Relationships between age-associated changes in context memory and cortical thickness across the adult lifespan

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Abstract

Episodic memory is the ability to remember an item or event in rich contextual detail. Healthy aging is associated with declines in this ability in addition to widespread cortical thinning. These parallel declines suggest that age-related changes in cortical thickness may contribute to episodic memory decline with age. As few studies have directly examined this association, the current study aims to cross-sectionally explore whether regional cortical thickness (CT) mediates the relationship between age and episodic memory as measured by a context memory task for faces. The brain regions examined in the current study have been previously associated with episodic memory performance and demonstrate age-associated cortical thinning in the current healthy lifespan sample (N= 114). The regions on the left were lingual, fusiform, rectus, parahippocampal, superior frontal, caudal middle frontal, inferior frontal, angular, and supramarginal gyri; and the regions on the right were parahippocampal, rectus, angular, supramarginal, superior temporal, middle temporal, superior frontal, caudal middle frontal, and inferior frontal gyri. Conditional mediation models were tested using bootstrapping in order to determine whether and how these regions mediate age-associated changes in performance on the context memory task. It was found that CT of the right parahippocampal and superior frontal gyri were related to performance differentially with age, lending support to the conception that grey matter-episodic memory relationships change with age. The models also demonstrated that regional CT mediated age-associated variance in context memory performance in a way that is conditional upon age. Furthermore, the current analysis identified a dissociation between CT of a region mediating age-associated variance in accuracy, and predicting accuracy after controlling for age. Overall, these findings underscore the importance of implementing a longitudinal approach because the examination of intra-individual changes over time would better tease out

how age-related changes in CT affect context memory, without the need to account for CT-episodic memory relationships due to factors other than age.

Résumé

La mémoire épisodique est la capacité à se souvenir d'un élément ou un événement dans le détail riche contextuel. Le vieillissement normale est associé à une baisse de cette capacité, en plus de l'amincissement cortical généralisée. Ces baisses parallèles suggèrent que les changements liés à l'âge dans l'épaisseur corticale (EC) peuvent contribuer au déclin de la mémoire épisodique avec l'âge. Comme peu d'études ont examiné directement cette association, cette étude vise à explorer par methode transversale si l'épaisseur corticale (EC) régionale médiatise la relation entre l'âge et la mémoire épisodique telle que mesurée par une tâche de mémoire de contexte pour les visages. Les régions du cerveau examinées dans la présente étude ont été précédemment associée à la performance de la mémoire épisodique et démontre un amincissement associée à l'âge dans un échantillon d'adultes en bonne santé (N = 114). Les régions sur la gauche étaient les gyri lingual, fusiforme, rectus, parahippocampal, frontal supérieur, frontal moyen caudale, frontal inférieur, angulaire, et supramarginal; et les régions sur la droite étaient les gyri parahippocampal, rectus, angulaire, supramarginal, supérieure temporelle, temporelle, frontale supérieure du milieu, frontal moyen caudale et frontal inférieur. Des modèles de médiation conditionnelle ont été testés à l'aide de bootstrapping afin de déterminer si et comment ces régions médiatisent les changements liés à l'âge de la performance sur la tâche de mémoire de contexte. Il a été constaté que la EC des gyri parahippocampal droite et frontale supérieure droite étaient liés à la performance différentiellement avec l'âge, ce qu'appuye la conception que les relations de mémoire épisodique- matière gris changent avec l'âge. Les modèles ont également démontré que EC régionale médite la variance associée à l'âge de la performance de mémoire de contexte d'une

manière qui est conditionnelle à l'âge. Aussi, l'analyse courante a identifié une dissociation entre la médiation de EC sur la variance de performance associée à l'âge, et la capacité de EC regionale pour prédire la performance après avoir ajuster pour l'âge. Dans l'ensemble, ces résultats soulignent l'importance de mettre en œuvre une approche longitudinale parce que l'examen des changements intra-individuels au fil du temps serait mieux pour démêler comment les changements d'EC associée à l'âge affectent la mémoire de contexte, sans la nécessité de tenir compte des relations d'EC- mémoire épisodique en raison de facteurs autres que l'âge.

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Contribution of Authors

As first author, I, Alexander Swierkot participated in all aspects of conducting the research for and preparing this thesis. This work included assisting in programming the behavioural task, supporting Stamatoula in testing participants, implementing the Chakravarty Lab's image analysis pipelines, designing and implementing all statistical analyses, and writing all sections of this thesis. Raihaan Patel provided support in implementing the Chakravarty Lab's image

analysis pipelines and edited the methods section of this thesis. Stamatoula Pasvanis tested participants and maintained the databases used. Mallar Chakravarty provided support and guidance in implementing the Chakravarty's Lab's image analysis pipelines. And finally, Maria Natasha Rajah designed the behavioural paradigm, established the imaging and testing protocols, provided support and guidance for all the research conducted, and edited the entire thesis.

Relationships between age-associated changes in context memory and cortical thickness across the adult lifespan

1. Introduction

Healthy aging is associated with declines in the ability to remember an item or event in rich contextual detail (episodic memory; Tulving, 1984) and widespread cortical thinning (Burzynska et al., 2012; Cansino et al., 2013, 2015; Dickerson et al., 2009; Erngrund, Mántylá, & Nilsson, 1996; Fjell et al., 2006; Fjell, Walhovd, Fischl, & Reinvang, 2007; Fonseca, Zimmermann, Scherer, Parente, & Ska, 2010; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Johnson & others, 1996; Lemaitre et al., 2012; M. Natasha Rajah, Kromas, Han, & Pruessner, 2010; M. N. Rajah & McIntosh, 2008; Salat et al., 2004; Spencer & Raz, 1995; Thambisetty et al., 2010; Trott, Friedman, Ritter, & Fabiani, 1997; Uttl & Graf, 1993; Ziegler et al., 2010). These parallel declines suggest that age-related changes in cortical thickness (CT) may in part contribute to episodic memory decline with age. As few studies have directly examined this association, it is the focus of the current study.

1.1. Parallel age-associated declines in episodic memory and cortical thickness

Behavioral and neuroimaging studies have shown that episodic memory tasks that assess one's ability to encode and retrieve contextual details (context memory tasks) are more sensitive at detecting age-associated episodic memory deficits, compared to item recognition tasks (Cansino et al., 2013; Johnson & others, 1996; M. Natasha Rajah et al., 2010; M. N. Rajah & McIntosh, 2008; Spencer & Raz, 1995; Trott et al., 1997). Additionally, studies examining item memory in young and middle-aged adults do not report significant age differences in performance (Fonseca et al., 2010; Grady et al., 2006). On the other hand, significant deficits on tasks of context memory have been detected between the 4th and 6th decades of life (Erngrund et

al., 1996; Kwon et al., 2015; Uttl & Graf, 1993). Furthermore, Cansino et al. (2013; 2015) report linear declines in context memory performance during each decade of adulthood. Overall, research to date indicates that recognition memory remains relatively stable from young adulthood to middle age, but shows some decline during older adulthood; whereas studies of context memory show a steady decline in episodic memory across the adult lifespan. Given evidence of age-associated variability in context memory performance throughout the entire adult life span, tests of context memory are a useful index of episodic memory to elucidate relationships between episodic memory and CT.

In addition to episodic memory declines, age-associated CT changes have been found to be widespread, but heterogeneous across the cortex (Burzynska et al., 2012; Fjell et al., 2006; Lemaitre et al., 2012; Salat et al., 2004; Thambisetty et al., 2010; Ziegler et al., 2010). Cross-sectional studies implementing full lifespan samples or strictly comparing younger and older adults have identified age-associated cortical thinning in frontal, lateral temporal, parietal, and visual regions (Burzynska et al., 2012; Fjell et al., 2006; Lemaitre et al., 2012; Salat et al., 2004; Ziegler et al., 2010). A longitudinal study implementing a sample of older adults has not only identified age-related cortical thinning in these regions, but also the cingulate cortex (Thambisetty et al., 2010). Cross-sectional studies, however, have uncovered discrepant results regarding the cingulate cortex (Burzynska et al., 2012; Fjell et al., 2006; Lemaitre et al., 2012; Salat et al., 2004; Thambisetty et al., 2010; Ziegler et al., 2010). Some studies have reported cortical thinning in this region (Burzynska et al., 2012; Lemaitre et al., 2012), no association (Salat et al., 2004), or thickening (Fjell et al., 2006; Ziegler et al., 2010). It should also be noted that Fjell et al. (2006) also reported age-associated cortical thickening in medial prefrontal cortex; however, they did not account for multiple comparisons. Overall, however, there is a

consensus of significant age-associated cortical-thinning in frontal, lateral temporal, parietal, and visual regions across the adult lifespan (Burzynska et al., 2012; Fjell et al., 2006; Lemaitre et al., 2012; Salat et al., 2004; Thambisetty et al., 2010; Ziegler et al., 2010).

1.2. Relationships between cortical grey matter and episodic memory

Walhovd et al. (2006) cross-sectionally examined the relationship between episodic memory as measured by long-term recall on the California Verbal Learning Task (CVLT) in a full lifespan sample. Through a whole-brain vertex-wise analysis they found that after controlling for age, long-term recall (across months) was positively associated with cortical thickness in bilateral gyrus rectus, bilateral MFG, bilateral parieto-occipital sulcus, bilateral lingual gyri, right temporal and parietal lobes, and left precuneus throughout the adult lifespan. These regions happen to overlap with regions demonstrating significant cortical thinning with age, suggesting that age-associated cortical thinning in these regions may underpin age-associated episodic memory declines. Head et al. (2008) confirmed this suggestion for the prefrontal cortex (PFC) by implementing a path analysis in a sample consisting strictly of young and older adults. They found that mean PFC volume mediates age-associated variance in episodic memory performance, as measured by a composite score from tasks of recognition and context memory, through performance on executive processing tasks.

Taking into account that episodic memory-grey matter relationships change with age, Gautman et al. (2011) examined relationships between cortical thickness of the lateral frontal cortex and episodic memory as measured by recall on the CVLT within middle-aged and older adults. They found that in middle-aged adults, greater cortical thickness in this region was associated with better performance on the CVLT; whereas, in older adults, smaller cortical thickness was associated with better performance on the CVLT. This negative relationship

between grey matter of the lateral prefrontal cortex and episodic recall in older adults was also found by Duarte et al. (2006). More specifically, they found via a voxel-based morphometry (VBM) analysis that regional volumes in the inferior frontal, middle frontal, and superior frontal gyri were negatively correlated with CVLT scores. Furthermore, Duarte et al. (2006) also found a negative relationship between inferior parietal volume and recall.

Collectively, mixed findings have indicated that episodic memory-grey matter relationships are age-dependent and both negative and positive. As no study has been comprehensive, findings seem to contradict eachother. The analyses implemented by Walhovd et al. (2006) and Head et al. (2008) did not consider the age-dependency of episodic memory-grey matter relationships and therefore identified relationships that are invariant over the course of adulthood. Also, although Gautman et al. (2011) and Duarte et al.'s (2006) within age group analyses are sensitive to age-dependent grey matter- episodic memory relationships, the age ranges examined are limited (excluding young adults and both young and middle-aged adults respectively). Additionally, Walhovd et al.'s (2006) analysis was the only one to examine these relationships across the whole brain, and Head et al. (2008) was the only study to measure episodic memory beyond recall on the CVLT. Overall these studies are either limited by the cortical regions examined, age-groups examined, use of item memory tasks that show little variability until late in life, or not accounting for age-related shifts in brain-behaviour relationships.

1.3. Objectives

To help clarify the nature of grey matter-episodic memory relationships the current study aims to comprehensively assess CT-context memory relationships across the adult lifespan. Specifically, the current study aims to confirm age-related episodic memory declines and age-related cortical thinning. Additionally, the current study aims to explore whether the cortical

thickness of brain regions that demonstrate significant age-associated cortical thinning and have been previously associated with episodic memory mediate the relationship between age and episodic memory. We also aim to determine whether these mediation relationships are conditional upon age. Due to previous findings of differential grey matter-episodic memory relationships according to age (Duarte et al., 2006; Gautman et al., 2011), we expect to find CT-context memory relationships that are conditional upon age, and that regional CT will conditionally mediate age-associated variance in context memory.

2. Methods

2.1. Participants

114 adults (age range 19-76 years; mean age 46.92; mean education 15.69 years; 77 females) participated in the study. At the time of testing, all participants were healthy and had no history of neurological or psychological illness. All participants were right-handed as measured by the Edinburgh Inventory for Handedness (Oldfield, 1971). To screen out individuals suffering from psychiatric symptoms and dementia, and to obtain measures of memory and language function, volunteers were administered a battery of neuropsychological tests (Kwon et al., 2015): the Mini-International Neuropsychiatric Interview (M.I.N.I.) [inclusion cut-off score ≤ 2, (Dahmani 2012)], Mini Mental Status Exam [MMSE, exclusion cut-off score < 27], (Folstein, Folstein et al. 1975)], the Beck Depression Inventory (BDI) [inclusion cut-off < 15 (Beck 1987)], the California Verbal Learning Task (CVLT) [exclusion cut off determined per case using age & education (Norman, Evans et al. 2000)], the American National Adult Reading Test (NART) [inclusion cut-off ≤ 2.5 SD (Spreen and Strauss 1997)]. Additional medical exclusion criteria included having a history of or current diagnosis of diabetes, untreated cataracts and glaucoma, and a current diagnosis of high cholesterol levels and/or high blood pressure left untreated in past

2 years. Moreover, anyone with a first-degree relative who had been diagnosed with Alzheimer's disease was excluded from the study.

2.2. Behavioural methods

As a measure of episodic memory, the current study used a spatial context memory for faces paradigm, described in detail in a previous study (Kwon et al., 2015). To summarize, subjects were told that they would be participating in a computer-based memory experiment for non-famous faces. Encoding and retrieval phases were separated by a 1-minute alphabetizing distraction task. Additionally, there were easy and hard versions of the task, based on encoding load. Prior to encoding, participants were informed to memorize the spatial location of the faces presented, and whether they were about to see 6 faces (easy tasks) or 12 faces (hard tasks). During the encoding phase, participants were instructed to focus on a centered fixation cross while faces appeared serially on either the left or the right of the cross as in figure 1. Faces were each presented for 2 seconds, with a variable inter stimulus time interval (ITI; mean = 4.66 seconds). Furthermore, participants were asked to make a pleasantness judgment in response to each face because it has been previously found that such evaluations at encoding improve subsequent memory (Grady et al., 2002). At retrieval, participants were shown pairs of previously viewed faces that were vertically oriented in relation to the centered fixation cross as in figure 1. Each pair was presented for 6 seconds with variable ITI (mean = 4.66 seconds). During this phase, participants were instructed to select which face they previously saw on either the left or the right, depending on the trial.

2.3. MRI data acquisition

Scanning of subjects was performed in a 3T Siemens Trio scanner at the Douglas Brain Imaging Center. Subjects were asked to lie in a supine position in the MRI scanner while

wearing a standard head coil. At the start of the experiment, T1-weighted structural volumes were acquired using a 5 min gradient echo (GRE) ADNI (Alzheimer's Disease Neuroimaging Initiative) sequence (TR = 2300 msec, TE = 2.98 msec, flip angle 9º, 176 1mm sagittal slices, 1x1x1 mm voxels, FOV 256mm^2).

2.4. Image processing and analysis

Cortical thickness was estimated at 81924 points across the cortex (40962 per hemisphere) on the T1-weighted images using the automated CIVET 1.1.10 pipeline (Collins et al., 1994; Lyttelton et al., 2006). The images were linearly registered to standardized MNI-Talairach space based on the ICBM 152 model using a 9-parameter linear transformation (Mazziotta et al., 2001) and corrected for intensity non-uniformity using the N3 algorithm (Sled et al., 1998). A non-linear registration to the model (Collins et al., 1994) was then applied. Next, images were segmented into WM, grey matter, CSF and background (Zijdenbos et al., 2002). Partial volume estimates were applied to define deep sulci (Kim et al., 2005). Deformable ellipsoid polygonal models were optimized using Constrained Laplacian Automated Segmentation with Proximities (CLASP) to fit the WM-grey matter and grey matter-CSF boundaries (Kim et al., 2005; MacDonald et al., 2000). Cortical thickness was calculated by measuring the distance between the white and grey surfaces (Lerch & Evans, 2005). These measurements were then blurred using a 20mm kernel to produce the final thickness maps (Lerch et al., 2006).

Using an automated tool (https://github.com/CobraLab/lpba40-local-civet-measures) mean cortical thickness and total surface area was calculated at 26 regions of interest (ROIs) per hemisphere, based on the LONI Probabilistic Brain Atlas (LPBA 40; Shattuck et al., 2008).

2.5. Statistical analyses

To mitigate concerns of education as a confounding variable, age was regressed against education to determine whether they were significantly related.

Accuracy on the spatial tasks was calculated as a percentage of correct responses on easy and hard tasks separately. Two simple linear regressions were run to examine age-related changes in spatial context memory. The two behavioural metrics (spatial easy accuracy and spatial hard accuracy) were regressed against age to examine age-associated variability in context memory within the current sample.

To examine relationships between cortical thickness and age in the current dataset, a whole brain vertex-wise analysis of cortical thickness changes with age was conducted, examining left and right hemispheres separately. The following general linear model (GLM) was fitted to each one of the 40962 cortical points per hemisphere:

$$Y = b_0 + b_1\text{Age} + b_2\text{Sex} + b_3(\text{Age*Sex}) + \varepsilon$$

False discovery rate (FDR) corrections were applied to p-values to account for multiple comparisons.

Next, to examine relationships between age-related cortical thickness and context memory changes, ROIs were selected based on regions that showed cortical thinning and have been previously associated with episodic memory (medial temporal lobe, parietal regions, prefrontal cortex, lingual gyurs, superior and middle temporal gyri).

Using the SPSS custom dialogue tool PROCESS (Hayes, 2013; Preacher & Hayes, 2008), parallel conditional mediation models were applied to answer whether the selected ROIs, mediate or conditionally mediate age-related episodic memory decline as measured by spatial

context memory tasks. Mediation effects were tested by calculating bias-corrected 95% confidence intervals using bootstrapping with 1000 resamples. In line with the vertex-wise analysis, separate models were applied for the left and right hemispheres.

3. Results

3.1. Age and education

Mitigating concerns of education confounding age-effects in our analyses, years of education was regressed against age, and it was found that age did not significantly predict education in our sample ($F(1,112)=3.583$, $p=0.061$; adjusted $R^2=0.022$).

3.2. Age related changes in spatial context accuracy

Our simple linear regression analysis uncovered that both behavioural metrics were significantly related to age. Spatial easy accuracy decreases with age ($F(1,112)= = 9.01$, $p = 0.003$; Adjusted $R^2=0.066$; table 1; figure 2), and spatial hard accuracy decreases with age ($F(1,112) = 18.92$, $p < 0.001$; Adjusted $R^2=0.137$; table 1; figure 2).

3.3. Age-related cortical thickness changes

The results from the vertex-wise whole brain analysis may be viewed in figure 3, a t-map for cortical thinning with age, while controlling for sex and age by sex interactions. Figure 3 illustrates significant cortical thinning with age in frontal, parietal, temporal, cingulate, and visual regions.

3.4. Selected ROIs for mediation analysis

The ROIs selected (see methods for criteria) on the left were lingual, fusiform, rectus, parahippocampal, superior frontal, caudal middle frontal, inferior frontal, angular, and supramarginal gyri. The ROIs selected on the right were parahippocampal, rectus, angular,

supramarginal, superior temporal, middle temporal, superior frontal, caudal middle frontal, and inferior frontal gyri. These ROIs are highlighted in figure 4.

3.5. Mediation analysis

Conditional mediation analyses were conducted using ordinary least squares path analysis to determine whether cortical thickness of the selected ROIs mediate, or conditionally mediate, age-associated variance in accuracy on spatial context memory tasks. Conceptual diagrams of the models may be viewed in figures 5a & b. Separate models were run for left and right hemispheres and for spatial easy and spatial hard tasks, for a total of 4 models (age-associated variance of spatial easy mediated by right hemisphere ROIs; age-associated variance of spatial easy mediated by left hemisphere ROIs; age-associated variance of spatial hard mediated by right hemisphere ROIs; and age-associated variance of spatial hard mediated by left hemisphere ROIs). The conditional mediation effects were tested at three different representative ages across the adult lifespan: younger adulthood (age=29.2504), midlife (age=46.9211), and older adulthood (age=64.5917). These ages were selected according to the mean age of the sample (46.9211) plus 1 (64.5917) and minus 1 (29.2504) standard deviation from the mean.

Mediation models examining age-associated variance of spatial easy task accuracy turned out to be insignificant ($p > 0.05$).

Significant path coefficients for the model examining how cortical thickness of the right hemisphere ROIs mediated age-associated variance in spatial hard accuracy may be found in table 2. These coefficients reaffirmed significant cortical thinning in the 9 selected ROIs. Also, significant age by ROI interactions indicated that cortical thickness of the right parahippocampal and superior frontal gyri were in turn related to task accuracy in an age-dependent manner. To understand the nature of these interactions, a follow-up sub-groups analysis was conducted. The

sample was divided into young (aged 19-35), middle-aged (aged 40-58 years), and older (aged 60-76 years) adults. Simple linear regressions, regressing task accuracy against cortical thickness, were run in each of the groups separately (see figure 6). In conjunction with the significant main effect of parahippocampal cortical thickness on task accuracy (coeff. = 0.5959), these regressions clarified that cortical thickness of this ROI was positively related to task accuracy throughout the entire lifespan sample, but more so in younger adults (beta = 0.139; figure 6). They also clarified that cortical thickness of the right superior frontal gyrus is positively related to task accuracy in middle-aged (beta = 0.455; figure 6) and older adults (beta = 0.294; figure 6). The tests of mediation found that age conditionally indirectly affected accuracy through both of these ROIs (figure 7a). Specifically, cortical thickness of the right parahippocampal gyrus (PHG) significantly negatively mediated age-associated variance in accuracy among young adults (bootstrap CI = -0.0029 to -0.0001); and cortical thickness of the right superior frontal gyrus (SFG) significantly negatively mediated age-associated variance in accuracy among older adults (bootstrap CI = -0.0075 to -0.0010). Additionally, although the path coefficients were not significant for the relationship between CT of the right caudal middle frontal gyrus (MFG) and accuracy, CT of right caudal middle frontal gyrus significantly positively mediated age-associated variance in older adults (bootstrap CI = 0.0003 to 0.0059). Finally, age did not significantly impact task accuracy independent of its effects on the 9 cortical regions in the model (coeff. = -0.0186, p = 0.3306).

Significant path coefficients for the model examining whether and how cortical thickness of the selected ROIs on the left mediate age-associated variance in spatial hard accuracy may be found in table 3. Again, this model reaffirms age-associated cortical thinning in the 9 left hemisphere selected ROIs. Within this model, cortical thickness of the left angular gyrus

negatively predicted accuracy, and cortical thickness of left lingual gyrus positively predicted accuracy throughout the entire lifespan sample. The tests of mediation found that CT of the left lingual gyrus significantly negatively mediated age-associated variance in task accuracy in young (bootstrap CI = -0.0040 to -0.007) and middle-aged (bootstrap CI = -0.0029 to -0.0005) adults; while cortical thickness of the left angular gyrus significantly positively mediated age-associated variance in task accuracy in young adults (bootstrap CI= 0.0001 to 0.0049). Also age did not significantly impact task accuracy, after taking into account its effects on the cortical thickness of these 9 selected ROIs (coeff. =-0.0383, p=0.0121).

4. Discussion

4.1. Strengths and limitations

The current study of CT-context memory relationships is the first to comprehensively implement a full lifespan sample, examine the grey matter of the entire cortex (excluding the hippocampus), measure episodic memory through accuracy on a context memory task showing variability throughout the lifespan, and treat CT-context memory relationships as being conditional upon age. Despite these strengths, the current study is limited by its cross-sectional nature. Causality may therefore not be inferred, and all findings discussed require confirmation from a longitudinal approach. Also, the current study is limited by the use of a narrow measure of episodic memory: accuracy on a spatial context memory task. Thus, from the results of the current study, inferences may only be made with regards to the specific task used rather than episodic memory in general.

4.2. Difficult vs. easy tasks of spatial context memory

The current study only found significant models when examining the difficult tasks, as opposed to the easier tasks. This finding may be due to greater variability in the difficult task, compared to the easier task.

4.3. Mediating age-associated variance in performance vs. predicting performance after controlling for age

Our results demonstrated that regional CT may predict age-associated variance in spatial context memory performance for circumscribed periods of the lifespan, rather than throughout the lifespan. Specifically, we found that CT of the right SFG and right PHG differentially predict accuracy throughout the lifespan. These results are in line with the conception that brain-behaviour relationships change over the course of the lifespan.

Additionally, the current results are the first to our knowledge to show that a single region may be predictive of context memory performance for one period of the lifespan while mediating age-associated variance in performance during another period of the lifespan. For instance, although CT of the right PHG and left lingual gyrus positively predicted accuracy at all ages, they only negatively mediated age-associated variance in accuracy at younger ages. This partial dissociation is characterized by the fact that when CT of a region is found to be significantly predictive of accuracy, it is predictive after controlling for the effects of age. Thus, such relationships are distinct from the mediation effects on age-associated variance in performance that these regions may have.

4.4. Prefrontal cortex grey matter and episodic memory:

Studies examining the relationship between prefrontal cortex (PFC) grey matter and episodic memory have yielded mixed results (Duarte et al., 2006; Head, Rodrigue, Kennedy, & Raz, 2008; Walhovd et al., 2006). The differing results are likely due to methodological differences,

such as different measures of episodic memory and/or grey matter. Duarte et al. (2006) found negative relationships between regional PFC volumes and short-term recall in older adults, while Walhovd et al. (2006) found positive relationships between regional PFC cortical thickness and long-term recall throughout the lifespan. Additionally, Head et al. (2008) found that global PFC volume negatively mediates age-associated variance in episodic memory, as measured by a composite of recognition and context memory tasks, through performance on tasks of executive processes.

The current study, implementing measures of cortical thickness and context memory, found that the right SFG and caudal MFG exhibited oppositional mediation effects on age-associated variance in task accuracy among older adults. The right SFG negatively mediates, whereas the right caudal MFG positively mediates age-associated variance in accuracy in older adults. The negative mediation effect the right SFG has on age-associated variance in accuracy in older adults may be explained by the theoretical framework of the neuropsychological perspective (Duarte et al., 2006; Gautam, Cherbuin, Sachdev, Wen, & Anstey, 2011; Van Petten, 2004). This perspective states that grey matter declines due to normal aging are accompanied by memory declines, or that increased variability due to age-associated cortical atrophy drives brain-behaviour relationships in adults (Duarte et al., 2006; Gautam et al., 2011; Van Petten, 2004). In this sense, the current results suggest that age-associated cortical thinning in the right SFG is associated with a decline in task accuracy. On the other hand, the positive mediation effect that the right caudal MFG had on age-associated variance in performance may be understood in light of possible heterogeneous neuromodulatory roles across different cortical regions. The right caudal MFG may have an inhibitory neuromodulatory role such that it inhibits other nodes in the episodic memory network, such as the parietal cortex, as previously suggested by Gautman et al.

(2011). The fact that this region exhibits lower CT with age suggests that age-associated disinhibition is occurring, establishing a positive mediation effect on age-associated variance in accuracy. Although speculative, this explanation lines up with the neuropsychological perspective because age-associated cortical thinning in the right caudal MFG may be associated with a decline in inhibition, which may be detrimental to performance on other cognitive tasks.

It should be noted that had the PFC been treated as a homogeneous structure, these oppositional effects would not have been detectable because they would have cancelled each other out. This result underscores the importance of considering the heterogeneity of the prefrontal cortex when examining relationships between grey matter and cognitive measures.

It should also be noted that CT of the right superior frontal gyrus also significantly positively predicted accuracy in middle-aged and older adults after controlling for age, indicating that factors other than age-associated variability are at play.

4.5. Inferior parietal cortex grey matter and episodic memory

CT of the left angular gyrus positively mediated age-associated variance in accuracy in young adults, and negatively predicts throughout the lifespan, which agrees with Duarte et al.'s (2006) finding of a negative relationship between inferior parietal volume and episodic memory as measured by recall in older adults. The positive mediation effect in young adults may be explained in two ways. First, it is possible that the angular gyrus has an inhibitory role in spatial context memory such that thinning in this region results in higher performance on a context memory task. Second, if this region does not have an inhibitory role, its mediation effect may be explained by the theoretical framework of the developmental perspective (Chantôme et al., 1999; Foster et al., 1999; Hensch, 2004; Huttenlocher & Dabholkar, 1997; Knudsen, 2004; Shaw et al., 2008; Tamnes et al., 2010; Van Petten, 2004). This perspective states that regressive events

during development may result in negative correlations between grey matter and cognitive performance (Chantôme et al., 1999; Foster et al., 1999; Hensch, 2004; Huttenlocher & Dabholkar, 1997; Knudsen, 2004; Shaw et al., 2008; Tamnes et al., 2010; Van Petten, 2004). Given that developmental regressive events progress well into young adulthood (Tamnes et al., 2010; Van Petten, 2004), the current results suggest that age-associated cortical thinning of the angular gyrus early on in adulthood results in greater performance on context memory tasks. Also, the finding that cortical thickness of this region negatively predicts accuracy throughout the lifespan after controlling for age indicates that there are additional factors at play, other than age, determining the inter-individual differences that foster the negative relationship between cortical thickness in this region and task accuracy. Duarte et al. (2006) comprehensively attributed the finding of such negative relationships to being the product of events or factors, such as poor pruning of neural circuits during developmental periods, leading to pre-existing differences in grey matter rather than age-associated decline.

4.6 The parahippocampal gyrus and episodic memory

The current study found that CT of the right PHG negatively mediates age-associated variance in context memory performance exclusively among younger adults; however, CT of this region is predictive throughout the adult lifespan after controlling for age. Although no study to our knowledge specifically examined relationships between the PHG and episodic memory, a couple of studies (Rodrigue & Raz, 2004; Yonelinas et al., 2007) have looked at entorhinal cortex volume, located on the anterior portion of the PHG.

Rodrigue and Raz (2004) implemented a 5 year longitudinal study in a lifespan sample and examined relationships between entorhinal cortex volume and episodic memory as measured by a composite score of recognition and context memory tasks. Longitudinally, they found that

entorhinal cortex shrinkage is associated with episodic memory decline. Cross-sectionally, in contrast to our results, they did not find that entorhinal cortex volume was related to episodic memory after controlling for age. Also contrasting our results, Yonelinas et al. (2007)'s cross-sectional study in healthy older adults found that age-associated entorhinal cortex volume reduction is related to familiarity but not recollection, indicating that volume in this region was not related to episodic memory tasks requiring memory for context (recollection tasks). These contrasting results may be due to differences in volumetric measures used (CT versus volume), the extent of the region under study (PHG versus entorhinal cortex), and the metric of episodic memory (composite of recognition and context memory versus context memory exclusively). These discrepancies underscore the importance of implementing more standardized and comprehensive structural measures in future studies aimed at understanding regional grey matter – episodic memory relationships.

5. Conclusions

The current study sought to clarify the nature of the relationships between inter-individual age-associated CT differences and inter-individual differences in context memory performance. We found that CT of the right PHG and SFG were related to context memory performance differentially with age, lending support to the conception that grey matter-episodic memory relationships change with age. Furthermore, the current results demonstrated that regional CT mediated age-associated variance in context memory performance in a way that is conditional upon age. Finally, the current analysis identified a dissociation between CT of a region mediating age-associated variance in accuracy and predicting accuracy after controlling for age. These findings underscore the importance of implementing a longitudinal approach because the examination of intra-individual changes over time would better tease out how age-

related changes in CT affect context memory, without having to deal with CT-context memory relationships due to factors other than age.

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7. Tables

Table 1. Regressions: Age-related changes in spatial context memory

Model	Predictor	Standardized Beta	T statistic (p-value)
Spatial Easy Accuracy [F(1,112) = 9.01, p = 0.003; Adjusted R^2=0.066]			
	Age	-0.27	-3.00*
Spatial Hard Accuracy [F(1,112) = 18.92, p < 0.001; Adjusted R^2=0.137]			
	Age	-0.38	-4.35*
Spatial Hard – Spatial Easy [F(1,112) = 5.42, p = 0.022; Adjusted R^2=0.038]			
	Age	-0.22	-2.33*

Note: This table presents the significant models resulting from a regression analysis to examine age-related changes of accuracy on spatial context memory tasks under easy (low-load) and hard (high-load) conditions. *Refers to t-values that were significant at p<0.05.

Table 2. Path coefficients for spatial hard accuracy conditional mediation model with right hemisphere ROIs[a]

Paths	**Coefficients**
Age → right parahippocampal gyrus	-0.0044***
Age → right gyrus rectus	-0.0042***
Age → right superior frontal gyrus	-0.0048***
Age → right caudal middle frontal gyrus	-0.0053***
Age → right inferior frontal gyrus	-0.0053***
Age → right middle temporal gyrus	-0.0040***
Age → right angular gyrus	-0.0037***
Age → right supramarginal gyrus	-0.0051***
Age → right superior temporal gyrus	-0.0066***
Right parahippocampal gyrus → spatial hard accuracy	0.5959*
Age*right parahippocampal gyrus → spatial hard accuracy	-0.0106*
Age*right superior frontal gyrus → spatial hard accuracy	0.0255**
Sex → right parahippocampal gyrus	0.0951**
Sex → right inferior frontal gyrus	0.0572*
Sex → right middle temporal gyrus	0.0764*
Sex → right superior temporal gyrus	0.0762*

*p<0.05; **p<0.01; ***p<0.001

a. The spatial easy accuracy conditional mediation model was non-significant at p > 0.05.

Table 3. Path coefficients for spatial hard accuracy conditional mediation model with left hemisphere ROIs[a]

Paths	Coefficients
Age → left parahippocampal gyrus	-0.0046***
Age → left fusiform gyrus	-0.0025***
Age → left gyrus rectus	-0.0034***
Age → left superior frontal gyrus	-0.0052***
Age → left caudal middle frontal gyrus	-0.0063***
Age → left inferior frontal gyrus	-0.0061***
Age → left supramarginal gyrus	-0.0049***
Age → left angular gyrus	-0.0033***
Age → left lingual gyrus	-0.0043***
Left angular gyrus → spatial hard accuracy	-1.1795*
Left lingual gyrus → spatial hard accuracy	0.7445*
Sex → left parahippocampal gyrus	0.0690*
Sex → left fusiform gyrus	0.0987***
Sex → left gyrus rectus	0.0657*
Sex → left lingual gyrus	0.0958***

*p<0.05; **p<0.01; ***p<0.001

a. The spatial easy accuracy conditional mediation model was non-significant at p > 0.05.

8. Figures

Figure 1. Spatial context memory task

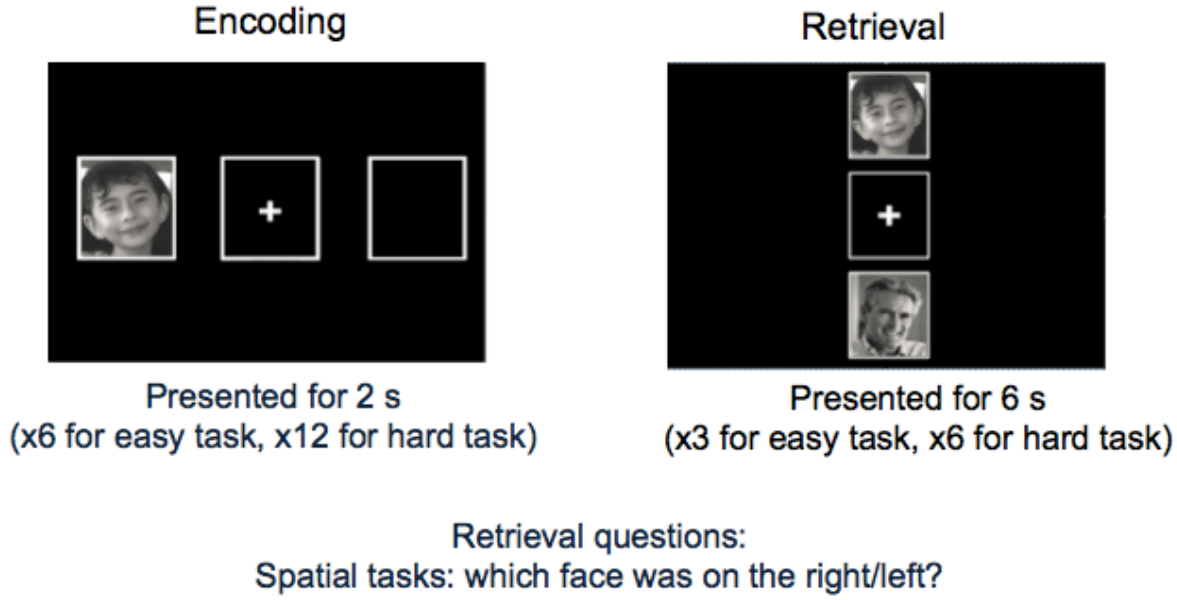


Figure 2. Scatterplots: Age vs. spatial context memory

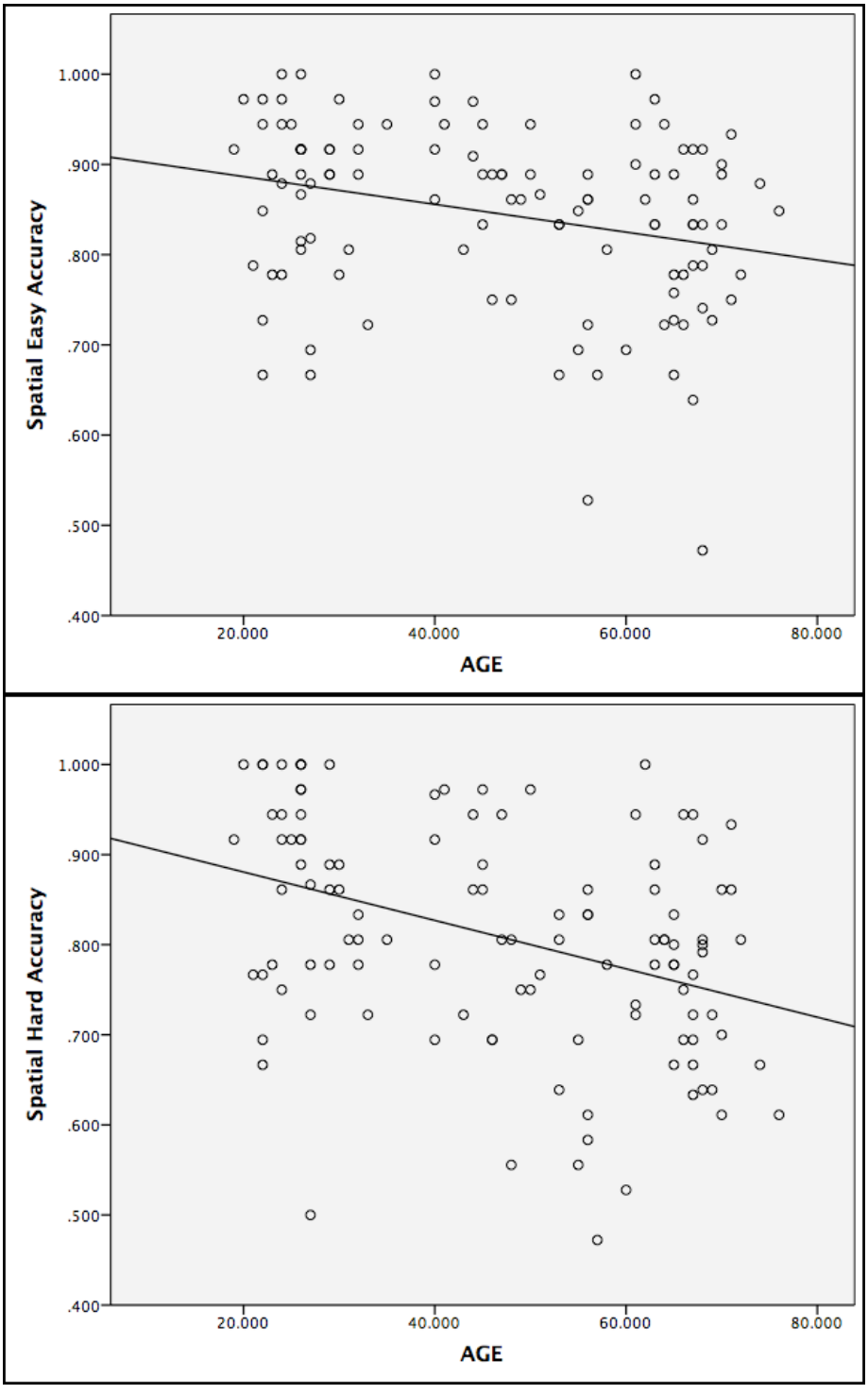


Figure 3. Cortical thinning with age: t-maps

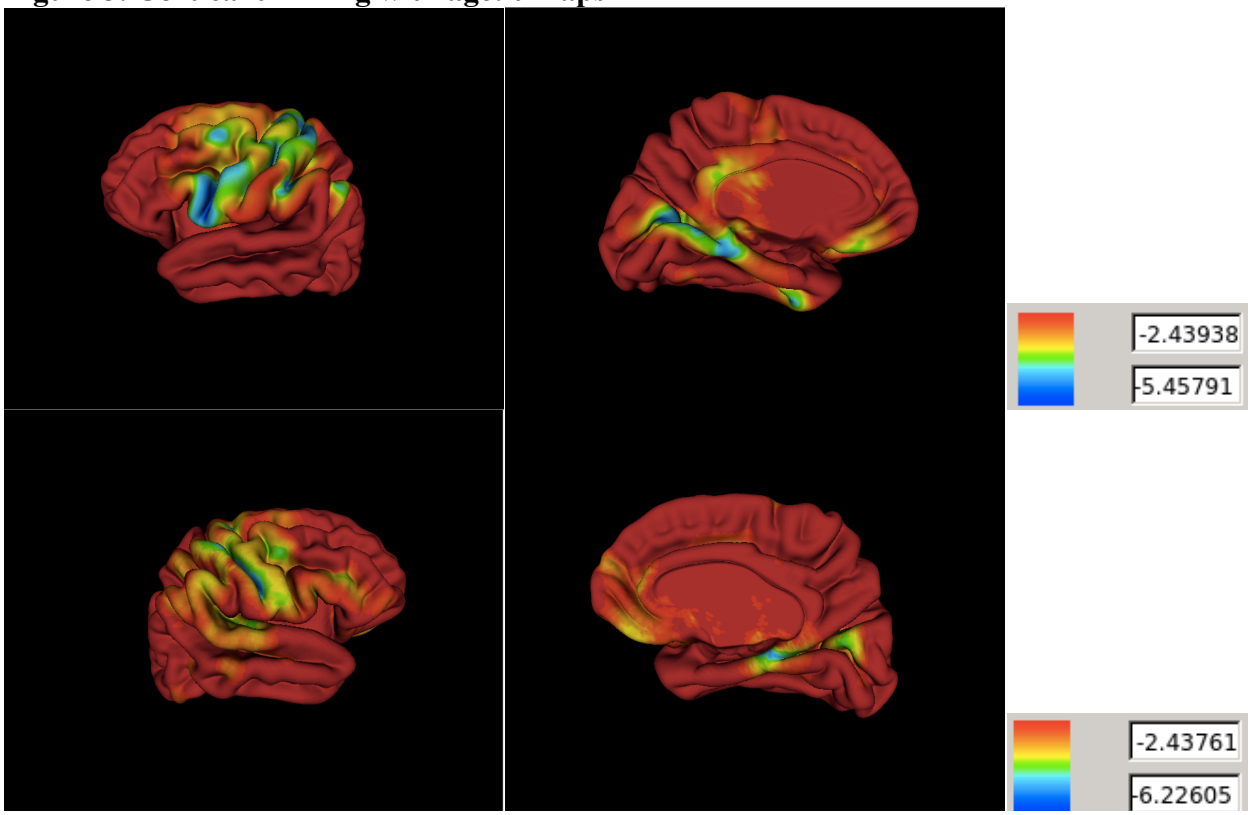
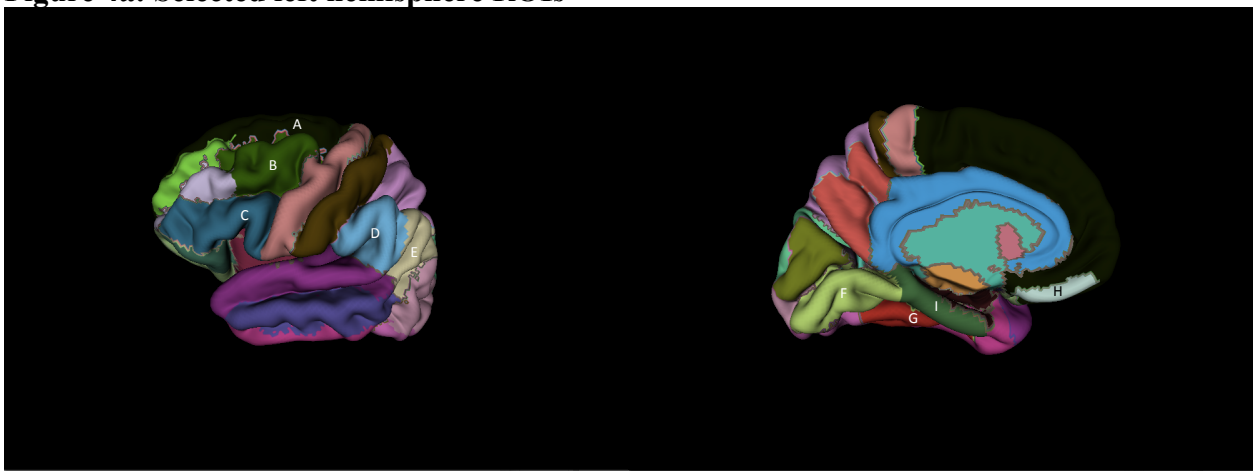
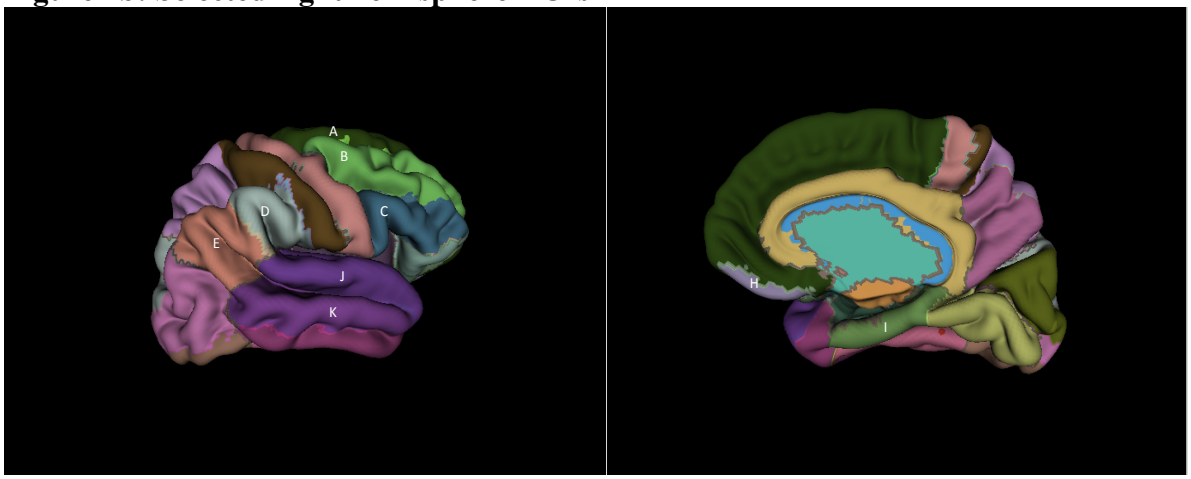


Figure 4a: Selected left hemisphere ROIs



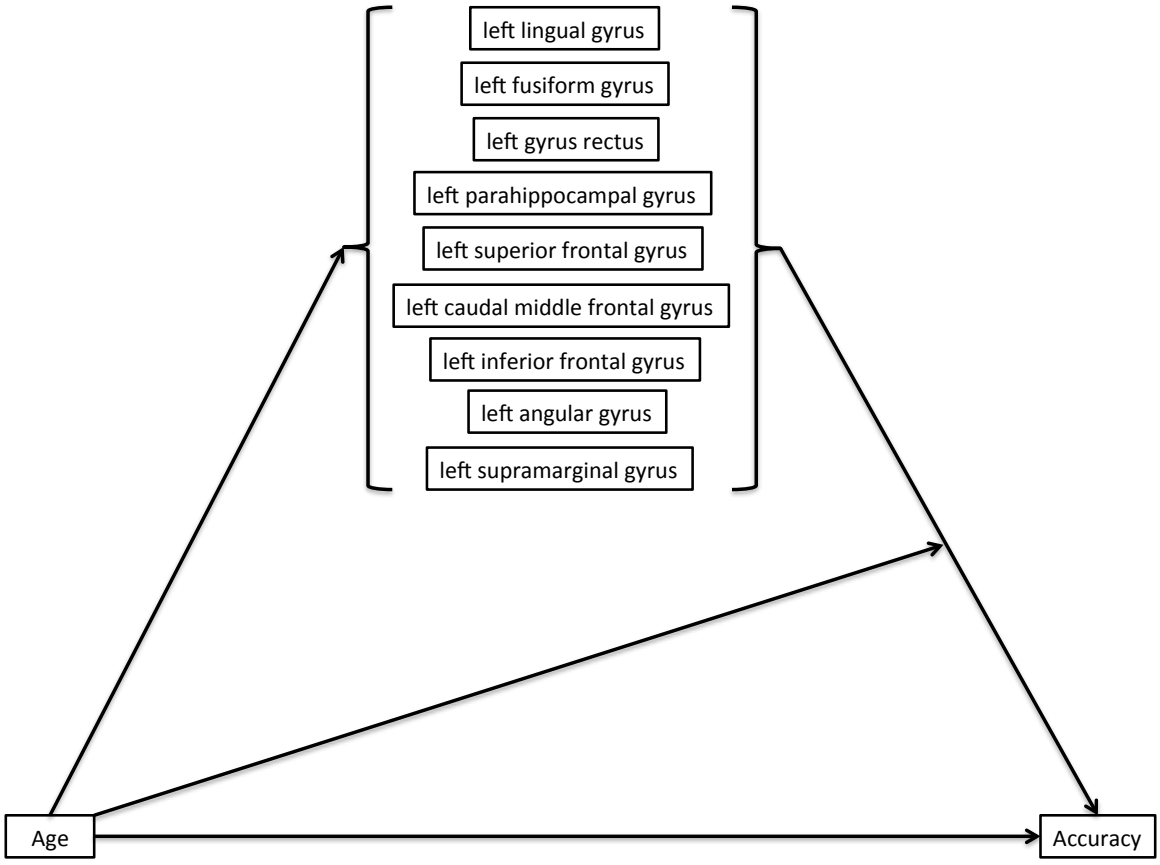
A. Superior frontal gyrus; B. Caudal middle frontal gryus; C. Inferior frontal gyrus; D. Supramarginal gyrus; E. Angular gyrus; F. Lingual gyrus; G. Fusiform gyrus; H. Gyrus rectus; I. Parahippocampal gyrus.

Figure 4b: Selected right hemisphere ROIs



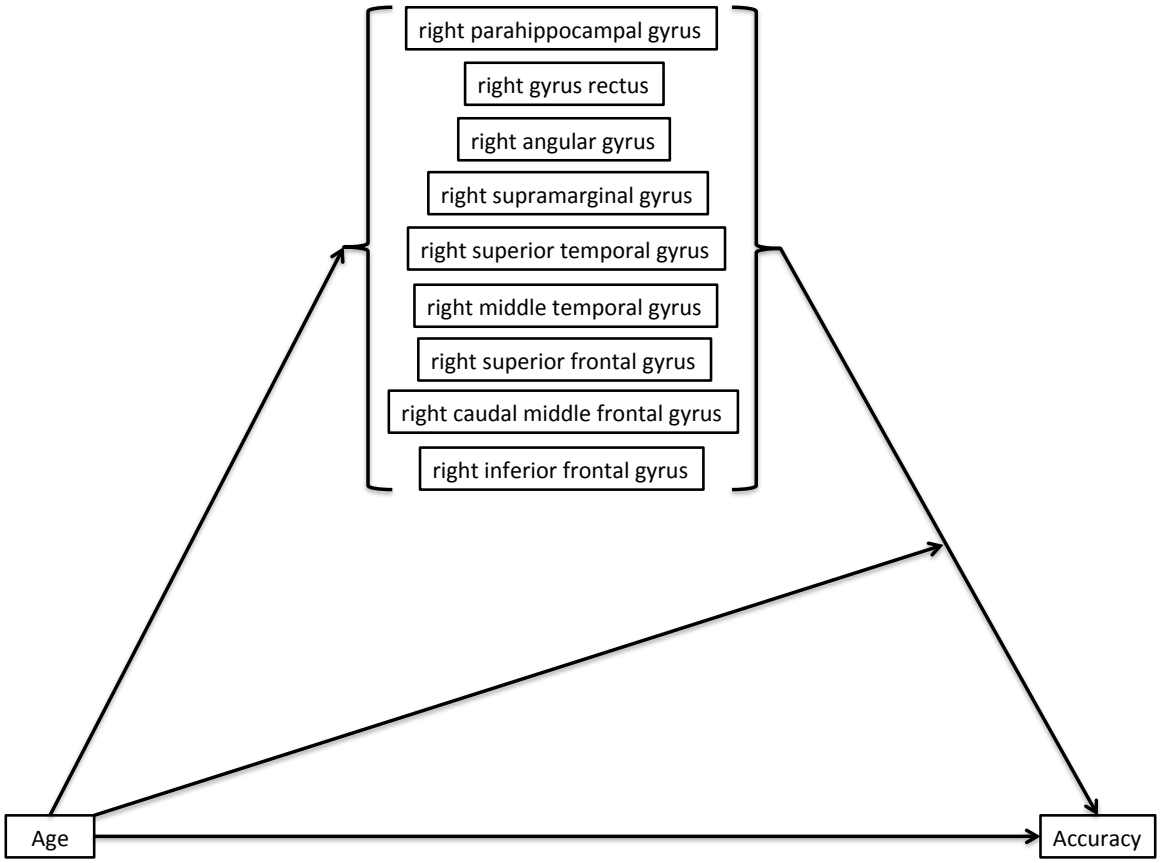
A. Superior frontal gyrus; B. Caudal middle frontal gyrus; C. Inferiror frontal gyrus; D. Supramarginal gyrus; E. Angular gyrus; H. Gyrus rectus; I. Parahippocampal gyrus; J. Superior temporal gyrus; K. Middle temporal gyrus.

Figure 5a. Conditional mediation model with left hemisphere ROIs



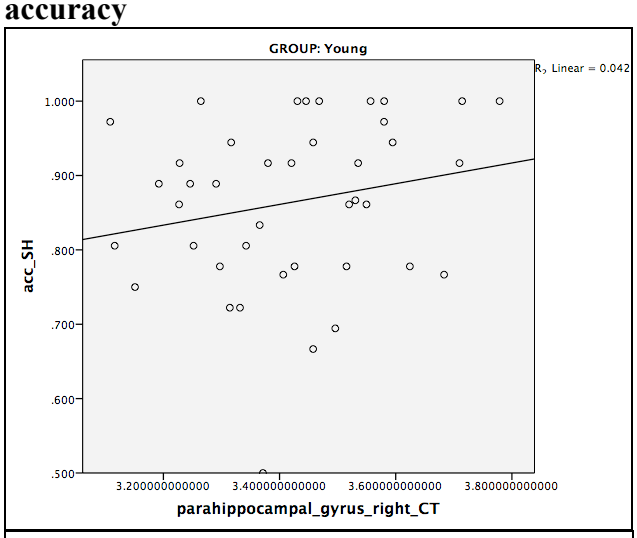
Note: This model was run for both spatial easy and spatial hard tasks. Although not depicted for clarity reasons, sex was entered into the model as a covariate.

Figure 5b. Conditional mediation model with right hemisphere ROIs

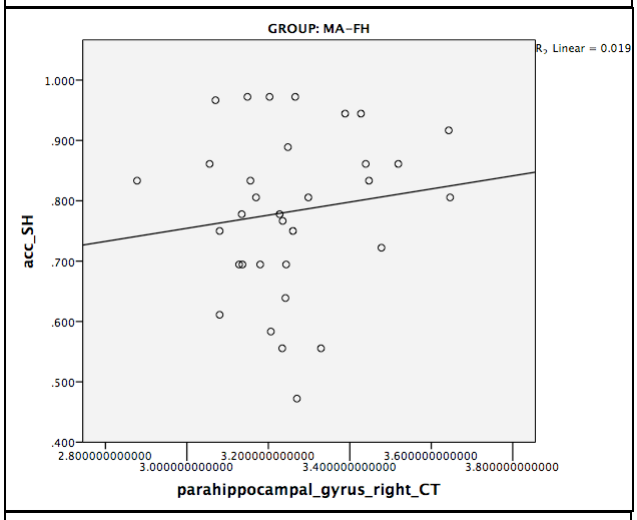


Note: This model was run for both spatial easy and spatial hard tasks. Although not depicted for clarity reasons, sex was entered into the model as a covariate.

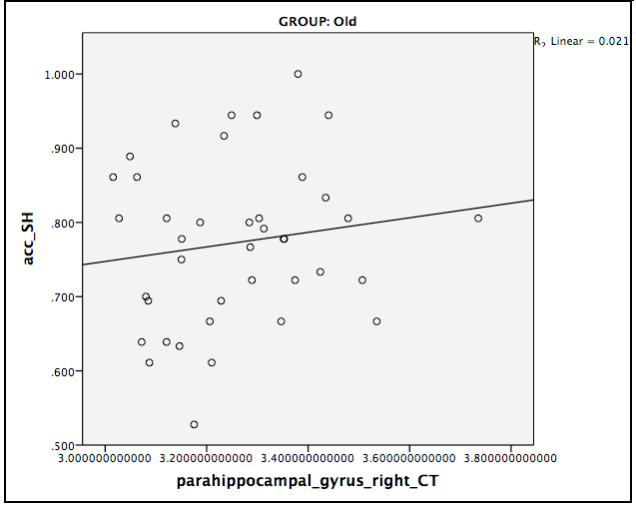
Figure 6. Within group right parahippocampal cortical thickness vs. spatial hard task accuracy



coeff.=0.139, p=0.198



coeff.=0.109, p=0.449



coeff.=0.098, p=0.372

Figure 7a.

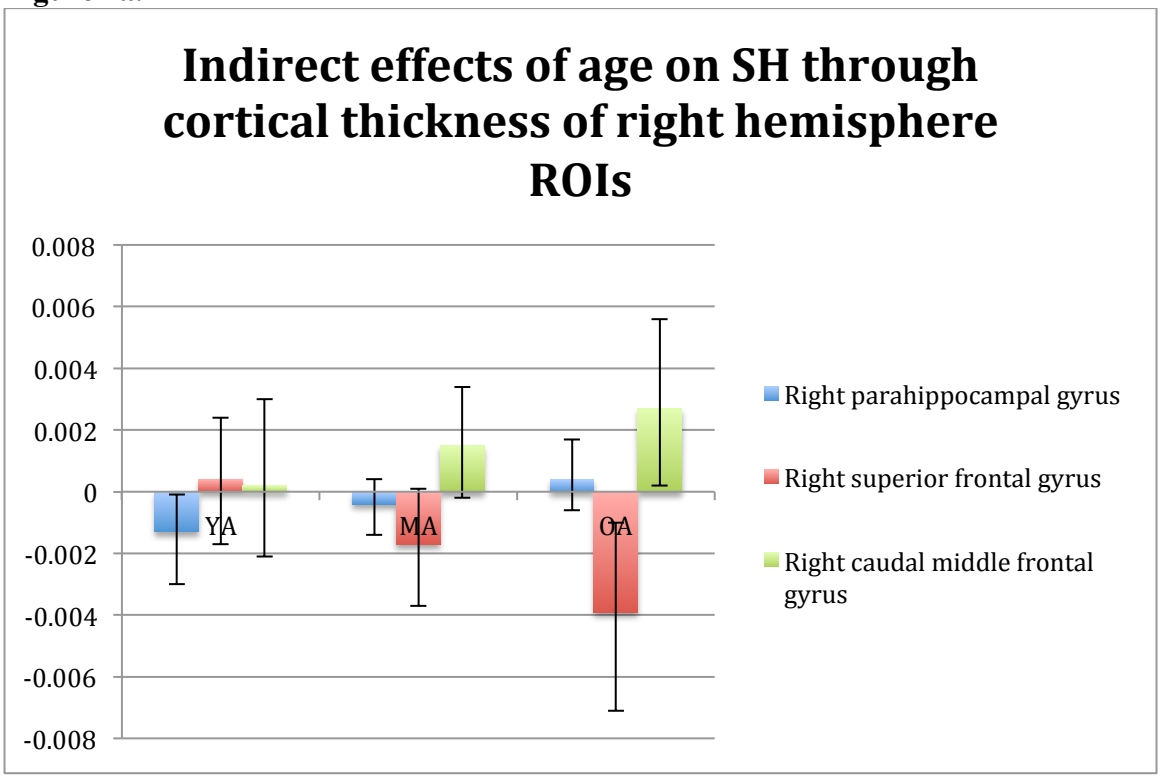


Figure 7b.