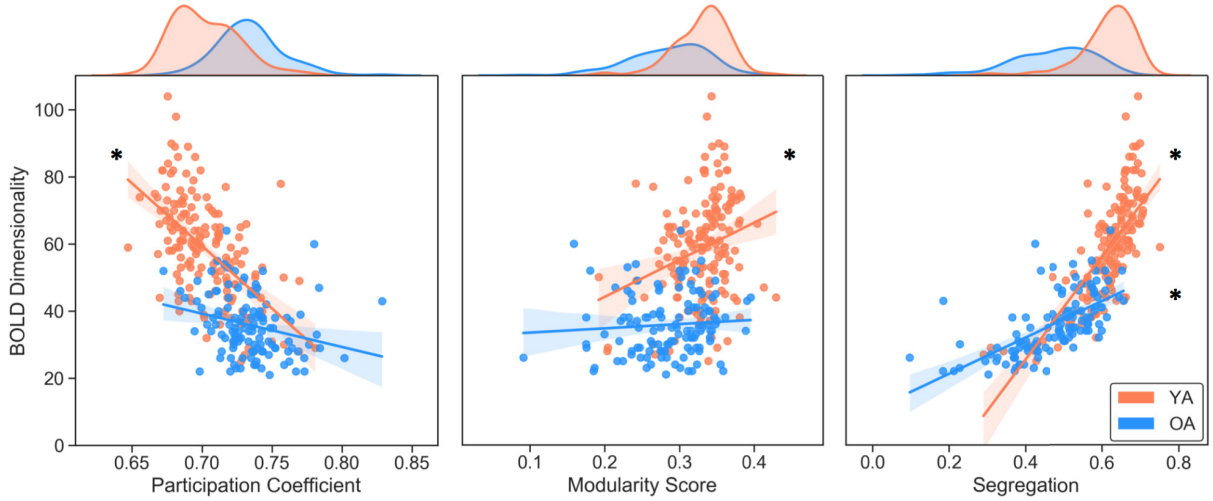
Supplemental Table 1

BOLD Dimensionality Associations with Graph Metrics

Metric	Younger Adults	Older Adults	Full Sample
Participation Coefficient	**-.491 (.000) [-.60, -.36]**	-.158 (.085) [-.33, .02]	**-.369 (.000) [-.47, -.26]**
Modularity	**.285 (.000) [.14, .42]**	.022 (.813) [-.16, .20]	**.129 (.030) [.01, .24]**
Segregation	**.689 (.000) [.60, .76]**	**.549 (.000) [.41, .66]**	**.536 (.000) [.45, .61]**

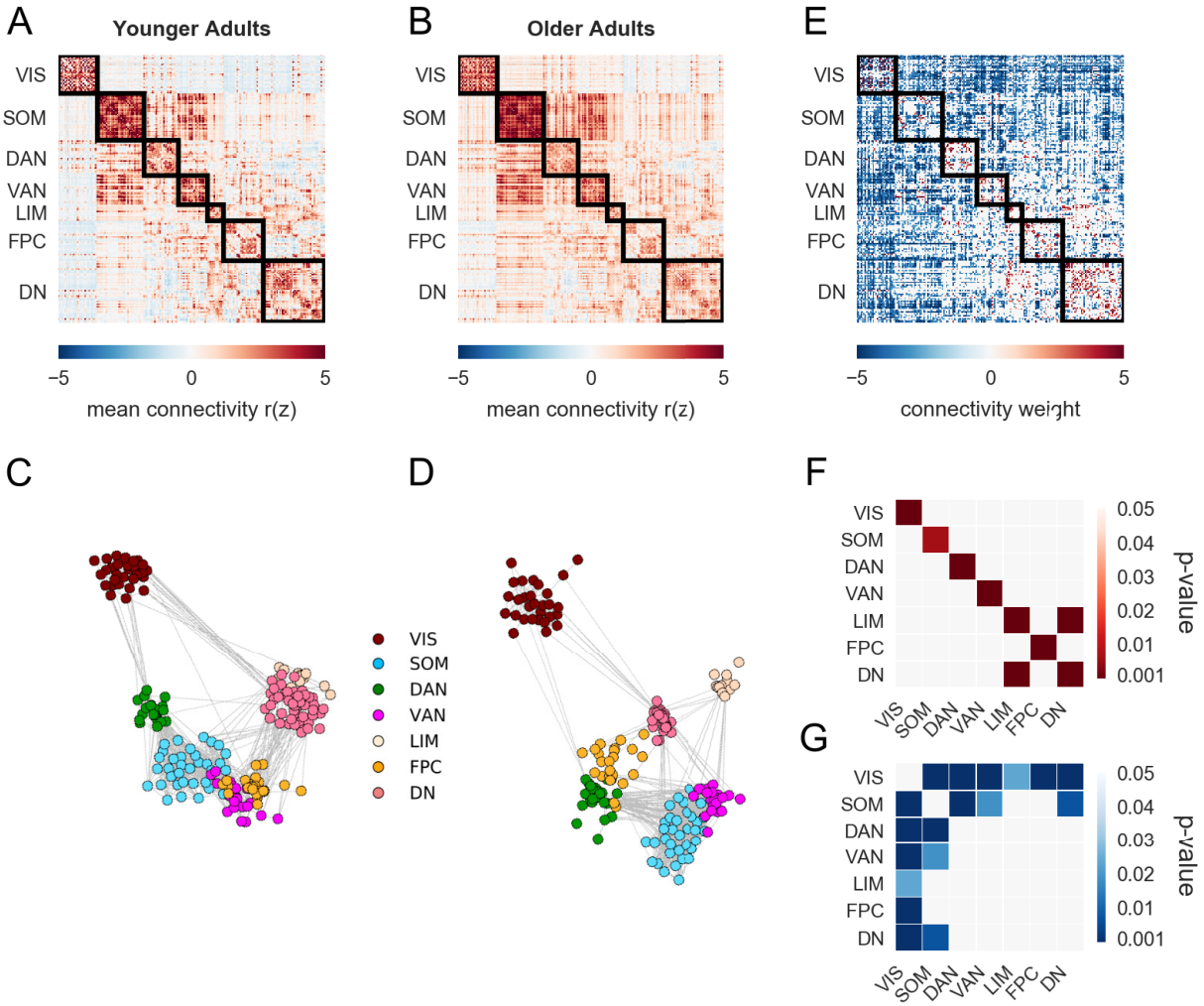
Note. Metrics were derived from unthresholded correlation matrices containing positive connection weights. Partial correlations (p*r*) were calculated with sex, education, eWBV, and site as covariates. Age was included as an additional covariate in associations on the full sample. *r* values are presented with *p* values in parentheses and 95% confidence intervals in brackets. Bold denotes associations deemed significant at $p < .05$.

Supplemental Figure 5



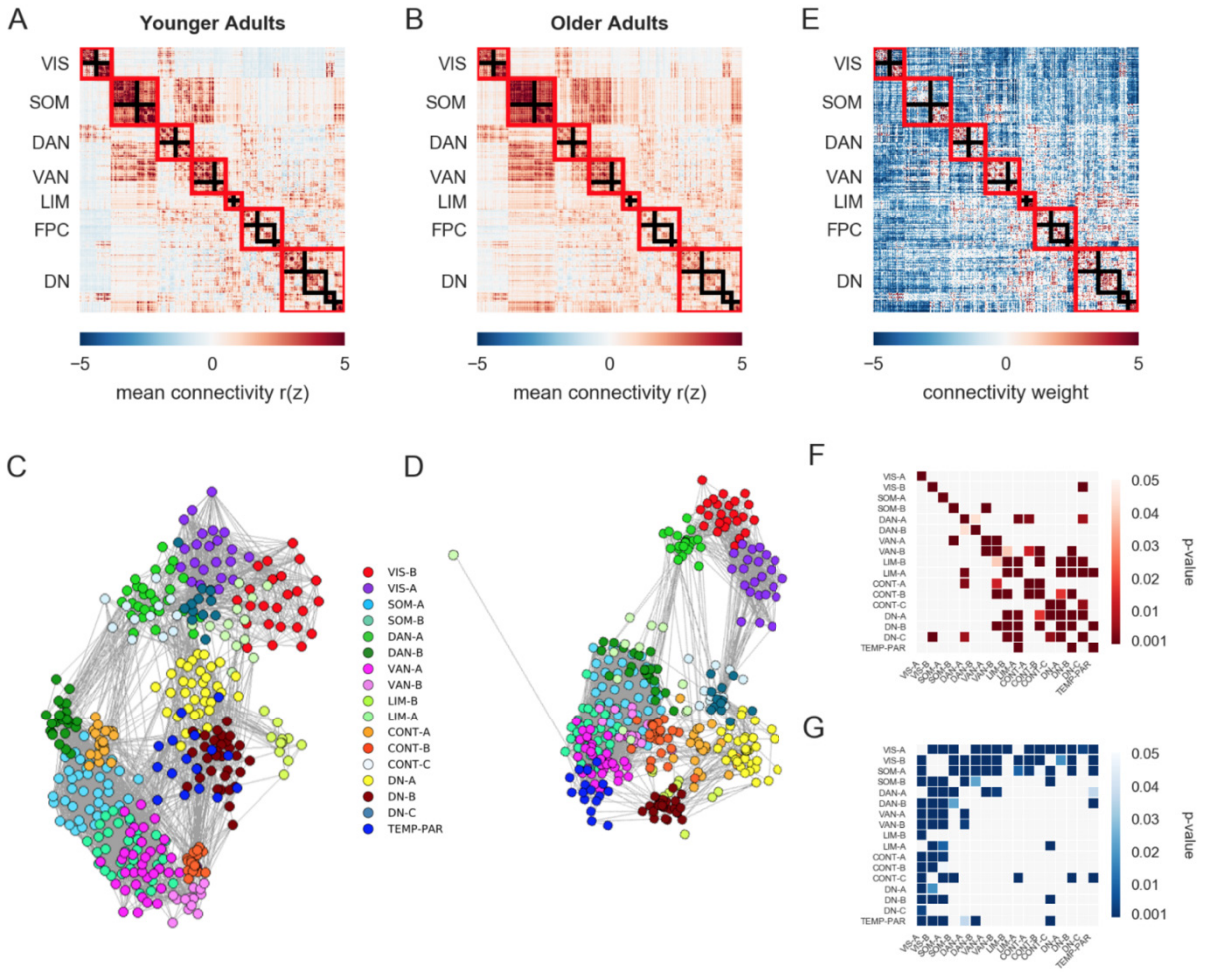
Supplemental Figure 5 Caption: Scatterplots between BOLD dimensionality and graph theory measures. Distributions of graph measures are shown at the top of each plot. BOLD dimensionality distributions are shown in the rightmost plot. * indicates significant correlations. YA= younger adults; OA = older adults.

Supplemental Figure 6



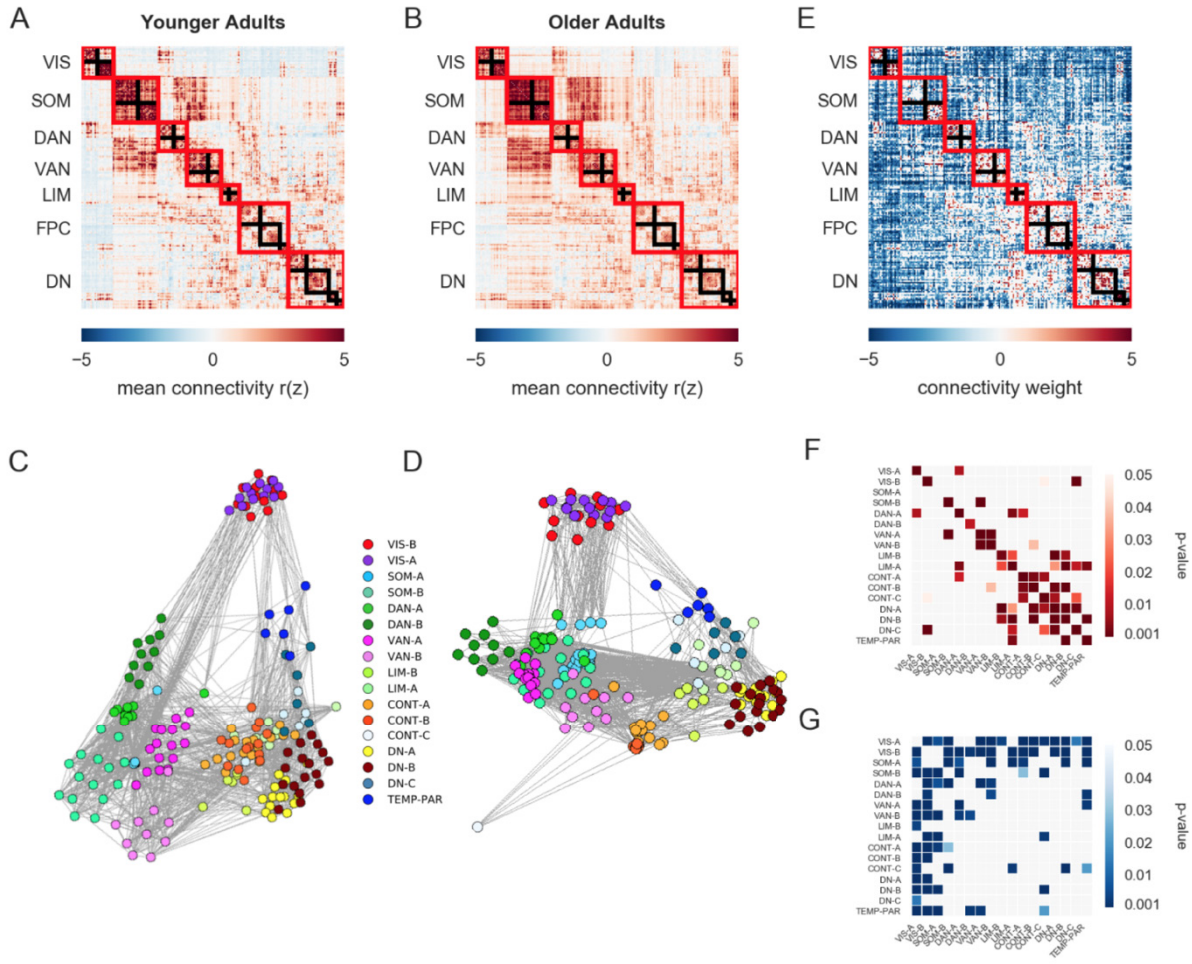
Supplemental Figure 6 Caption: Functional connectomics in younger and older adults. Mean RSFC for the 200-parcellated MEFC data in (A) younger and (B) older adults. Spring-embedded plots with a 7-network solution (5% edge density) of the mean correlation matrices for (C) younger and (D) older adults. (E) Multivariate PLS analysis was used to identify age-related differences in RSFC between younger and older adults. Red color indicates greater RSFC in younger adults, and blue color indicates greater RSFC in older adults. (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. The mean positive and negative bootstrap ratios within and between networks are expressed as a *p* value for each z-score relative to a permuted null model. Higher values indicate greater connectivity than predicted by the null distribution. VIS = visual, SOM= somatomotor, DAN= dorsal attention, VAN = ventral attention, LIM = limbic, FPC= frontoparietal control, DN= default.

Supplemental Figure 7



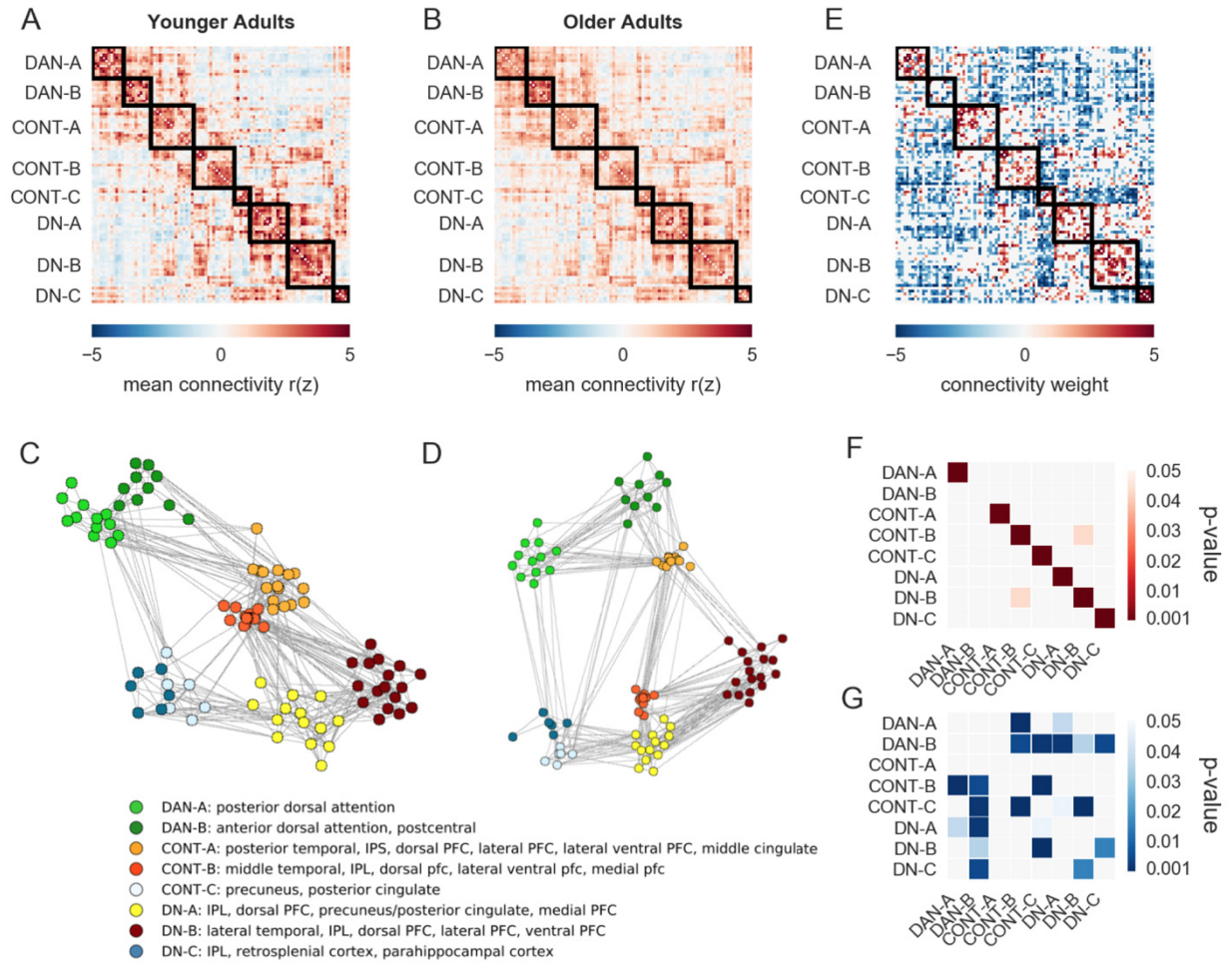
Supplemental Figure 7 Caption: Functional connectomics in younger and older adults. Mean RSFC for the 400-parcellated MEFC data in (A) younger and (B) older adults. Spring-embedded plots with a 17-network solution (5% edge density) of the mean correlation matrices for (C) younger and (D) older adults. (E) Multivariate PLS analysis was used to identify age-related differences in RSFC between younger and older adults. Red color indicates greater RSFC in younger adults, and blue color indicates greater RSFC in older adults ($p < 0.0001$; 100% variance explained). (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. The mean positive and negative bootstrap ratios within and between networks are expressed as a *p* value for each z-score relative to a permuted null model. Higher values indicate greater connectivity than predicted by the null distribution. VIS = visual, SOM = somatomotor, DAN = dorsal attention, VAN = ventral attention, LIM = limbic, FPC = frontoparietal control, DN = default.

Supplemental Figure 8



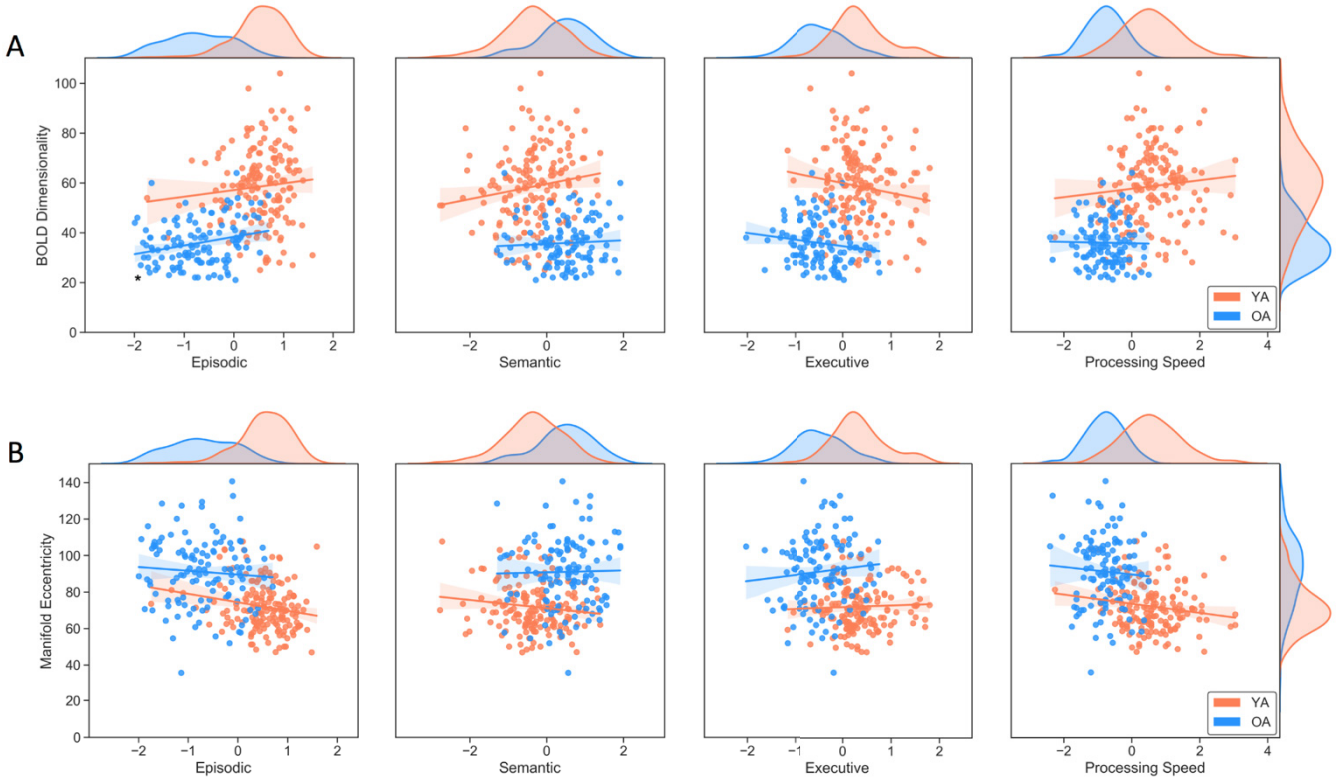
Supplemental Figure 8 Caption: Functional connectomics in younger and older adults. Mean RSFC for the 200-parcellated MEFC data in (A) younger and (B) older adults. Spring-embedded plots with a 17-network solution (10% edge density) of the mean correlation matrices of (C) younger and (D) older adults. The threshold used for the spring-embedded plots was set higher due to the sparsity of the graph at thresholds lower than 10%. (E) Multivariate PLS analysis was used to identify age-related differences in RSFC between younger and older adults ($p < 0.0001$; 100% variance explained). Red color indicates greater RSFC in younger adults, and blue color indicates greater RSFC in older adults. (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. The mean positive and negative bootstrap ratios within and between networks are expressed as a *p* value for each z-score relative to a permuted null model. Higher values indicate greater connectivity than predicted by the null distribution. VIS = visual, SOM = somatomotor, DAN = dorsal attention, VAN = ventral attention, LIM = limbic, FPC = frontoparietal control, DN = default.

Supplemental Figure 9



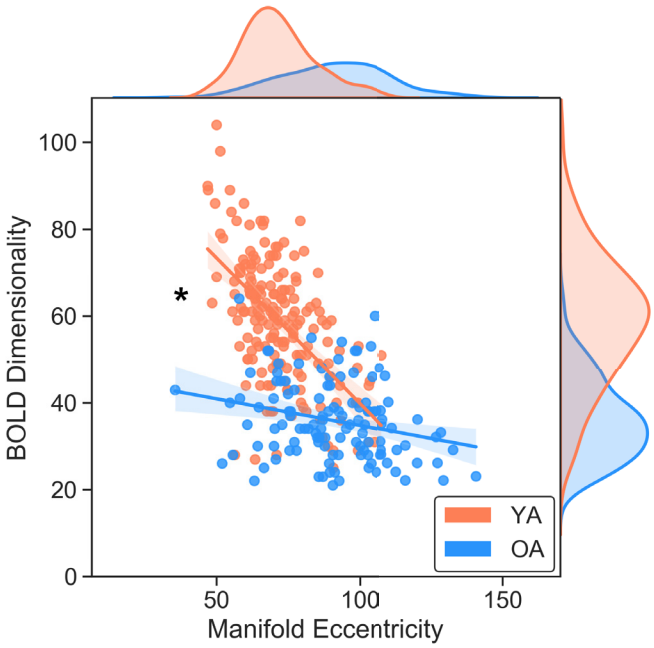
Supplemental Figure 9 Caption: Functional connectivity of the dorsal attention (DAN), frontoparietal control (CONT), and default (DN) sub-networks following Yeo 17-network solution. Mean group connectivity for the 200-parcellated MEFC data in (A) younger and (B) older adults. Spring-embedded plots (10% edge density) of the mean correlation matrices for (C) younger and (D) older adults. A lower threshold was used for the spring-embedded plots due to the sparsity of the graph at higher thresholds. (E) Differences in RSFC between younger and older adults among DAN, CONT, and DN ($p < 0.0001$; 100% variance explained). (F-G) Network contributions represent the summary of positive and negative edge weights within and between networks in younger (F) and older (G) adults. The mean positive and negative bootstrap ratios within and between networks are expressed as a p value for each z-score relative to a permuted null model. Higher values indicate greater connectivity than predicted by the null distribution. DAN = dorsal attention, FPC = frontoparietal control, DN = default.

Supplemental Figure 10



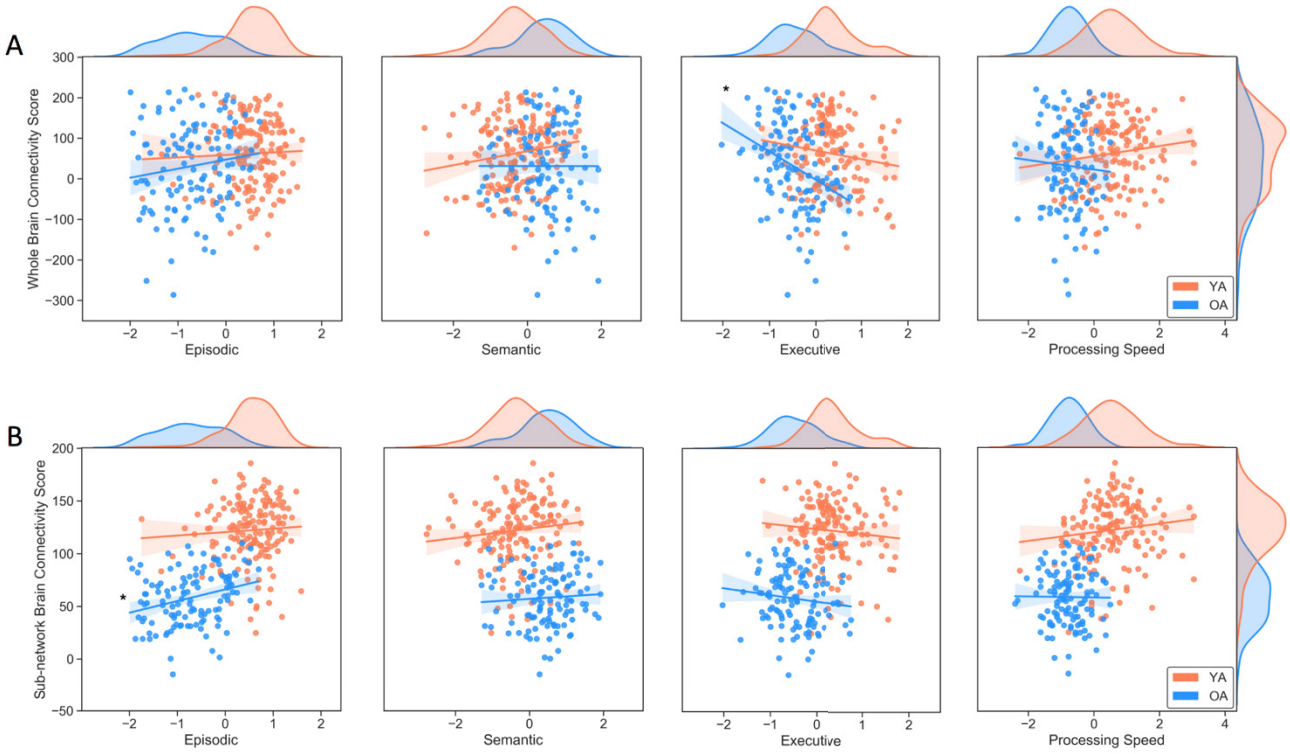
Supplemental Figure 10 Caption: Scatterplots between cognitive scores and (A) BOLD dimensionality and (B) manifold eccentricity. Cognition distributions are shown at the top of each plot. Distributions for BOLD dimensionality and manifold eccentricity are shown in the rightmost plots. * indicates significant correlations. YA = younger adults; OA = older adults.

Supplemental Figure 11



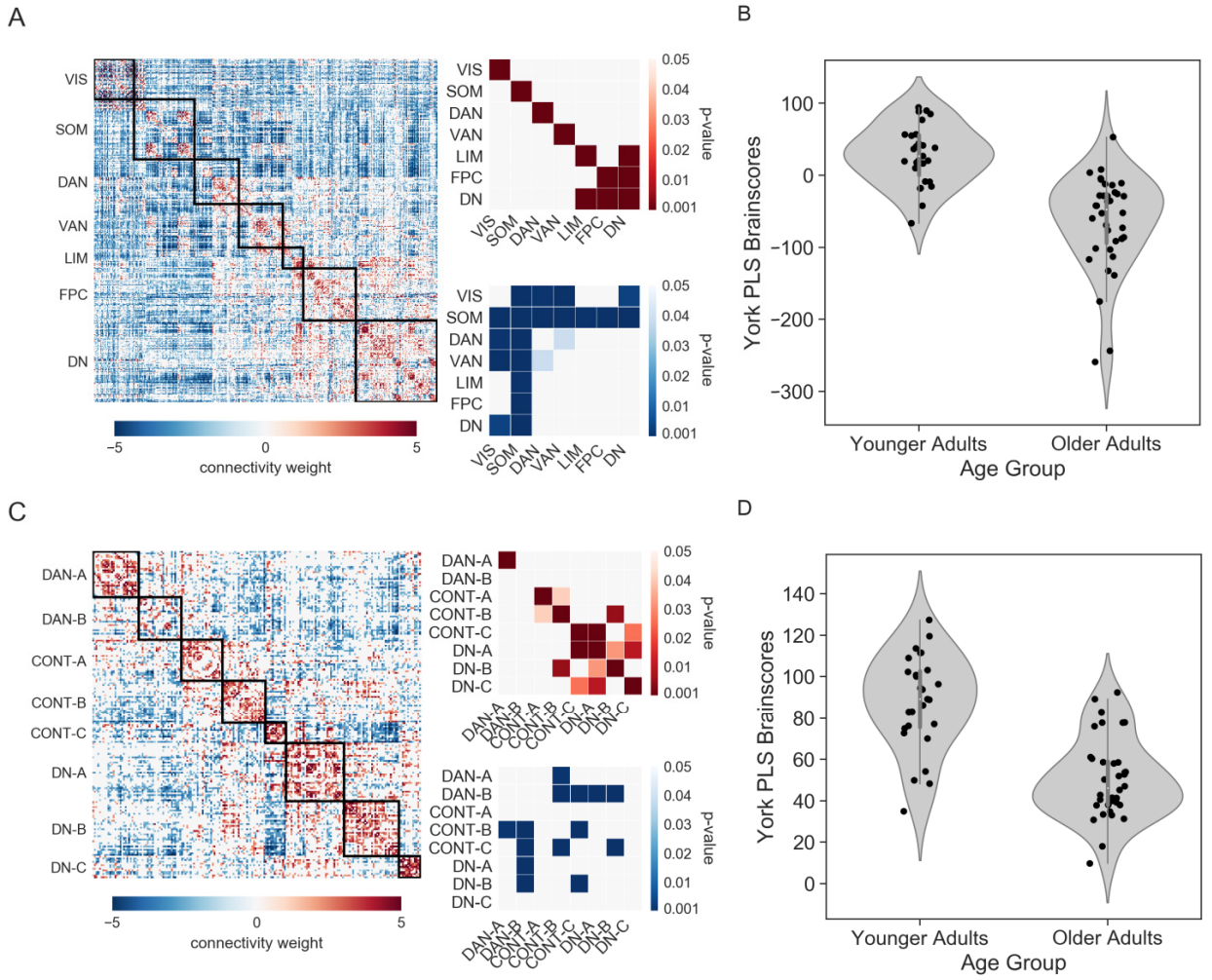
Supplemental Figure 11 Caption: Scatterplot between BOLD dimensionality and manifold eccentricity. Distributions are shown on the respective axes. * indicates a significant difference between correlations. YA = younger adults; OA = older adults.

Supplemental Figure 12



Supplemental Figure 12 Caption: Scatterplots between cognitive scores and brain connectivity scores for the (A) full 7-network and (B) 3 sub-network analyses. Cognition distributions are shown at the top of each plot. Brain connectivity score distributions are shown in the rightmost plots. * indicates significant correlations. YA = younger adults; OA = older adults.

Supplemental Figure 13



Supplemental Figure 13 Caption: Replication of PLS results across sites. (A) Age differences in the full functional connectome for Ithaca participants. (B) Group differences in brain scores computed for York participants, based upon the edge-weights determined in the Ithaca sample. (C) Age differences in the functional connectivity of the dorsal attention (DAN), frontoparietal control (CONT), and default (DN) sub-networks from Ithaca participants. (D) Group differences in brain scores computed from Toronto participants, based upon the edge-weights from the sub-networks determined in Ithaca participants. DAN = dorsal attention, FPC = frontoparietal control, DN = default.

Supplemental Table 2

Table S2

Brain-Behavior Correlations without Covariates

Factor	Younger Adults	Older Adults	Full Sample
BOLD Dimensionality			
Episodic Memory	.094 (.235) [-.06, .24]	**.251 (.006) [.08, .41]**	.084 (.159) [-.03, .20]
Semantic Memory	.155 (.048) [.00, .03]	.057 (.539) [-.12, .23]	**.158 (.008) [.04, .27]**
Executive Function	-.146 (.062) [-.29, .01]	-.155 (.090) [-.33, .02]	**-.177 (.003) [-.29, -.06]**
Processing Speed	.096 (.221) [-.06, .25]	-.018 (.848) [-.20, .16]	.016 (.784) [-.10, .13]
Manifold Eccentricity			
Episodic Memory	-.191 (.014) [-.34, -.04]	-.073 (.430) [-.25, .11]	-.084 (.157) [-.20, .03]
Semantic Memory	-.134 (.088) [-.28, .02]	.020 (.832) [-.16, .20]	-.077(.196) [-.19, .04]
Executive Function	.040 (.609) [-.11, .19]	.094 (.305) [-.09, .27]	.085 (.154) [-.03, .20]
Processing Speed	-.168 (.032) [-.31, -.01]	-.061 (.506) [-.24, .12]	-.080 (.182) [-.19, .04]
Brain Connectivity Score (Whole Brain)			
Episodic Memory	.039 (.624) [-.12, .19]	.139 (.131) [-.04, .31]	.063 (.294) [-.05, .18]
Semantic Memory	.158 (.044) [.00, .30]	-.001 (.993) [-.18, .18]	.101 (.090) [-.02, .21]
Executive Function	-.145 (.064) [-.29, .01]	**-.350 (.000) [-.50, -.18]**	**-.258 (.000) [-.36, -.15]**
Processing Speed	.128 (.103) [-.03, .28]	-.062 (.504) [-.24, .12]	.027 (.647) [-.09, .14]
Brain Connectivity Score (Sub-network)			
Episodic Memory	.059 (.452) [-.10, .21]	**.283 (.002) [.11, .44]**	.097 (.103) [-.02, .21]
Semantic Memory	.116 (.139) [-.04, .27]	.066 (.476) [-.11, .24]	.132 (.027) [.02, .24]
Executive Function	-.097 (.218) [-.25, .06]	-.132 (.150) [-.30, .05]	-.138 (.020) [-.25, -.02]
Processing Speed	.121 (.125) [-.03, .27]	-.011 (.908) [-.19, .17]	.023 (.697) [-.09, .14]

Note. *r* values displayed with *p* values in parentheses and 95% confidence intervals in brackets. p*r* values displayed for the full sample with age as a covariate. Bold denotes significance with a Bonferroni correction at $p < .013$ for 4 tests.

Supplemental Table 3

Table S3

Brain-Behavior Correlations with Covariates (Sex, Education, eWBV)

Factor	Younger Adults	Older Adults	Full Sample
BOLD Dimensionality			
Episodic Memory	.054 (.497) [-.10, .21]	**.243 (.007) [.07, .40]**	.056 (.351) [-.06, .17]
Semantic Memory	**.216 (.006) [.06, .36]**	.042 (.650) [-.14, .22]	**.174 (.003) [.06, .28]**
Executive Function	-.149 (.057) [-.30, .00]	-.154 (.094) [-.32, .03]	**-.182 (.002) [-.29, -.07]**
Processing Speed	.064 (.418) [-.09, .22]	-.011 (.903) [-.19, .17]	.009 (.884) [-.11, .13]
Manifold Eccentricity			
Episodic Memory	-.185 (.018) [-.33, .-.03]	-.092 (.319) [-.27, .09]	-.097 (.104) [-.21, .02]
Semantic Memory	-.184 (.019) [-.33, -.03]	.007 (.938) [-.17, .19]	-.094 (.114) [-.21, .02]
Executive Function	.046 (.557) [.11, .20]	.058 (.531) [-.12, .23]	.085 (.152) [-.03, .20]
Processing Speed	-.134 (.089) [-.28, .02]	-.101 (.272) [-.28, .08]	-.084 (.161) [-.20, .03]
Brain Connectivity Score (Whole Brain)			
Episodic Memory	.068 (.390) [-.09, .22]	.056 (.543) [-.12, .23]	.006 (.919) [-.11, .12]
Semantic Memory	.126 (.108) [-.03, .27]	-.102 (.268) [-.28, .08]	.058 (.333) [-.06, .17]
Executive Function	-.136 (.084) [-.28, .02]	**-.320 (.000) [-.47, -.15]**	**-.249 (.000) [-.35, -.14]**
Processing Speed	.164 (.037) [.01, .31]	-.015 (.870) [-.19, .16]	.045 (.449) [-.07, .16]
Brain Connectivity Score (Sub-network)			
Episodic Memory	.012 (.884) [-.14, .16]	**.229 (.012) [.05, .39]**	.031 (.602) [-.09, .15]
Semantic Memory	.169 (.031) [.02, .31]	.034 (.709) [-.15, .21]	.136 (.022) [.02, .25]
Executive Function	-.096 (.222) [-.25, .06]	-.145 (.115) [-.32, .04]	-.138 (.020) [-.25, -.02]
Processing Speed	.102 (.196) [-.05, .25]	-.016 (.862) [-.19, .16]	.019 (.753) [-.10, .14]

Note. p*r* values displayed with *p* values in parentheses and 95% confidence intervals in brackets. Full sample includes age as a covariate. Bold denotes significance with a Bonferroni correction at $p < .013$ for 4 tests.

Supplemental Table 4

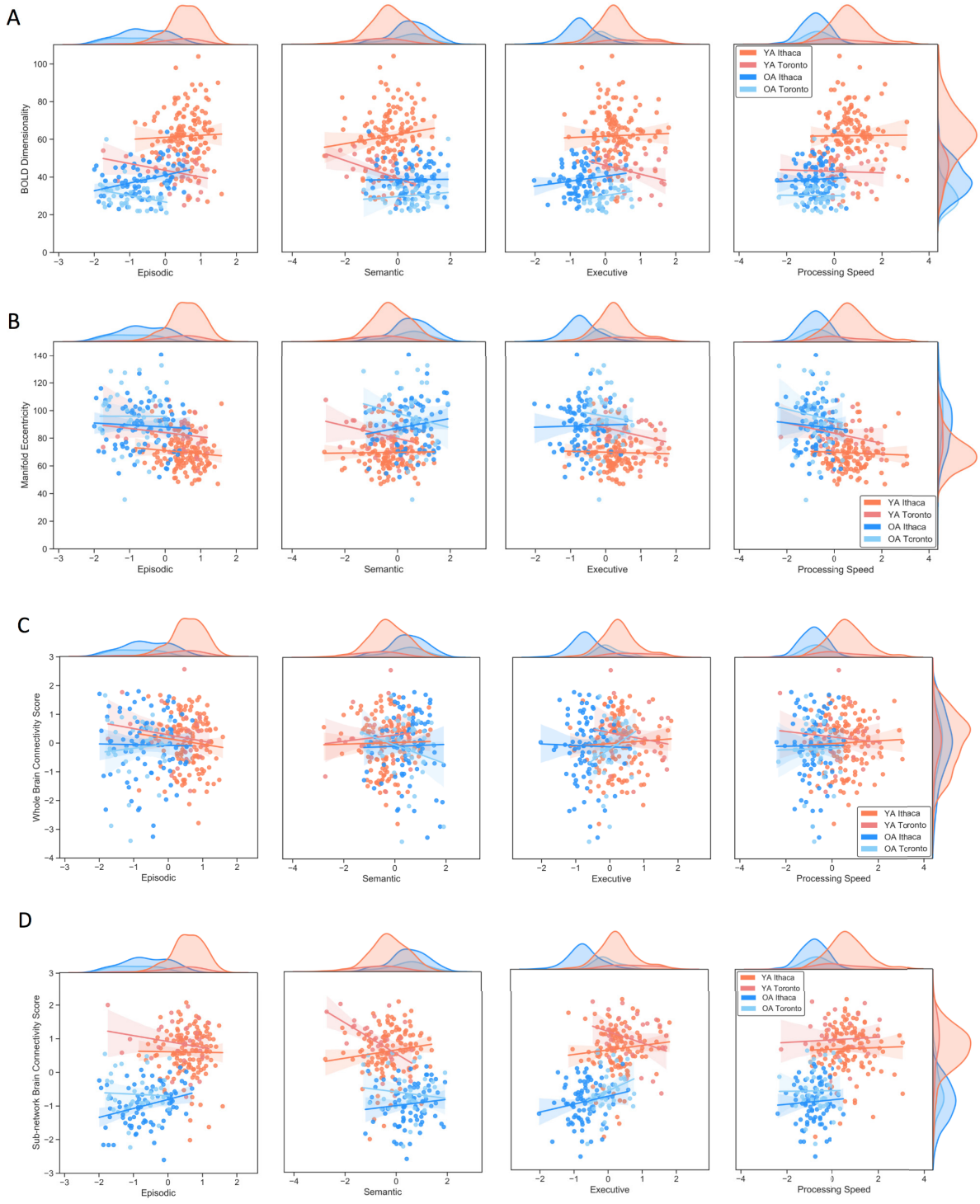
Table S4

Brain-Behavior Correlations with Covariates (Sex, Education, eWBV, Site)

Factor	Younger Adults	Older Adults	Full Sample
BOLD Dimensionality			
Episodic Memory	-.094 (.232) [-.24, .06]	.182 (.047) [.00, .35]	-.010 (.864) [-.13, .11]
Semantic Memory	.126 (.109) [-.03, .27]	.076 (.409) [-.10, .25]	.129 (.030) [.01, .24]
Executive Function	-.008 (.916) [-.16, .15]	.126 (.171) [-.05, .30]	.013 (.823) [-.10, .13]
Processing Speed	-.059 (.454) [-.21, .10]	-.002 (.984) [-.18, .18]	-.023 (.703) [-.14, .09]
Manifold Eccentricity			
Episodic Memory	-.082 (.296) [-.23, .07]	-.067 (.470) [-.24, .11]	-.061 (.306) [-.18, .06]
Semantic Memory	-.102 (.196) [-.25, .05]	-.001 (.988) [-.18, .18]	-.063 (.294) [-.18, .05]
Executive Function	-.088 (.264) [-.24, .07]	-.028 (.765) [-.21, .15]	-.034 (.574) [-.15, .08]
Processing Speed	-.042 (.599) [-.19, .11]	-.106 (.248) [-.28, .07]	-.069 (.250) [-.18, .05]
Brain Connectivity Score (Whole Brain)			
Episodic Memory	-.096 (.222) [-.25, .06]	-.074 (.423) [-.25, .11]	-.101 (.091) [-.21, .02]
Semantic Memory	.007 (.929) [-.15, .16]	-.083 (.367) [-.26, .10]	-.024 (.683) [-.14, .09]
Executive Function	.026 (.740) [-.13, .18]	.030 (.749) [-.15, .21]	.017 (.778) [-.10, .13]
Processing Speed	.048 (.540) [-.11, .20]	.003 (.971) [-.18, .18]	.007 (.912) [-.11, .12]
Brain Connectivity Score (Sub-network)			
Episodic Memory	-.130 (.098) [-.28, .02]	.161 (.079) [-.02, .33]	-.036 (.551) [-.15, .08]
Semantic Memory	.077 (.326) [-.08, .23]	.07 (.433) [-.11, .25]	.089 (.135) [-.03, .20]
Executive Function	.043 (.590) [-.11, .19]	.174 (.058) [-.01, .34]	.061 (.308) [-.06, .18]
Processing Speed	-.004 (.961) [-.16, .15]	-.002 (.981) [-.18, .18]	-.011 (.857) [-.13, .11]

Note. p*r* values displayed with *p* values in parentheses and 95% confidence intervals in brackets. Full sample includes age as a covariate. Bold denotes significance with a Bonferroni correction at $p < .013$ for 4 tests.

Supplemental Figure 14



Supplemental Figure 14 Caption: Scatterplots between cognitive scores and (A) BOLD dimensionality, (B) manifold eccentricity, (C) whole brain connectivity scores, and (D) sub-network brain connectivity scores by age group and

site. Cognition distributions are shown at the top of each plot. Distributions for BOLD dimensionality, manifold eccentricity, and brain connectivity scores are shown in the rightmost plots. YA = younger adults; OA = older adults.

Supplemental Table 5A

Sample Demographics: Ithaca

	Descriptive Statistics		Inferential Statistics				
	Younger Adults	Older Adults	*T*	df	*p*	95% CI	Cohen's *d*
N	154 (86 female)	84 (47 female)					
Age (years)							
Range	18-34	60-83					
M	22.92	67.54					
SD	3.12	5.69					
Education (years)*			-7.06	218	< .001	[-3.05, -1.72]	0.98
Range	12-24	12-24					
M	15.28	17.65					
SD	1.97	3.02					
MMSE*			4.38	218	< .001	[.39, 1.04]	0.61
Range	25-30	25-30					
M	29.13	28.420					
SD	1.11	1.27					
Episodic Memory*			15.67	218	< .001	[1.05, 1.35]	2.18
Range	-0.85 - 1.59	-1.99 - 0.70					
M	0.58	-0.62					
SD	0.46	0.67					
Semantic Memory*			-7.68	218	< .001	[-.97, -.57]	1.07
Range	-2.78 - 1.39	1.20 - 1.91					
M	-0.27	0.50					
SD	0.73	0.71					
Executive Function*			14.10	218	< .001	[.84, 1.11]	1.96
Range	-1.16 -1.80	-2.03 - 0.59					
M	0.28	-0.69					
SD	0.52	0.45					
Processing Speed*			14.71	218	< .001	[1.27, 1.67]	2.04
Range	-0.99 - 3.05	-2.40 - 0.50					
M	0.65	-0.82					
SD	0.80	0.54					

Note. Episodic Memory, Semantic Memory, and Executive Function reflect composite scores. Processing Speed reflects z scores on Symbol Digits Modalities Task, Oral. * denotes significant group differences. Education was not recorded for 14 participants. Age group differences in MMSE, episodic memory, semantic memory, executive function, and processing speed were tested in 220 participants. Positive T values reflect higher scores in younger adults, negative values reflect higher scores in older adults. Statistical tests are nearly identical when including sex, education, and estimated whole brain volume as covariates in an ANCOVA.

Supplemental Table 5B

Sample Demographics: Toronto

	Descriptive Statistics		Inferential Statistics				
	Younger Adults	Older Adults	*T*	df	*p*	95% CI	Cohen's *d*
N	27 (17 female)	36 (19 female)					
Age (years)							
Range	18-30	60-89					
M	24.26	71.19					
SD	3.62	7.37					
Education (years)*			-2.88	61	< .01	[-2.48, -.45]	0.73
Range	18-Dec	13-22					
M	14.81	16.28					
SD	1.49	2.30					
MMSE			-.74	61	0.47	[-.96, .45]	0.18
Range	22-30	25-30					
M	28.85	29.11					
SD	1.66	1.14					
Episodic Memory*			7.10	61	< .001	[.85, 1.51]	1.81
Range	-1.75 - 1.19	-1.83 - 0.05					
M	0.25	-0.92					
SD	0.73	0.58					
Semantic Memory*			-5.86	61	< .001	[-1.57, -.77]	1.49
Range	-2.72 - 0.61	-1.29 - 1.91					
M	-0.75	0.42					
SD	0.85	0.74					
Executive Function*			5.69	61	< .001	[.46, .96]	1.45
Range	-0.45 - 1.71	-.61 - .76					
M	0.71	0.00					
SD	0.63	0.36					
Processing Speed*			4.27	61	< .001	[.46, 1.27]	1.09
Range	-2.26 - 2.06	-2.33 - 0.36					
M	0.18	-0.60					
SD	1.01	0.59					

Note. Episodic Memory, Semantic Memory, and Executive Function reflect composite scores. Processing Speed reflects z scores on Symbol Digits Modalities Task, Oral. * denotes significant group differences. Age group differences in MMSE, episodic memory, semantic memory, executive function, and processing speed were tested in 63 participants. Positive T values reflect higher scores in younger adults, negative values reflect higher scores in older adults. Statistical tests are nearly identical when including sex, education, and estimated whole brain volume as covariates in an ANCOVA.

Appendix B: Supplementary Material to anterior hippocampus and temporal pole volumes are associated with episodic autobiographical memory in healthy older adults

Methods

Cognitive Battery

259 of the 263 participants completed additional cognitive assessments of episodic memory and semantic memory. Two younger and two older adults were excluded for having more than 50% missing data. Measures of episodic memory included Verbal Paired Associates from the Wechsler Memory Scale-IV (Wechsler, 2009), Associative Recall Paradigm (Brainerd et al., 2014), and NIH Cognition measures of Auditory Verbal Learning (Rey) and Picture Sequence Memory (Gershon et al., 2013). Semantic Memory measures included Shipley-2 Vocabulary (Shipley et al., 2009) and NIH Cognition measures of Picture Vocabulary and Oral Reading Recognition. Composite scores were created by taking the average of Z-scores within each cognitive domain. Two additional younger adults were excluded for outlying episodic index scores, leaving a final sample of 257.

In order to characterize the sample, we include descriptive and inferential statistics on composite measures of episodic and semantic memory in Table 1. GEEs were also conducted on hippocampal and temporal pole volumes to test for age differences in brain-behavior relationships with laboratory-based measures.

Results

Posterior Hippocampal Volumes Are Smaller Early into Older Age

To determine whether posterior hippocampal volumes were reduced only in later stages of older adulthood, we binned the older adult cohort into younger (60-69 years, N=66) and older (70+, N=39) groups for a total of three age categories. The ANCOVA on hippocampal volume was then repeated (Supplementary Figure 2).

We observed main effects of age group ($F(2,257)=3.48$, $p < .05$, $\eta_p^2=.01$), segment ($F(1,779)=27.57$, $p < .001$, $\eta_p^2=.03$), and hemisphere ($F(1,779)=16.13$, $p < .001$, $\eta_p^2=.02$). Several interactions qualified these effects. First, a segment by hemisphere interaction ($F(1,779)=59.01$, $p < .001$, $\eta_p^2=.07$) indicated that right anterior volumes were larger than left

anterior volumes ($t(779)=7.04$, $p < .001$, Cohen's $d = .50$), right posterior volumes ($t(779)=9.26$, $p < .001$, Cohen's $d=.66$), and left posterior volumes ($t(779)=7.16$, $p < .001$, Cohen's $d=.51$). A segment by sex interaction ($F(1,779)=11.87$, $p < .001$, $\eta_p^2=.01$) showed that anterior volumes were larger than posterior in both males ($t(779)=6.81$, $p < .001$, Cohen's $d=.49$) and females ($t(779)=3.06$, $p < .05$, Cohen's $d=.22$), but more so in males. Critically, a segment by age group interaction ($F(2,779)=8.54$, $p < .001$, $\eta_p^2=.02$) demonstrated that both groups of older adults had smaller posterior hippocampus volumes compared to younger adults (younger older: $t(257)=2.88$, $p < .05$, Cohen's $d=.36$; older older: $t(257)=3.45$, $p < .005$, Cohen's $d=.43$). There were no differences between younger older and older older adults. No differences were observed for anterior hippocampus volumes. As with the main results, education and site were included as covariates.

Episodic Memory is Not Associated with Hippocampal Segment Volumes

A GEE was modeled to test for relationships between composite episodic memory scores and different hippocampal segment volumes across age groups. Although an age group by episodic memory interaction was observed in the full sample (Wald χ^2 (1)=4.12, $p < .05$; Supplementary Figure 4), episodic memory was not a significant predictor of volume within each age group alone. A sex by episodic memory interaction term was included due to a sex effect observed in an ANCOVA on episodic memory scores ($F(1,252)= 19.03$, $p < .001$, $\eta_p^2=.07$).

Semantic, but Not Episodic, Memory is Associated with Temporal Pole Volumes in Younger Adults

GEEs were also modeled to separately examine relationships between episodic and semantic memory with temporal pole volumes across age groups. No association was observed between episodic memory and temporal pole volumes. Results from the GEE with semantic memory also revealed no effect of semantic memory on volume. However, product-moment correlations demonstrated a significant association between temporal pole volumes and semantic memory in younger adults (Table S8), which suggested that a weaker association in the older group was likely dampening effects in the full GEE. We ran a post-hoc GEE in younger adults, which demonstrated a significant main effect of semantic memory (Wald χ^2 (1)=10.34, $b=.05$, SE=.02, $p < .005$) and a marginal hemisphere by semantic memory interaction (Wald χ^2

(1)=3.81, p = .05; Supplemenatry Figure 7). Follow-up GLMs confirmed that semantic memory was positively related to the left temporal pole volume (b=.05, SE=.02, p < .01) and not the right. Models included sex as well as site, education, and eWBV as effects of no interest.

Associations with Volume Ratio of Posterior to Anterior Hippocampus

Prior work has shown that the proportion of posterior to anterior hippocampus volumes contributes to episodic memory (Poppenk & Moscovitch, 2011), spatial navigation (Maguire et al., 2000), and cognitive mapping (Brunec et al., 2019) beyond either volume alone. All analyses conducted on hippocampal segment volumes were repeated using a ratio of posterior to anterior volumes as the dependent variable. The aim was to determine whether the proportion of segments provides unique information about hippocampal volume relationships to AM.

The ANCOVA on volume ratio revealed three main effects. A main effect of hemisphere (F (1,261)=159.06, p < .001, η_p^2= .35) showed that left ratios were larger than right. A main effect of sex (F(1,258)=4.02, p < .05, η_p^2=.01) demonstrated that females had a larger ratio compared to males. Lastly, a main effect of age group (F(1, 258)=5.74, p < .05, η_p^2= .02) indicated that older adults had smaller ratios compared to younger adults. Site and education were included as covariates.

Next, GEEs were modeled separately for internal and external density. Terms included age group, hemisphere, internal density, and the three-way interaction. Consistent with models from the main text, a sex by internal density interaction term was also included, along with site, education, and eWBV as effects of no interest. Follow-up GEEs were conducted to break down marginal and significant interactions. GLMs were then performed on each hemisphere to inspect simple effects.

Results from the GEE with internal density were qualitatively similar to those from the GEE on hippocampal segment volumes. Full results are listed in Table S7 for completeness. Notably, we observed an age group by hemisphere by internal density interaction (Wald χ^2 (1)=7.45, p < .01). The follow-up GEE in younger adults showed a marginal hemisphere by internal density interaction (Wald χ^2 (1)=3.35, p = .067), but internal density showed no significant relationship to either left or right volume ratios.

In older adults, interactions were observed between hemisphere and internal density (Wald χ^2 (1)=4.23, p < .05) as well as between sex and internal density (Wald χ^2 (1)=6.53, p <

.05). To break down these interactions, a GLM was first performed on volume ratios in each hemisphere. As depicted in Supplementary Figure 5 (left), internal density was negatively related to the left volume ratio in all older adults (b=-.188, SE=.86, $p < .05$). In the right hemisphere, a main effect of internal density (b=-1.78, SE=.79, $p < .05$) was accompanied by an interaction with sex (Wald χ^2 (1)= 11.52, $p < .001$; Supplementary Figure 5, right). A final set of GLMs performed within each sex on the right volume ratio revealed that internal density positively predicted volume ratios for older men (b=2.18, SE=1.03, $p < .05$), and negatively predicted volume ratios for older women (b=-1.80, SE = .63, $p < .005$).

The GEE with external density showed no effect of density on volume ratio. This complemented results reported in the main text, where females showed a negative relationship to external density across both anterior and posterior volumes.

As in the main text, this result highlights the interindividual variability in brain-behavior associations in older age. While the left proportion of hippocampal segment volume similarly impacts internal density in older adults, sex differences arose in the right hemisphere: the proportion of right hippocampal segment volumes contributed to internal density in older males, whereas in older females the volume of anterior hippocampus alone aided internally dense recollections. Sex differences in older age may reflect an exacerbation of effects seen in the full group: diminished volume ratio in the right hemisphere, males, and older adults.

GEEs were also modeled to examine the effects of laboratory episodic and semantic composite scores on volume ratio. Neither variable was a significant predictor. The episodic GEE was repeated in older adults alone based on an observed association between volume ratio and episodic memory scores (Table S8), but episodic memory remained a nonsignificant predictor.

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Table S1

Hippocampal and Temporal Pole Volumes Adjusted for eTIV

Age Group	Region	Males		Females		Full Sample		
		Mean	SD	Mean	SD	Mean	SD	Range
Younger Adults								
	Whole hippocampus	8334.37	660.8	8213.88	580.48	8264.98	616.68	6773.63 - 10109.43
	L anterior hippocampus	1763.99	251.87	1699.83	210.43	1727.04	230.36	1189.42 - 2380.27
	R anterior hippocampus	1862.58	255.38	1817.99	217.47	1836.9	234.56	1253.79 - 2483.07
	L posterior hippocampus	1768.57	163.29	1795.5	164.59	1784.08	164.06	1368.89 - 2156.48
	R posterior hippocampus	1749	181.07	1743.6	163.99	1745.89	170.9	1293.34 - 2148.77
	L temporal pole	2487.16	442.96	2456.12	385.71	2469.28	409.89	1226.94 - 3461.54
	R temporal pole	2482.4	378.6	2452.79	302.46	2465.35	336.02	1468.71 - 3357.31
Older Adults								
	Whole hippocampus	7708.13	615.88	7586.78	631.32	7641.1	624.42	6376.61 - 9332.13
	L anterior hippocampus	1734.07	212.46	1713.08	210.86	1722.48	210.82	1190.53 - 2194.75
	R anterior hippocampus	1845.88	242.96	1814.34	219.62	1828.46	229.76	1321.54 - 2331.98
	L posterior hippocampus	1678.37	165.83	1704.9	142.09	1693.03	152.99	1372.68 - 2221.62
	R posterior hippocampus	1644.19	154.43	1682.72	131.65	1665.47	142.89	1327.94 - 2014.26
	L temporal pole	2500.18	367.74	2303.27	337.11	2391.41	363.02	1363.9 - 3304.13
	R temporal pole	2489.88	250.9	2388.47	314.89	2433.86	291.13	1542.04 - 3005.56

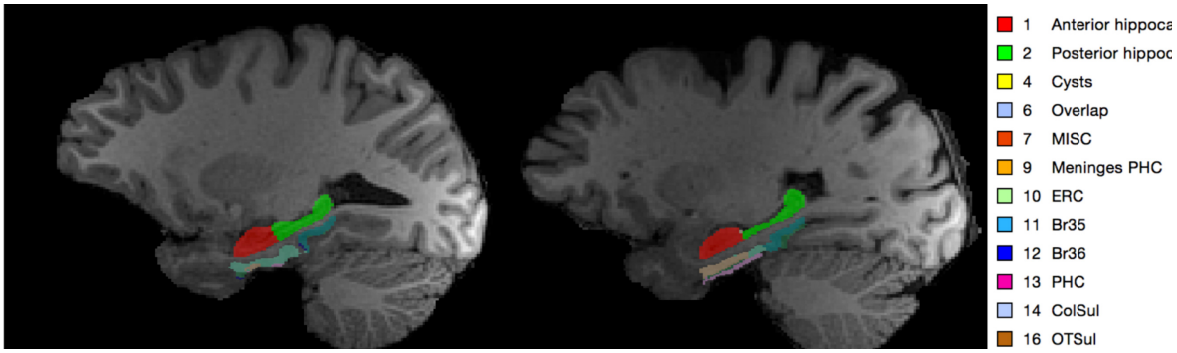
Note. Volumes shown in mm^3 after adjustment for estimated total intracranial volume (eTIV).

Table S2

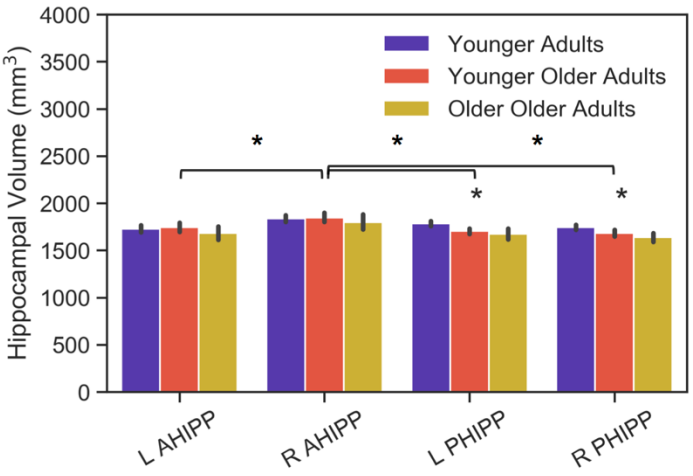
Raw Hippcampal, Temporal Pole, and Whole Brain Volumes

Age Group	Region	Males		Females		Full Sample		
		Mean	SD	Mean	SD	Mean	SD	Range
Younger Adults								
	Whole hippocampus	8545.45	778.66	8071.34	649.63	8272.39	743	6579.1 - 10486.0
	L anterior hippocampus	1830.4	289.15	1654.98	233.29	1729.37	271.86	1092.0 - 2498.75
	R anterior hippocampus	1933.68	296.1	1769.97	247.5	1839.39	280.29	1149.5 - 2591.25
	L posterior hippocampus	1815.4	178.72	1763.88	182.56	1785.72	182.17	1296.75 - 2217.25
	R posterior hippocampus	1800.94	189.17	1708.53	180.19	1747.72	189.09	1324.75 - 2241.0
	L temporal pole	2541.66	451.06	2419.32	382.24	2471.2	415.89	1331.0 - 3514.0
	R temporal pole	2541.37	376.46	2412.97	303.17	2467.42	341.05	1363.0 - 3366.0
	eWBV	0.73	0.04	0.74	0.05	0.74	0.05	0.68 - 1.00
	eTIV	1664021.32	167252.79	1491213.98	147177.6	1564493.04	177529.27	1083364.68 - 1983058.78
Older Adults								
	Whole hippocampus	7927.23	601.02	7379.46	673.64	7624.65	695.26	6172.1 - 9439.0
	L anterior hippocampus	1803.01	203.1	1647.85	214.6	1717.3	222.47	1127.25 - 2264.0
	R anterior hippocampus	1919.68	242.94	1744.51	219.04	1822.92	245.07	1214.5 - 2401.25
	L posterior hippocampus	1726.98	184.25	1658.91	167.41	1689.38	177.58	1340.25 - 2299.75
	R posterior hippocampus	1698.1	183.05	1631.7	168.15	1661.42	177.25	1319.0 - 2149.25
	L temporal pole	2556.74	365.6	2249.74	337.4	2387.16	380.84	1326.0 - 3395.0
	R temporal pole	2551.09	270.85	2330.55	327.54	2429.27	321.54	1526.0 - 3113.0
	eWBV	0.67	0.04	0.69	0.06	0.68	0.05	0.56 - 0.93
	eTIV	1667937.91	150562.56	1459558.62	152213.7	1552833.16	183206.68	1094149.66 - 2042058.21

Note. ROI values represent volumes measurements in mm^3 prior to adjusting for eTIV. Hippocampal segment volumes were extracted from ASHS. Whole hippocampus, temporal pole, estimated total intracranial, grey matter, and white matter volumes were extracted from FreeSurfer. eWBV = (grey matter + white matter)/eTIV. eTIV = estimated total intracranial volume; eWBV = estimated whole brain volume.



Supplementary Figure 1. ASHS Output. Representative left hemisphere segmentations from the T1 ASHS pipeline in one younger (left) and one older (right) adult in native space. Outputs included segmentations and volume measurements of the anterior and posterior hippocampus, entorhinal cortex, BA35, BA36, parahippocampal cortex, meninges, and other regions (see legend). The present study limited its examination to the longitudinal axis of the hippocampus. Anterior hippocampus = head. Posterior hippocampus = body + tail.



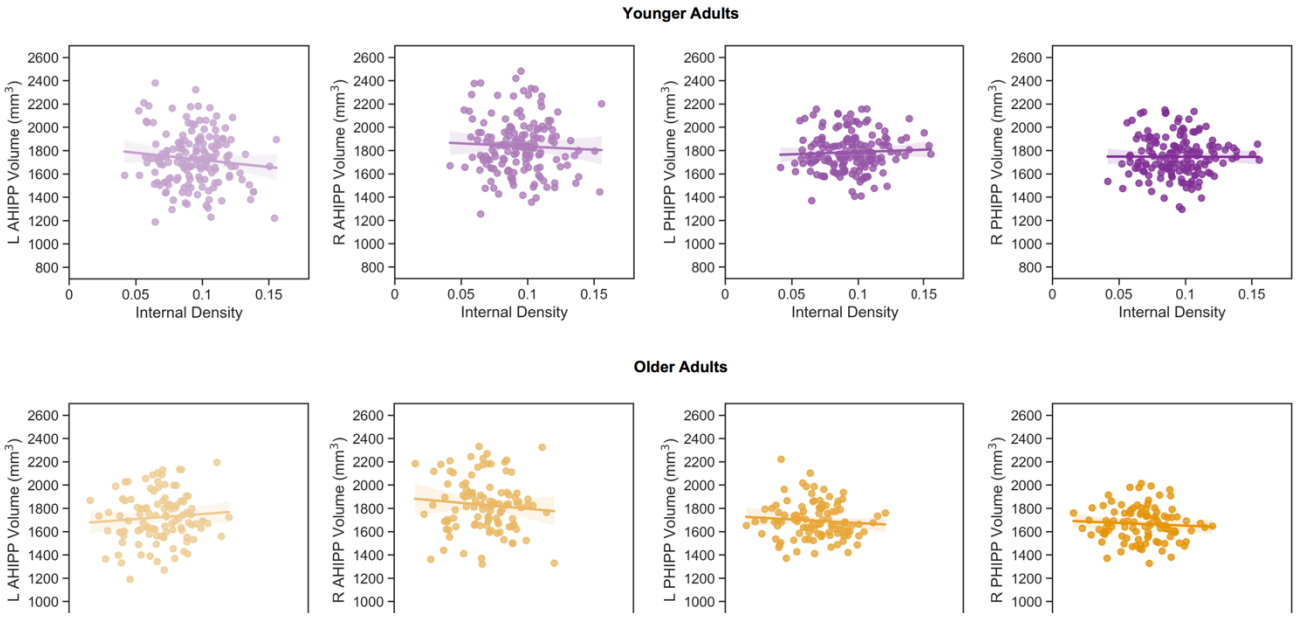
Supplementary Figure 2. Age by Hippocampal Volume Interaction Present at Early Stage of Older Adulthood. Mean volumes of anterior and posterior hippocampal segments plotted by hemisphere and expanded age group categories. Both groups of older adults had smaller posterior, but not anterior, hippocampus volumes than younger adults. Volumes were adjusted for eTIV. Sex was included in the model. Site and education were included as covariates. * denote significant effects. L AHIPP = left anterior; R AHIPP = right anterior; L PHIPP = left posterior; R PHIPP = right posterior.

Table S3

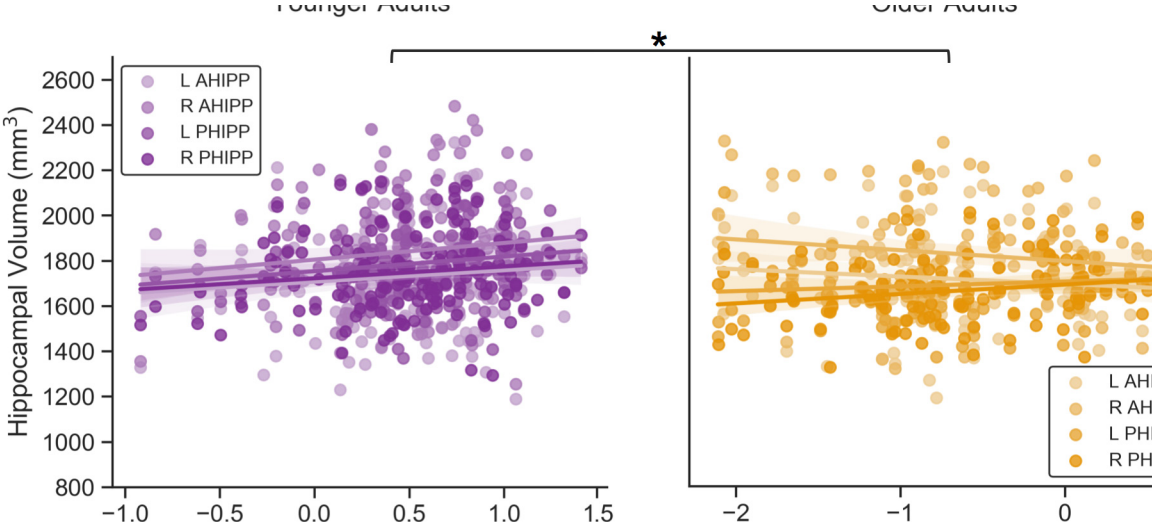
Generalized Estimating Equations with Internal Density on Hippocampal Volumes

Model	Effect	Wald $\chi 2$	df	*p*
Full Sample				
	age group	1.07	1	0.300
	hemisphere	**17.23**	**1**	**< .001**
	segment	0.46	1	0.496
	sex	**5.66**	**1**	**< .05**
	internal density	0.14	1	0.710
	age group x hemisphere	**8.18**	**1**	**< .005**
	age group x segment	1.79	1	0.181
	hemisphere x segment	**18.28**	**1**	**< .001**
	sex x segment	**4.40**	**1**	**< .05**
	age group x internal density	3.06	1	0.080
	hemisphere x internal density	**5.32**	**1**	**< .05**
	segment x internal density	2.64	1	0.104
	sex x internal density	2.39	1	0.122
	age group x hemisphere x segment	**7.42**	**1**	**< .01**
	age group x hemisphere x internal density	**8.36**	**1**	**< .005**
	age group x segment x internal density	**4.68**	**1**	**< .05**
	hemisphere x segment x internal density	**4.89**	**1**	**< .05**
	age group x hemisphere x segment x internal density	**8.53**	**1**	**< .005**
	education	0.02	1	0.877
	eWBV	**42.95**	**1**	**< .001**
	site	**26.48**	**1**	**<.001**
Younger Adults				
	hemisphere	1.36	1	0.243
	segment	1.33	1	0.248
	sex	1.55	1	0.213
	internal density	1.82	1	0.178
	hemisphere x segment	0.62	1	0.432
	sex x segment	2.29	1	0.13
	hemisphere x internal density	**3.58**	**1**	**0.059**
	segment x internal density	1.98	1	0.159
	sex x internal density	0.53	1	0.468
	hemisphere x segment x internal density	**3.84**	**1**	**0.050**
	education	0.56	1	0.453
	eWBV	**19.09**	**1**	**< .001**
	site	**11.93**	**1**	**<.005**
Older Adults				
	hemisphere	**17.21**	**1**	**< .001**
	segment	0.44	1	0.509
	sex	**6.56**	**1**	**< .05**
	internal density	0.13	1	0.721
	hemisphere x segment	**18.27**	**1**	**< .001**
	sex x segment	2.15	1	0.143
	hemisphere x internal density	**5.36**	**1**	**< .05**
	segment x internal density	2.58	1	0.108
	sex x internal density	**4.89**	**1**	**< .05**
	hemisphere x segment x internal density	**4.94**	**1**	**< .05**
	education	0.03	1	0.856
	eWBV	**22.19**	**1**	**< .001**
	site	**16.61**	**1**	**<.001**

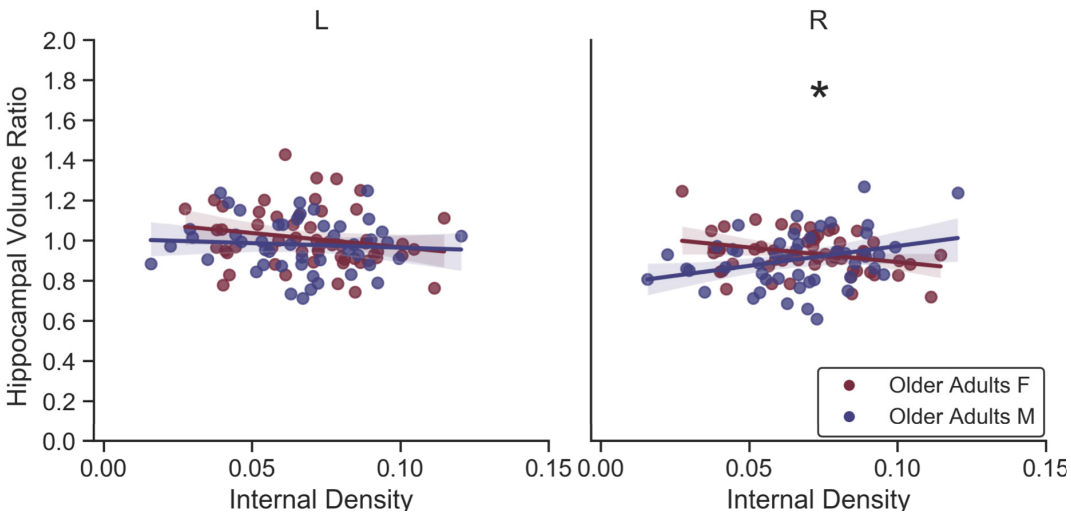
Note. Marginal and significant predictors are bolded.



Supplementary Figure 3. Scatterplots of Internal Density Relationships with Hippocampal Volumes. Individual scatterplots are shown for relationships between internal density and hippocampal volume in younger (top) and older (bottom) adults. No relationships were statistically significant. Volumes were adjusted for eTIV. L AHIPP = left anterior; R AHIPP = right anterior; L PHIPP = left posterior; R PHIPP= right posterior.



Supplementary Figure 3. Laboratory Episodic Memory Ability is Not Related to Hippocampal Segment Volumes. Scatterplots demonstrating a significant interaction between episodic memory scores and age group on hippocampal volumes. All volumes were corrected for eTIV. Sex was included in the model. Site, estimated whole brain volume, and education were included as effects of non-interest. * denote significant effects. L AHIPP = left anterior; R AHIPP = right anterior; L PHIPP = left posterior; R PHIPP = right posterior.



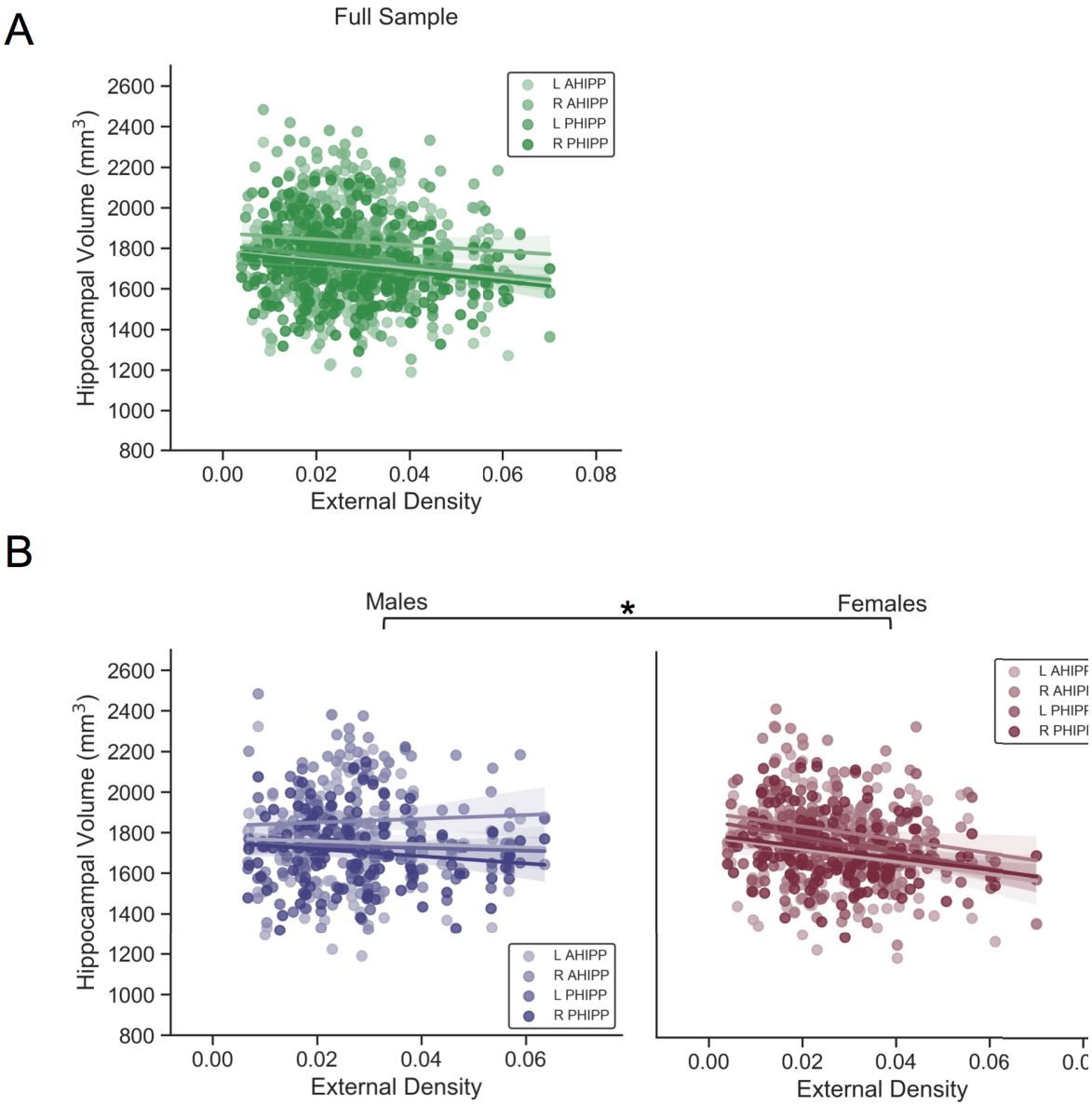
Supplementary Figure 4. Interaction Between Sex and Internal Density on Older Adult Volume Ratios. Scatterplots show significant main effect of internal density (left hemisphere) and interaction with sex (right hemisphere) on volume ratio. In the left hemisphere, more internally dense recollections were related to a smaller volume ratio, or difference between posterior and anterior hippocampal volumes. In the right hemisphere, more internally dense recollections were related to higher ratios in older males and lower ratios in older females. All volumes were corrected for eTIV. Site, education, and estimated whole brain volume were included as effects of no interest in the model. Volume ratio = posterior/anterior hippocampus. * denote significant effects. F = female; M = male.

Table S4

Generalized Estimating Equations with External Density on Hippocampal Volumes

Model	Effect	Wald χ^2	df	*p*
Full Sample				
	age group	**3.77**	**1**	**0.052**
	hemisphere	1.07	1	0.300
	segment	0.88	1	0.348
	sex	0.08	1	0.771
	external density	**3.77**	**1**	**0.052**
	age group x hemisphere	0.65	1	0.422
	age group x segment	1.75	1	0.185
	hemisphere x segment	1.43	1	0.231
	sex x segment	**4.86**	**1**	**< .05**
	age group x external density	0.62	1	0.433
	hemisphere x external density	1.28	1	0.249
	segment x external density	0.92	1	0.338
	sex x external density	**4.36**	**1**	**< .05**
	age group x hemisphere x segment	**0.74**	1	0.391
	age group x hemisphere x external density	0.29	1	0.590
	age group x segment x exteral density	0.00	1	0.944
	hemisphere x segment x external density	1.07	1	0.301
	age group x hemisphere x segment x external density	0.20	1	0.655
	education	0.00	1	0.975
	eWBV	**42.95**	**1**	**< .001**
	site	**23.42**	**1**	**< .001**

Note. Marginal and significant predictors are bolded.



Hippocampal Volume. (A) Scatterplots demonstrating a significant relationship between external detail density and hippocampal volumes across all participants. (B) Scatterplots demonstrating a significant interaction between density and sex: larger hippocampal volumes were related to less external density in females only. All volumes were corrected for eTIV. Site, estimated whole brain volume, and education were included as effects of no interest. * denote

significant effects. L AHIPP = left anterior; R AHIPP = right anterior; L PHIPP = left posterior; R PHIPP = right posterior.

Table S5

Generalized Estimating Equations with Internal Density on Temporal Pole Volumes

Model	Effect	Wald $\chi 2$	df	*p*
Full Sample				
	age group	**4.50**	**1**	**< .05**
	hemisphere	0.61	1	0.435
	sex	**5.55**	**1**	**< .05**
	internal density	**6.18**	**1**	**< .05**
	age group x hemisphere	0.38	1	0.537
	age group x internal density	**4.56**	**1**	**< .05**
	hemisphere x internal density	0.17	1	0.680
	sex x internal density	2.73	1	0.098
	age group x hemisphere x internal density	0.15	1	0.703
	education	1.78	1	0.182
	eWBV	**7.78**	**1**	**< .01**
	site	**3.24**	**1**	**0.072**
Younger Adults				
	hemisphere	0.01	1	0.917
	sex	0.09	1	0.767
	internal density	0.16	1	0.685
	hemisphere x internal density	0.01	1	0.938
	sex x internal density	0.01	1	0.923
	education	0.76	1	0.384
	eWBV	**6.22**	**1**	**< .05**
	site	1.55	1	0.214
Older Adults				
	hemisphere	0.59	1	0.442
	sex	**4.16**	**1**	**< .05**
	internal density	**5.54**	**1**	**< .05**
	hemisphere x internal density	0.16	1	0.688
	sex x internal density	1.42	1	0.233
	education	0.81	1	0.367
	eWBV	2.53	1	0.112
	site	1.53	1	0.216

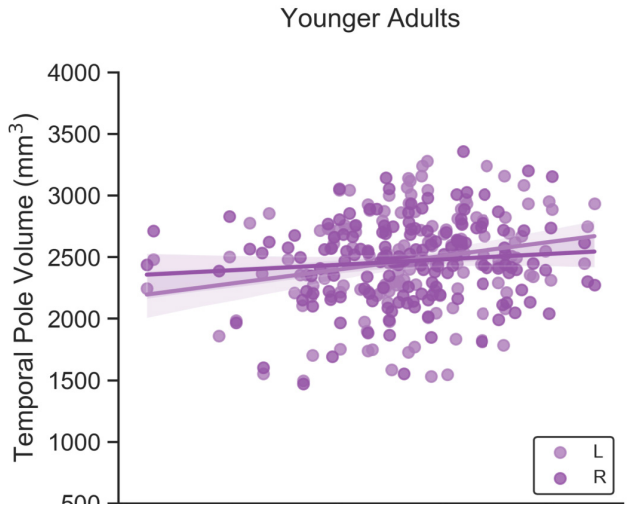
Note. Marginal and significant predictors are bolded.

Table S6

Generalized Estimating Equations with External Density on Temporal Pole Volumes

Model	Effect	Wald $\chi 2$	df	*p*
Full Sample				
	age group	**4.42**	**1**	**< .05**
	hemisphere	0.03	1	0.860
	sex	0.09	1	0.765
	external density	**3.42**	**1**	**0.065**
	age group x hemisphere	0.93	1	0.334
	age group x external density	**7.91**	**1**	**< .005**
	hemisphere x external density	0.43	1	0.510
	sex x external density	1.85	1	0.174
	age group x hemisphere x external density	2.69	1	0.101
	education	0.96	1	0.328
	eWBV	**7.79**	**1**	**< .01**
	site	1.93	1	0.165
Younger Adults				
	hemisphere	1.85	1	0.174
	sex	0.06	1	0.810
	external density	2.36	1	0.124
	hemisphere x external density	2.65	1	0.103
	sex x external density	0.40	1	0.528
	education	1.05	1	0.305
	eWBV	**6.76**	**1**	**< .01**
	site	0.72	1	0.395
Older Adults				
	hemisphere	0.03	1	0.860
	sex	0.20	1	0.652
	external density	1.51	1	0.219
	hemisphere x external density	0.43	1	0.512
	sex x external density	0.11	1	0.739
	education	0.11	1	0.743
	eWBV	2.06	1	0.151
	site	1.43	1	0.231

Note. Marginal and significant predictors are bolded.



Supplementary Figure 6. Laboratory Semantic Memory Ability is Related to Temporal Pole Volumes in Younger Adults. Scatterplot demonstrating relationships between temporal pole volumes and composite semantic memory scores in younger adults. General semantic memory abilities were positively related to left temporal pole volumes in younger adults. Volumes were corrected for eTIV. Sex was included in each model. Site, estimated whole brain volume, and education were included as effects of non-interest. L = left; R = right.

Table S7

Generalized Estimating Equations with Internal Density on Volume Ratio

Model	Effect	Wald $\chi 2$	df	*p*
Full Sample				
	age group	1.24	1	0.265
	hemisphere	**15.75**	**1**	**<. 001**
	sex	**3.76**	**1**	**0.052**
	internal density	**5.00**	**1**	**< .05**
	age group x hemisphere	**6.65**	**1**	**< .05**
	age group x internal density	**5.68**	**1**	**< .05**
	hemisphere x internal density	**4.29**	**1**	**< .05**
	sex x internal density	1.64	1	0.200
	age group x hemisphere x internal density	**7.45**	**1**	**< .01**
	education	0.17	1	0.678
	eWBV	**3.63**	**1**	**0.057**
	site	0.03	1	0.859
Younger Adults				
	hemisphere	0.74	1	0.390
	sex	0.23	1	0.633
	internal density	1.23	1	0.268
	hemisphere x internal density	**3.35**	**1**	**0.067**
	sex x internal density	0.04	1	0.834
	education	0.19	1	0.661
	eWBV	0.26	1	0.611
	site	0.68	1	0.410
Older Adults				
	hemisphere	**15.72**	**1**	**< .001**
	sex	**9.35**	**1**	**< .005**
	internal density	**10.89**	**1**	**< .005**
	hemisphere x internal density	**4.23**	**1**	**< .05**
	sex x internal density	**6.53**	**1**	**< .05**
	education	2.68	1	0.102
	eWBV	**19.1**	**1**	**< .001**
	site	0.67	1	0.412

Note. Marginal and significant predictors are bolded.

Table S8

Correlations Between Grey Matter Volume and Cognition

Age Group	Region	Episodic Memory	Semantic Memory
Younger Adults			
	Whole hippocampus	**.19 (.019)***	.01 (.929)
	L anterior hippocampus	.11 (.178)	.05 (.522)
	R anterior hippocampus	.14 (.081)	.05 (.538)
	L posterior hippocampus	.14 (.090)	.03 (.678)
	R posterior hippocampus	.12 (.151)	-.04 (.661)
	L p/a hippocampus ratio	-.01 (.916)	-.02 (.825)
	R p/a hippocampus ratio	-.04 (.621)	-.06 (.488)
	L temporal pole	.12 (.128)	**.22 (.005)***
	R temporal pole	.17 (.041)	.11 (.186)
Older Adults			
	Whole hippocampus	.00 (.979)	.00 (.975)
	L anterior hippocampus	-.14 (.146)	.15 (.126)
	R anterior hippocampus	-.21 (.033)	.04 (.699)
	L posterior hippocampus	-.03 (.745)	.03 (.773)
	R posterior hippocampus	.09 (.371)	.02 (.836)
	L p/a hippocampus ratio	.07 (.466)	-.13 (.183)
	R p/a hippocampus ratio	**.24 (.017)***	-.01 (.886)
	L temporal pole	.07 (.503)	-.01 (.944)
	R temporal pole	.00 (.991)	.06 (.526)
Full Sample			
	Whole hippocampus	**.19 (.002)***	-.07 (.260)
	L anterior hippocampus	-.12 (.061)	.14 (.025)
	R anterior hippocampus	-.13 (.044)	.09 (.136)
	L posterior hippocampus	.10 (.100)	-.02 (.697)
	R posterior hippocampus	.12 (.059)	-.04 (.485)
	L p/a hippocampus ratio	**.15 (.015)***	-.14 (.030)
	R p/a hippocampus ratio	**.18 (.004)***	-.10 (.099)
	L temporal pole	.10 (.111)	.10 (.106)
	R temporal pole	.05 (.386)	.07 (.268)

Note. Partial product-moment (pr) correlations were conducted between region volumes (adjusted for eTIV) and episodic and semantic memory index scores. Site, sex, education, and eWBV were included as covariates for each set of correlations. * and bold denote significance after Bonferroni correction at $p < .025$ for 2 tests. *p* values are shown in parentheses. eTIV= estimated total intracranial volume; eWBV= estimated whole brain volume.

Appendix C: Supplemental Material to age effects and individual differences in episodic and semantic autobiographical memory relate to resting-state functional connectivity of the hippocampus and temporal pole with the default network

Table S1

RSFC-AI Subcategory Correlations with Covariates (Sex, Education, eWBV)

Factor	Younger Adults	Older Adults
First Pattern (Figure 4A)		
Internal Density	**.209 (.008) [.05, .35]**	**.439 (.000) [.26, .58]**
Event	**.164 (.039) [.01, .31]**	**.334 (.001) [.15, .50]**
Place	.039 (.629) [-.12, .19]	.166 (.100) [-.03, .35]
Time	.117 (.144) [-.04, .27]	.156 (.123) [-.04, .34]
Perceptual	.080 (.316) [-.08, .23]	**.385 (.000) [.20, .54]**
Emotion/Thought	.093 (.247) [-.06, .25]	**.228 (.023) [.03, .41]**
External Density	**-.266 (.001) [-.41, -.11]**	**-.421 (.000) [-.57, -.24]**
Event	-.032 (.692) [-.19, .12]	**-.363 (.000) [-.52, -.18]**
Place	**-.343 (.000) [-.47, -.20]**	**-.491 (.000) [-.63, -.32]**
Time	-.126 (.116) [-.28, .03]	**-.245 (.015) [-.42, -.05]**
Perceptual	-.140 (.080) [-.29, .02]	**-.369 (.000) [-.53, -.19]**
Emotion/Thought	.065 (.420) [-.09, .22]	**-.222 (.027) [-.40, -.03]**
Semantic	**-.165 (.038) [-.31, -.01]**	-136 (.178) [-.33, .06]
Repetition	**-.255 (.001) [-.40, -.10]**	.028 (.784) [-.17, .22]
Other	**-.219 (.006) [-.36, -.06]**	-.140 (.166) [-.33, .06]
Second Pattern (Figure 4B)		
Internal Density	**.361 (.000) [.22, .49]**	-.015 (.881) [-.21, .18]
Event	**.302 (.000) [.15, .44]**	-.156 (.149) [-.33, .05]
Place	**.312 (.000) [.16, .45]**	.028 (.783) [-.17, .22]
Time	**.373 (.000) [.23, .50]**	-.027 (.790) [-.22, .17]
Perceptual	.080 (.315) [-.08, .23]	.121 (.233) [-.08, .31]
Emotion/Thought	-.142 (.075) [-.29, .01]	.133 (.190) [-.07, .32]
External Density	**.373 (.000) [.23, .50]**	-.100 (.323) [-.29, .10]
Event	**.313 (.000) [.16, .45]**	-.037 (.719) [-.23, .16]
Place	**.318 (.000) [.17, .45]**	.031 (.763) [-.17, .23]
Time	**.215 (.007) [.06, .36]**	.076 (.456) [-.12, .27]
Perceptual	**.194 (.015) [.04, .34]**	.050 (.626) [-.15, .24]
Emotion/Thought	.143 (.055) [.00, .30]	-.067 (.511) [-.26, .13]
Semantic	.030 (.705) [-.13, .19]	-.058 (.566) [-.25, .14]
Repetition	**.151 (.044) [.00, .31]**	-.098 (.336) [-.29, .10]
Other	**.265 (.001) [.11, .40]**	-.169 (.094) [-.35, .03]

Note. p*r* values displayed with *p* values in parentheses and 95% confidence intervals in brackets. Bold denotes $p < .05$.

Table S2

RSFC-AI Subcategory Correlations with Covariates (Sex, Education, eWBV, Site)

Factor	Younger Adults	Older Adults
First Pattern (Figure 4A)		
Internal Density	**.201 (.011) [.05, .35]**	**.424 (.000) [.25, .57]**
Event	**.190 (.017) [.03, .34]**	**.312 (.002) [.12, .48]**
Place	.054 (.502) [-.10, .21]	.160 (.113) [-.04, 35]
Time	**.190 (.017) [.03, .34]**	.163 (.107) [-.04, .35]
Perceptual	.026 (.743) [-.13, .18]	**.407 (.000) [.23, .56]**
Emotion/Thought	-.013 (.872) [-.17, .14]	.185 (.067) [-.01, .37]
External Density	-.084 (.296) [-.24, .07]	**-.365 (.000) [-.52, -.18]**
Event	.004 (.964) [-.15, .16]	**-.322 (.001) [-.49, -.13]**
Place	-.096 (.228) [-.25, .06]	**-.451 (.000) [-.60, -.28]**
Time	.056 (.483) [-.10, .21]	**-.203 (.044) [-.38, -.01]**
Perceptual	-.008 (.921) [-.16, .15]	**-.305 (.002) [-.47, -.11]**
Emotion/Thought	.095 (.237) [-.06, .25]	-.178 (.078) [-.36, .03]
Semantic	**-.177 (.026) [-.32, -.02]**	-.126 (.213) [-.32, .07]
Repetition	-.063 (.429) [-.22, .09]	.081 (.426) [-.12, .27]
Other	.004 (.958) [-.15, .16]	-.101 (.322) [-.29, .10]
Second Pattern (Figure 4B)		
Internal Density	**.463 (.000) [.33, .58]**	.025 (.808) [-.17, .22]
Event	**.363 (.000) [22, .49]**	-.111 (.272) [-.30, .09]
Place	**.355 (.000) [.21, .48]**	.045 (.659) [-.15, .24]
Time	**.404 (.000) [.27, .53]**	-.028 (.781) [-.22, .17]
Perceptual	.144 (.070) [-.01, .29]	.123 (.224) [-.08, .31]
Emotion/Thought	-.076 (.343) [-.23, .08]	**.206 (.041) [.01, .39]**
External Density	**.264 (.001) [.11, .40]**	**-.217 (.031) [-.40, -.02]**
Event	**.329 (.000) [.18, .46]**	-.113 (.267) [-.30, .09]
Place	.141 (.077) [-.02, .29]	-.055 (.590) [-.25, .14]
Time	.106 (.185) [-.05, .26]	.018 (.858) [-.18, .21]
Perceptual	.109 (.173) [-.05, .26]	-.058 (.567) [-.25, .14]
Emotion/Thought	**.169 (.034) [.01, .32]**	-.136 (.179) [-.32, .06]
Semantic	.008 (.919) [-.15, .16]	-.080 (.430) [-.27, .13]
Repetition	.004 (.955) [-.15, .16]	-.161 (.111) [-.35, .04]
Other	.120 (.132) [-.04, .27]	**-.234 (.020) [-.41, -.04]**

Note. p*r* values displayed with *p* values in parentheses and 95% confidence intervals in brackets. Bold denotes $p < .05$.