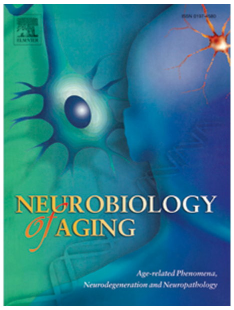

Specific and general relationships between cortical thickness and cognition in older adults: a longitudinal study

Mingzhu Hou, Marianne de Chastelaine, Brian E. Donley, Michael D. Rugg

PII: S0197-4580(20)30351-1

DOI: https://doi.org/10.1016/j.neurobiolaging.2020.11.004

Reference: NBA 11002

To appear in: *Neurobiology of Aging*

Received Date: 26 June 2020

Revised Date: 22 September 2020

Accepted Date: 2 November 2020

Please cite this article as: Hou, M., de Chastelaine, M., Donley, B.E., Rugg, M.D., Specific and general relationships between cortical thickness and cognition in older adults: a longitudinal study, *Neurobiology of Aging* (2020), doi: https://doi.org/10.1016/j.neurobiolaging.2020.11.004.

Mingzhu Hou: Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Review & Editing, Visualization.

Marianne de Chastelaine: Methodology, Validation, Investigation, Writing – Review & Editing, Supervision, Project Administration.

Brian E. Donley: Investigation, Project administration, Methodology.

Michael D. Rugg: Conceptualization, Methodology, Validation, Formal Analysis, Resources, Writing – Original Draft, Review & Editing, Supervision, Project Administration, Funding Acquisition.

Specific and general relationships between cortical thickness and cognition in older adults: a longitudinal study

Mingzhu Hou[a], Marianne de Chastelaine[a], Brian E. Donley[a]

and Michael D. Rugg[a,b]

[a]Center for Vital Longevity and School of Behavioral and Brain Sciences,

The University of Texas at Dallas, Dallas, TX 75235, USA

[b]School of Psychology,

University of East Anglia, Norwich NR4 7TJ, UK

Corresponding author: Mingzhu Hou, 1600 Viceroy Drive, Suite 800, Dallas, TX 75235.

Email: mingzhu.hou@utdallas.edu

Abstract

Prior studies suggest that relationships between regional cortical thickness and domain-specific cognitive performance can be mediated by the relationship between global cortical thickness and domain-general cognition. Whether such findings extend to longitudinal cognitive change remains unclear. Here, we examined the relationships in healthy older adults between cognitive performance, longitudinal cognitive change over three years, and cortical thickness at baseline of the left and right inferior frontal gyrus (IFG) and left and right hemispheres. Both right IFG and right hemisphere thickness predicted baseline general cognition and domain-specific cognitive performance. Right IFG thickness was also predictive of longitudinal memory change. However, right IFG thickness was uncorrelated with cognitive performance and memory change after controlling for the mean thickness of other ipsilateral cortical regions. Additionally, most identified associations between cortical thickness and specific cognitive domains were non-significant after controlling for the variance shared with other cognitive domains. Thus, relationships between right IFG thickness, cognitive performance and memory change appear to be largely accounted for by more generic relationships between cortical thickness and cognition.

Keywords: aging, cognitive performance, inferior frontal gyrus, memory change

1. Introduction

In comparison with adults aged in their 20's, from their mid-60's onward healthy adults typically demonstrate reduced performance in multiple cognitive domains, including episodic memory (Nyberg & Pudas, 2019), executive control (Braver & West, 2008) and speed of processing (Salthouse & Madden, 2007). As we discuss below, these age-related cognitive declines have been linked to structural changes in the brain.

Among available structural neuroimaging measures, cortical thickness has received extensive attention since the advent of automatic image analysis pipelines (Fischl & Dale, 2000). Both cross-sectional and longitudinal studies employing such pipelines have identified widespread and regionally heterogeneous age-related reductions in cortical thickness. The strongest and most consistent effects of age are reported for prefrontal, temporal and parietal regions (Ecker et al., 2009; Fjell et al., 2009, 2010, 2014; Lemaitre et al., 2012; Pacheco et al., 2015; Rast et al., 2018; Salat et al., 2004; Zhao et al., 2019). By contrast, thickness of primary somatosensory and motor regions, as well as the cingulate, insula, and occipital cortex, appears less sensitive to age (Fjell et al., 2009, 2010; Lemaitre et al., 2012; Thambisetty et al., 2010; Vinke et al., 2018; Zhao et al., 2019), although age-related reductions in these regions have also been reported (McGinnis et al., 2011; Salat et al., 2004; van Velsen et al., 2013).

Numerous studies have examined the relationship between cortical thickness and cognition (for review, see Kaup et al., 2011; Oschwald et al., 2019), focusing mainly on associations between thickness of discrete brain regions and performance in specific cognitive domains. Of the studies that have examined such associations in cognitively healthy older adults, most have reported positive correlations between regional thickness and cognitive performance (e.g. Burzynska et al., 2012; Fjell et al., 2006; Sun et al., 2016; Vonk et al., 2019; Westlye et al., 2011). For example, Sun et al. (2016) reported that the thickness of anterior temporal, rostral medial prefrontal, and anterior mid-cingulate cortex were each correlated with memory performance as indexed by long delay free recall scores on the California Verbal Learning Test (CVLT). Similarly, Westlye et al. (2011) reported that anterior cingulate, lateral prefrontal, and right inferior frontal cortical thickness measures were correlated with a measure of executive control. Lastly, Vonk et al. (2019) reported that while greater thickness of inferior frontal and insular temporal regions was related to higher letter fluency, thickness of other frontal regions, together with posterior temporal and inferior parietal regions, was positively correlated with category fluency.

Findings from longitudinal studies suggest that not only is there a positive relationship between regional cortical thickness and cognitive performance in older adults, but that regional thickness is also predictive of longitudinal cognitive change (e.g. Fjell et al., 2014; Knopman et al., 2018; Murphy et al., 2010; Sala-Llonch et al., 2017). For example, Knopman et al. (2018) reported that the thickness at baseline of entorhinal, inferior temporal, middle temporal and fusiform cortex correlated with both baseline performance and annualized decline over 3 years in 'general cognition' (estimated by summing standardized composite scores of memory, executive function, language and visuospatial ability). In another study, Murphy et al. (2010) reported that longitudinal reduction in the thickness of the right fusiform and inferior temporal gyri over a period of 6 months predicted subsequent decline on two long-term memory tests over 2 years. More recently, Sala-Llonch et al. (2017) reported that longitudinal reduction in the thickness of the right supramarginal, postcentral and inferior parietal cortex over 2 years positively correlated with decline on a verbal fluency test over the same period.

Although most studies investigating relationships between cortical thickness and cognitive performance have focused on individual regions, measures of thickness in different regions are strongly correlated (Ecker et al., 2009; Salthouse et al., 2015). In a small number of cross-sectional studies, general, rather than regional, measures of cortical thickness have been linked to performance in individual cognitive domains (de Chastelaine et al., 2019; Hedden et al., 2016; Kranz et al., 2018; MacPherson et al., 2017). For example, in a recent study focusing on the relationship across the adult lifespan between cortical thickness and cognitive performance (de Chastelaine et al., 2019), it was reported that mean thickness of the entire cortical mantle correlated positively with associative recognition memory performance in older adults. Similar but weaker relationships were observed for latent constructs related to memory, speed, fluency and crystallized IQ derived from a neuropsychological test battery. Similarly, Kranz et al. (2018) reported that mean cortical thickness was significantly correlated with executive function and memory performance. These authors further reported that whereas the mean thickness of individual cortical regions belonging to different large-scale brain networks (e.g. the 'default mode network') predicted executive function and memory performance in older adults, the relationships were no longer evident when mean thickness across the entire cortex was employed as a covariate.

Like regional thickness measures, measures of performance in different cognitive domains are also strongly correlated across individuals (Agelink van Rentergem et al., 2020; Carroll, 1993; Hildebrandt et al., 2011; Salthouse & Davis, 2006; Spearman, 1927). A small number of studies have examined whether cortical thickness is predictive of domain-specific cognitive abilities after controlling for the variance in performance shared across multiple domains (Lee et al., 2016; Salthouse et al., 2015; Tsapanou et al., 2019). In one study, for example, Tsapanou et al. (2019) reported that the thickness of the entorhinal cortex predicted cognitive speed in older adults independently of total cortical thickness and several other brain biomarkers. However, this relationship was no longer significant after controlling for general cognition, estimated as the sum of scores measuring speed, memory and executive function. In another study along similar lines, Salthouse et al. (2015) controlled for both overall cortical thickness and general cognition in an effort to identify unique associations between regional thickness and specific cognitive domains. The authors reported a positive correlation between a general thickness factor and a general cognition factor derived from neuropsychological test scores tapping different cognitive domains. Of importance, after controlling for these factors, nearly all associations between regional thickness and individual cognitive scores, including those related to memory, perceptual speed and vocabulary, were non-significant.

Together, the findings from the above-cited studies suggest that previously reported associations between the thickness of circumscribed cortical regions and domain-specific measures of cognitive performance in older adults are strongly mediated by relationships between more general measures of thickness and cognition. It remains to be established whether these findings extend beyond cognitive measures acquired at a single time-point to measures of longitudinal cognitive change.

Here, we examined these and related issues in the context of possible relationships between thickness of the inferior frontal gyrus (IFG) and cognitive performance. We selected the IFG as the region of interest (ROI) for these analyses because it has been strongly implicated as a moderator of the efficacy of associative memory encoding in older adults in two prior functional neuroimaging studies (de Chastelaine et al., 2011, 2016a) and, in addition, is well recognized for its role in verbal, semantic and executive processing more generally (e.g. Badre & Wagner, 2007; Costafreda et al., 2006; Moss et al., 2005). Using fMRI, de Chastelaine et al. (2011) compared encoding-related activity elicited by word pairs in young and older adults and identified age-invariant subsequent associative recognition effects (greater activity for later remembered pairs compared to later misremembered pairs) in several cortical regions, including left IFG. In older adults only, the magnitude of the effects in both left and right IFG correlated with later associative recognition performance (positively on the left, negatively on the right). In the subsequent study, which employed a similar paradigm, encoding-related activity in samples of young, middle-aged and older adults was examined (de Chastelaine et al., 2016a). Age-invariant subsequent associative recognition effects were identified in the left IFG but were evident in the right IFG only in the older group (see Duverne et al., 2009, for similar findings). Moreover, only in this age group did the effects in the IFG reliably predict associative recognition performance, albeit with both left and right IFG effects now demonstrating positive correlations with performance (see de Chastelaine et al., 2016a, for a proposed explanation of the opposite signs of the right IFG correlations in the two studies). To account for these findings, the authors proposed that with advancing age, the left IFG plays an increasingly important role as a determinant of memory performance. They conjectured that this role emerges as a result of a combination of life-long individual differences in the functional capacity of the region, and individual differences in the degradation suffered by the region over the course of an individual's lifetime. Consequently, with the passage of time the region emerges as a 'bottleneck' on episodic memory performance because of its key role in supporting the processing and encoding of inter-item associations. By this argument, the subsequent memory effects observed exclusively in the right IFG of older adults reflect an attempt to compensate for the diminished neural resources of its left-hemisphere counterpart (cf. Cabeza et al., 2018).

In the present study we investigated the relationships between individual differences in the thickness of the left and right IFG acquired at baseline, baseline performance in different cognitive domains, and longitudinal change in performance, guided by the hypothesis that greater thickness would be associated with higher cognitive function, especially in the domain of long-term memory. Motivated by prior findings indicating that relationships between region-specific structural measures and cognitive performance can be mediated by more global metrics (e.g. Salthouse et al., 2015; see also Sun et al., 2016), we also examined the relationships between the thickness of the entire left and right hemispheres and cognition, and tested whether any relationships between IFG thickness and domain-specific cognitive measures remained after controlling for either the mean thickness of all other cortical regions or performance in other cognitive domains.

2. Methods

Mean cortical thickness measures and session 1 neuropsychological test data were described in a prior report (de Chastelaine et al., 2019). Neuropsychological test data from all three test sessions were reported in Hou et al. (2020). Here, we describe relationships between baseline IFG and mean cortical thickness measures from the left and right hemispheres, baseline neuropsychological test scores, and scores obtained at follow-up after 3 years. These data have not been reported previously.

2.1 Participants

Sixty-nine heathy older adults recruited from the greater Dallas community participated in the study. They undertook the same neuropsychological test battery twice (see below), separated by a one-month period (sessions 1 and 2 respectively). Two participants were excluded from all analyses of these data (including the PCA conducted on the session 1 neuropsychological test scores, see below) because of abnormal anatomical scans.

A subgroup of 55 participants were re-administrated the neuropsychological test battery around 3 years later (session 3). Twelve older adults did not participate in session 3 due to death (*N* =1), moving away from the Dallas area (*N* = 5), loss of contact (*N* = 5) or failure to attend (*N* = 1). Cortical thickness data from two participants who participated in all three sessions could not be used because of the low quality of their T1-weighted MR images.

All participants were right-handed, fluent in English by age 5, had no history of neurological or psychiatric disease and had normal or corrected to normal vision. They each gave informed consent according to procedures approved by the UT Dallas and University of Texas Southwestern Institutional Review Boards. They were compensated at the rate of $30 per hour for their participation.

2.2 Neuropsychological test battery

The neuropsychological test battery consisted of the California Verbal Learning Test-II (CVLT; short and long delayed cued recall and free recall and delayed recognition, Delis et al., 2000), the immediate- and delayed Logical Memory tests of Wechsler Memory Scale (Wechsler, 2009), the Digit span test (Forward and Backward tests) of the Wechsler Adult IQ Scale Revised (WAIS-R), the Digit/Symbol Coding test of the WAIS-R (SDMT, Wechsler, 2001), Trail Making Tests A and B (Reitan & Wolfson, 1985), letter and category fluency tests (FAS; Spreen & Benton, 1977), the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) and Raven's Progressive Matrices (short version). For CVLT delayed recognition, both hits and false alarms were recorded. Forward and Backward tests scores were summed to provide a single digit span score. Because they were highly correlated, we calculated a composite CVLT recall score by averaging the scores from short and long delayed free and cued recall. Similarly, a composite Logical memory score was computed by averaging the scores of the immediate- and delayed Logical memory tests. These composite memory scores, together with the scores on each of the other neuropsychological tests, were used for all further analysis (see Supplemental Table 1).

Following the initial administration of the test battery, potential participants were excluded from the MRI session if they had 1) scores > 1.5 SDs below the age-appropriate norm on any long-term memory sub-test (CVLT or WMS) or on any two other tests; 2) an estimated full-scale IQ < 100 as indexed by performance on the WTAR, or 3) a score on the Mini-Mental State Examination (MMSE) < 27.

Participants who met the inclusion criteria were re-administered the test battery approximately one month later (session 2, range = 14-64 days, mean = 32 days) and, for a sub-set of these participants (see above), again after approximately 3 years (session 3, range = 2.9-3.2 years, mean = 3.0 years). The second test session was employed in an effort to attenuate re-test effects at session 3, which would lead to an underestimation of cognitive change. This approach was based on evidence that re-test effects tend to be greater for an initial re-test session than for subsequent sessions (Salthouse & Tucker-Drob, 2008), and are evident after delays of several years (Salthouse, 2009). As is detailed below, we used the mean of the scores obtained on the two sessions as the baseline for the assessment of change at Session 3. Averaging scores across sessions 1 and 2 has the additional advantage of providing more reliable estimates of baseline performance than those provided by a single test session, not least by attenuating the effects of regression to the mean (Bland & Altman, 1994).

Missing session 3 values from one participant for the SDMT, Trails A and Trails B tests were replaced by the mean performance of the remaining participants for that session. Test scores for Trail A and Trail B were in any case excluded from further analyses because of their low across-session reliability (correlations between session 1 and session 2 scores, *r* =. 45 and .40 for Trails A and B respectively; the equivalent correlations for the other tests ranged between .47 - .88, see Supplemental Table 2).

We conducted a principal component analysis (PCA) to reduce the raw test scores obtained from the neuropsychological test battery to scores on latent cognitive constructs (component scores). The PCA was conducted on the session 1 test data of the 67 eligible participants who provided scores for that session (see above). As was just mentioned, Trails A and B were not entered into this analysis because of their low test-retest reliabilities.

Test scores were standardized prior to being subjected to PCA. Three principal components with eigenvalues > 1 were retained and subjected to Varimax rotation (Kaiser, 1958). The resulting components can be broadly characterized as representing constructs associated with memory, fluency, and crystallized IQ. Loadings for each component are given in Supplemental Table 3. It is worth noting that the outcome of this PCA differs from those described previously by virtue of the absence of a ‘speed’ component (de Chastelaine et al., 2019; Hou et al., 2020; Koen et al., 2019), reflecting the omission of the Trails scores. The factor loadings for the remaining components were unaffected by this omission. To generate a relative metric that enabled comparisons of component scores across sessions, for each test in the full group, we standardized the test scores across sessions 1 and 2. The component loadings were then applied to the standardized test scores from each session to obtain the component scores for that session. A similar procedure was used to calculate the standardized component scores for the longitudinal subgroup, with the exception that for each test, the scores from all three sessions were combined into a single dataset and then standardized. General cognition scores for each session were calculated by averaging the three domain-specific scores.

In both the full group and the longitudinal subgroup, scores for each cognitive component were averaged across sessions 1 and 2 to provide baseline scores. Baseline general cognition scores were calculated by averaging the three individual baseline component scores. For both general cognition and the individual cognitive domains, longitudinal change scores were estimated for each member of the longitudinal subgroup as the difference between baseline and session 3 scores.

For both baseline and change scores in each individual cognitive domain, we calculated the mean scores of the other two domains (i.e. $M_{OTH\text{-}COG}$). For example, for memory baseline scores, the mean of the baseline scores for fluency and crystallized IQ were calculated. The $M_{OTH\text{-}COG}$ scores were included as covariates in the relevant statistical analyses to evaluate the specificity of the relationships identified between structural brain measures and performance in a given cognitive domain (see below).

2.3 In-scanner associative memory task

The details of the MRI experimental and scanning procedures have been described in prior publications (e.g. de Chastelaine et al., 2015, 2016a, 2016b). A single MRI scanning session, during which both structural and functional data were acquired, was conducted between the initial two administrations of the neuropsychological test battery (average of 22 days after Session 1). In brief, participants encoded a series of 240 trial-unique pairs of concrete words, judging on each trial which of the denoted objects would ‘fit’ into which. After the encoding phase, participants exited the scanner and rested. They re-entered the scanner 15 minutes later and undertook an associative recognition test, which was split into three consecutive test blocks. The test items comprised 160 ‘intact’ word pairs (pairs re-presented from study), 80 ‘rearranged pairs’ (comprising studied words that were re-paired between study and test), and 80 ‘new’ pairs (pairs of unstudied words). Instructions were to identify the class of word pair presented on each trial by pressing a button corresponding to ‘intact’, ‘rearranged’ or ‘new’. Associative recognition performance (pR) was estimated as the difference between the proportion of correctly endorsed intact pairs (associative hits) and the proportion of intact pairs incorrectly identified as rearranged (associative misses) (de Chastelaine et al., 2015, 2016a, 2016b).

Potential relationships between cortical thickness and pR were examined (see below). To determine whether any such relationships reflected variance unique to the pR metric, we employed the mean of the baseline component scores of all domains other than memory as a covariate. The findings were unchanged when we examined the unique relationships between thickness and pR after controlling baseline general cognition scores.

2.4 MRI acquisition

Functional and structural images were acquired with a Philips Achieva 3T MR scanner (Philips Medical System, Andover, MA USA) equipped with a 32-channel head coil. Functional images were acquired during both study and test phases. Diffusion tensor images (DTI) and high-resolution T1-weighted images were acquired following the functional scanning session. The T1-weighted images were acquired with an MP-RAGE pulse sequence (TR = 8.1 ms, TE = 3.7 ms, FOV = 256 × 224, voxel size = 1×1×1 mm, 160 slices, sagittal acquisition).

2.5 Measurement of cortical thickness

Cortical thickness was estimated from the T1-weighted image of each participant in multiple steps (see also de Chastelaine et al., 2019). First, cortical reconstruction was performed through a standard analysis pipeline in FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/fswiki; Dale et al. 1999; Fischl & Dale 2000; Fischl et al., 2002). After this initial automated analysis, the segmented gray/white matter surfaces were visually checked by two trained raters. If necessary, edits such as control points, white matter edits and pial edits were added to improve tissue classification and the automated reconstruction procedure was then repeated. Thickness was calculated as the distance from the gray/white matter boundary to the pial surface on a vertex-by-vertex basis across the entire cortical mantle.

The mean cortical thickness of each hemisphere was estimated as the mean of the vertex-weighted thickness estimates. Global mean thickness was measured as the mean thickness averaged over the left and right hemispheres. To estimate thickness of left and right IFG, we calculated the mean thickness of opercular, orbital and triangular parcels of the IFG as demarcated in the Destrieux atlas (Destrieux et al., 2010). For the purposes of some of the analyses reported below, we also calculated the thickness of all cortical regions in each hemisphere other than the IFG by averaging the thickness estimates of each cortical parcel excluding the three parcels comprising the IFG (henceforth: extra-IFG thickness).

2.6 Head motion

Because prior studies have indicated that within-scan head motion can lead to the underestimation of cortical thickness (e.g. de Chastelaine et al., 2019; Geerligs et al., 2017; Reuter et al., 2015; Savalia et al., 2017), we residualized thickness measures against head motion estimates derived from temporally adjacent functional scans (see Savalia et al., 2017 and de Chastelaine et al., 2019 for evidence that such estimates can serve as a proxy for within-scanner head movement during a structural scan). The methods are described in detail in de Chastelaine et al. (2019). Briefly, following the procedure described by Power et al. (2012), we calculated framewise displacement (FD) as the sum of the absolute values of the 6 volume-wise realignment parameters output following motion correction of the functional images. We used the average of the FD values from the three immediately preceding functional scans to predict amount of head motion during the anatomical scan.

2.7 Statistical analyses

The present study examined whether individual differences in IFG thickness and mean cortical thickness were predictive of 1) individual differences in baseline cognitive performance or 2) individual differences in longitudinal change in general cognition or in one or more cognitive domains.

To examine whether measures of thickness were related to baseline cognitive performance, we computed partial correlations between thickness and cognitive performance after controlling for age and, in subsequent analyses, for additional variables as specified in the relevant sections of the Results. To examine whether IFG thickness or mean cortical thickness was predictive of longitudinal cognitive change, we employed a set of linear mixed effects models. We included chronological age as a predictor in all of these analyses because this variable was correlated with measures of cortical thickness and cognitive performance with small-to-medium effect sizes (absolute *r*s ranging from .03 to .41, see Supplemental Table 5). Each linear mixed model included a random intercept term to accommodate individual differences in baseline performance. The models took the following general form:

$$\text{Cognition}_{ij} = \text{B}_0 + \text{B}_1 Age_i + \text{B}_2 Session_j + \text{B}_3 Thickness_i + \text{B}_4(Thickness_i \times Session_j) + \text{b}_{0i} + \text{e}_{ij},$$

where Cognition_{ij} refers to individual i’s cognitive performance (either globally or in an individual cognitive domain) at session j, age refers to a participant’s age at baseline, Session refers to test session (baseline coded as 0, session 3 coded as 1), Thickness refers to thickness at baseline, and Thickness × Session refers to the interaction between thickness and test session. B denotes fixed-effects estimates, b_0 denotes estimates for participant-specific random-effects (i.e. baseline cognitive performance), and e is the residual error. Models in which one or more variables accounted for a significant fraction of the variance in cognitive performance or cognitive change were expanded to include additional covariates (see Results). Note that we repeated the analyses of the general cognition and fluency scores after exclusion of a single participant whose performance on the measures was > 3 standard deviations above the group mean. All of the findings reported below were unchanged. This was also the case when (at the request of a reviewer) we included years of education as an additional covariate.

Because of our focus on the relationships between left and right IFG thickness and cognition, here we report findings for the mean thickness of each hemisphere separately. The findings for mean thickness across the entire cortical mantle were highly similar to those for the right hemisphere, albeit with slightly reduced effect sizes (see Supplementary materials).

3. Results

3.1 Sample characteristics

Demographic information pertaining to the study samples and summary measures of cortical thickness are given in Table 1. As is evident from the table, the full group and the longitudinal subgroup had highly similar demographic characteristics and measures of thickness. As noted previously (see Methods) thickness was residualized against an estimate of head motion (FD) prior to the analyses described in the following sections.

Table 1. Demographic information, summary measures of cortical thickness and framewise displacement for the study participants (standard deviations in parentheses).

	Full Group	Longitudinal subgroup
N	67	55
Age at Session 1 (yrs)		
M	68.2 (3.6)	68.3 (3.7)
Range	63 – 76	63 – 76
Gender	37 F, 30 M	28 F, 27 M
Education (yrs)	17.2 (2.3)	17.3 (2.3)
LH_mean (mm)	2.30 (.10)	2.30 (.11)
RH_mean (mm)	2.30 (.11)	2.30 (.11)
LH_IFG (mm)	2.49 (.19)	2.49 (.19)
RH_IFG (mm)	2.46 (.24)	2.46 (.21)
LH_extra-IFG (mm)	2.31 (.11)	2.31 (.11)
RH_extra-IFG (mm)	2.31 (.12)	2.31 (.11)
FD (mm)	.33 (.14)	.34 (.15)

Note. LH_mean: mean cortical thickness of the left hemisphere; RH_mean: mean cortical thickness of the right hemisphere; LH_IFG: left IFG thickness; RH_IFG: right IFG thickness; LH_extra-IFG: mean thickness of areas other than IFG of the left hemisphere; RH_extra-IFG: mean thickness of areas other than IFG of the right hemisphere.

3.2 Neuropsychological test performance

Neuropsychological test scores were fully reported in Hou et al. (2020). The data are however re-described in Supplemental Table 1 for the convenience of the reader. As is evident from the table, the full group and the longitudinal subgroup were well matched in terms of performance on the first two sessions. Also, in both groups, test performance showed an overall improvement from session 1 to session 2. In the longitudinal subgroup, mean performance showed only modest evidence of change between sessions 2 and 3.

Component scores for general cognition and the three individual cognitive domains are given in Table 2. Pairwise *t* tests comparing performance between session 1 and session 2 revealed reliable re-test effects in all domains in both the full group (*t*s > 4.54, *p*s <.001) and the longitudinal subgroup (*t*s > 3.32, *p*s < .003).

Also included in Table 2 are the mean component scores averaged across sessions 1 and 2 (i.e. the baseline scores, see Methods) and the difference scores between baseline and session 3 in the longitudinal subgroup. Comparisons of performance between baseline and Session 3 scores did not identify significant changes in either general cognition or in the individual cognitive domains [general cognition, *t*(54) = 1.42, *p* = .161; memory, *t*(54) = 1.02, *p* = .313; fluency, *t*(54) = 1.43, *p* = .160; crystallized IQ, *t*(54) = .65, *p* = .516].

Table 2. Component scores for each session and change scores over three years (standard deviations in parentheses).

	Session				
	1	2	3	baseline (1&2)	change (1&2 – 3)
Full group					
General cognition	-.45 (1.75)	.45 (1.60)	—	.00 (1.63)	—
Memory	-.82 (2.60)	.82 (2.23)	—	.00 (2.32)	—
Fluency	-.28 (2.05)	.28 (2.01)	—	.00 (1.98)	—
Crystalized IQ	-.25 (1.89)	.25 (1.79)	—	.00 (1.79)	—
Longitudinal					
General cognition	-.35 (1.80)	.46 (1.62)	-.11 (1.82)	.05 (1.67)	.16 (.83)

Memory	-.71 (2.63)	.83 (2.29)	-.12 (2.67)	.06 (2.37)	.18 (1.32)
Fluency	-.17 (2.13)	.32 (2.07)	-.15 (2.06)	.08 (2.05)	.23 (1.18)
Crystalized IQ	-.18 (1.85)	.23 (1.76)	-.05 (1.75)	.02 (1.74)	.07 (.78)

Note. Component scores in session 2 were significantly higher than session 3 for both general cognition and the individual cognitive domains (*t*s > 2.14, *p*s < .037).

We further examined the simple correlations among baseline cognitive scores for the different domains, along with in-scanner associative recognition performance (pR). These scores were reliably inter-correlated in the full group (*r*s > .26, *p*s < .031) and similarly, in the longitudinal subgroup [*r*s > .38, *p*s < .004, with the exception of the correlation between pR and crystallized IQ (*r* = .26, *p* = .058), see Supplemental Table 4 for the complete results of these analyses].

Analogously to the baseline scores, in the longitudinal subgroup the change scores in individual cognitive domains were also inter-correlated: memory change scores were significantly correlated with change scores in both fluency and crystallized IQ (respectively: *r* = .35, *p* = .009; *r* = .44, *p* = .001). A positive but non-significant correlation was evident between the change scores in fluency and crystallized IQ (*r* = .26, *p* = .058).

3.3 Association between cortical thickness and baseline cognitive performance

For all analyses of the baseline data the findings for the full group and the longitudinal subgroup were closely similar. Therefore, we only report the findings from the full group here.

We first examined correlations between the different thickness measures employed in the analyses reported below. In brief, both left and right IFG thickness correlated strongly with thickness of the respective ipsilateral extra-IFG regions as well as with thickness of the entire ipsilateral hemisphere (*r*s > .73, *p*s < .001). In addition, significant inter-hemispheric correlations were identified for each of these measures (*r*s > .62, *p*s < .001, for complete results of these analyses, see Supplemental Table 6).

Table 3 shows the correlations between measures of IFG thickness and baseline cognitive scores in the full group (see also Figure 1). As is evident from the table, after controlling for age, right IFG thickness was positively correlated with general cognition. Right IFG thickness was also significantly correlated with fluency and crystallized IQ scores while the relationship between right IFG thickness and memory scores approached significance. As is also evident in

Table 3, right IFG thickness significantly correlated with associative recognition performance (pR, see also Figure 2). In contrast with the findings for the right IFG, left IFG thickness did not correlate significantly with any cognitive measure.

Table 3 also shows the correlations between IFG thickness and performance in each cognitive domain after controlling for the variance shared with other cognitive domains ($M_{OTH\text{-}COG}$) and with extra-IFG thickness. As is evident from the table, all of the previously identified relationships between right IFG thickness and the individual cognitive measures were non-significant after controlling for either one or both of these variables.

Table 3. Correlations between IFG thickness and baseline scores in the full group, after controlling for age, for the variance shared with other cognitive domains, and for extra-IFG thickness (*p* values in parentheses).

	LH_IFG				RH_IFG			
	Age	+ $M_{OTH\text{-}COG}$	+ extra-IFG	+ $M_{OTH\text{-}COG}$ & extra-IFG	Age	+ $M_{OTH\text{-}COG}$	+ extra-IFG	+ $M_{OTH\text{-}COG}$ & extra-IFG
General cognition	.17 (.169)	—	.05 (.712)	—	**.30 (.015)**	—	.07 (.576)	—
Memory	.11 (.401)	.01 (.930)	-.02 (.890)	-.07 (.585)	.24 (.057)	.11 (.389)	.04 (.751)	.00 (.975)
Fluency	.20 (.110)	.16 (.226)	.11 (.383)	.13 (.302)	**.25 (.047)**	.11 (.409)	.06 (.624)	.03 (.797)
Crystallized IQ	.12 (.352)	.03 (.824)	.03 (.813)	.01 (.965)	**.25 (.050)**	.11 (.370)	.07 (.583)	.05 (.718)
pR	.17 (.188)	.11 (.386)	.02 (.866)	-.01 (.966)	**.28 (.024)**	.20 (.110)	.17 (.172)	.16 (.217)

Note. LH_IFG: left IFG thickness; RH_IFG: right IFG thickness.

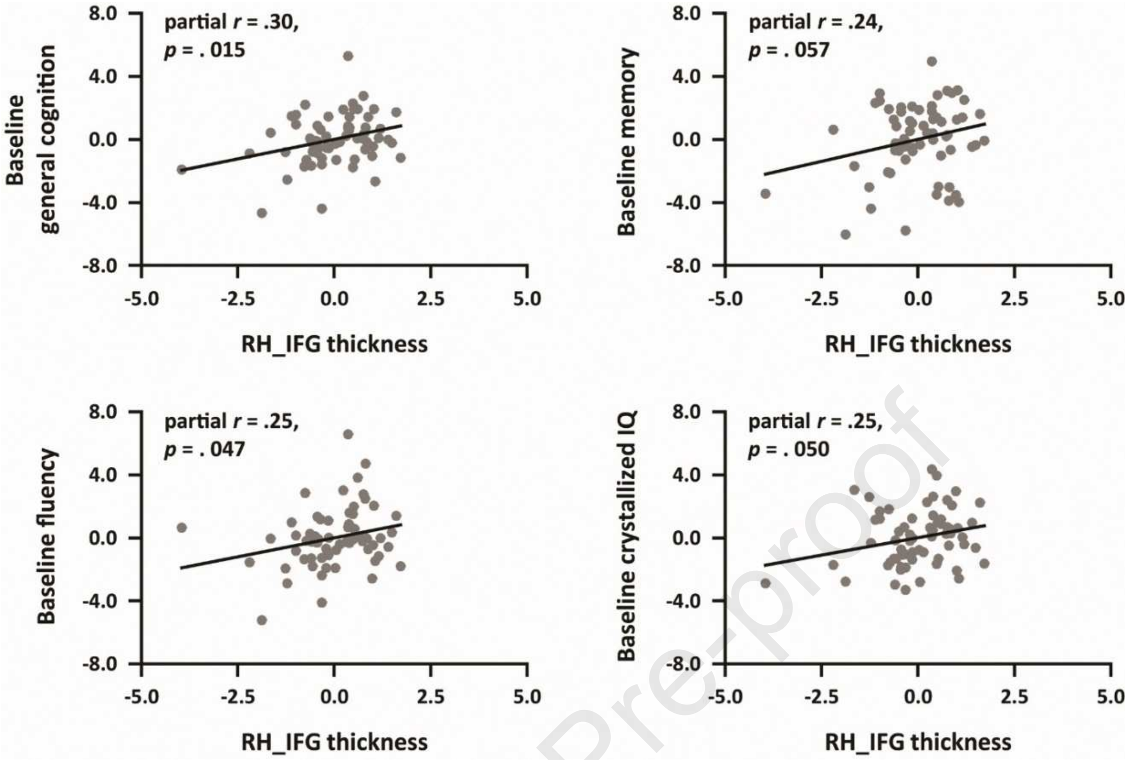

Figure 1. Scatter plots of the relationship between right IFG thickness and baseline component scores for general cognition and individual cognitive domains, after controlling for age.

Correlations between the thickness of the left and right hemispheres and baseline cognitive scores in the full group are shown in Table 4 (see also Figure 3). As is evident from the table, after controlling for age, general cognition was positively and significantly correlated with mean thickness of the right hemisphere. A similar, albeit, non-significant trend was evident for the left hemisphere. Table 4 also shows the correlations between these thickness measures and each of the 3 individual cognitive components. Component scores in all three cognitive domains were significantly correlated with mean thickness of the right hemisphere. Similar but non-significant relationships were observed for the left hemisphere. Correlations between left and right hemisphere thickness and pR are also given in Table 4. While both thickness measures were positively correlated with pR, only the correlation with right hemisphere thickness was significant (see also Figure 2).

Table 4 also reports the correlations between left and right hemisphere thickness and the different domain-specific cognitive measures after controlling for the variance shared with the other measures. As is evident from the table, none of the previously identified relationships approached significance after controlling for the means of the scores in the other two domains. Similarly, with $M_{OTH\text{-}COG}$ as an additional covariate, the correlation between pR and right hemisphere thickness was non-significant.

Table 4. Correlations between mean cortical thickness of each hemisphere and baseline scores in the full group, after controlling for age and for the variance shared with other cognitive domains (*p* values in parentheses).

	LH_mean		RH_mean	
	Age	+ $M_{OTH\text{-}COG}$	Age	+ $M_{OTH\text{-}COG}$
General cognition	.24 (.060)	—	**.37 (.003)**	—
Memory	.19 (.127)	.09 (.461)	**.31 (.014)**	.16 (.201)
Fluency	.22 (.074)	.13 (.301)	**.31 (.012)**	.15 (.250)
Crystallized IQ	.15 (.235)	.02 (.851)	**.27 (.033)**	.09 (.471)
pR	.23 (.072)	.17 (.195)	**.25 (.050)**	.15 (.247)

Note. LH_mean: mean cortical thickness of the left hemisphere; RH_mean: mean cortical thickness of the right hemisphere.

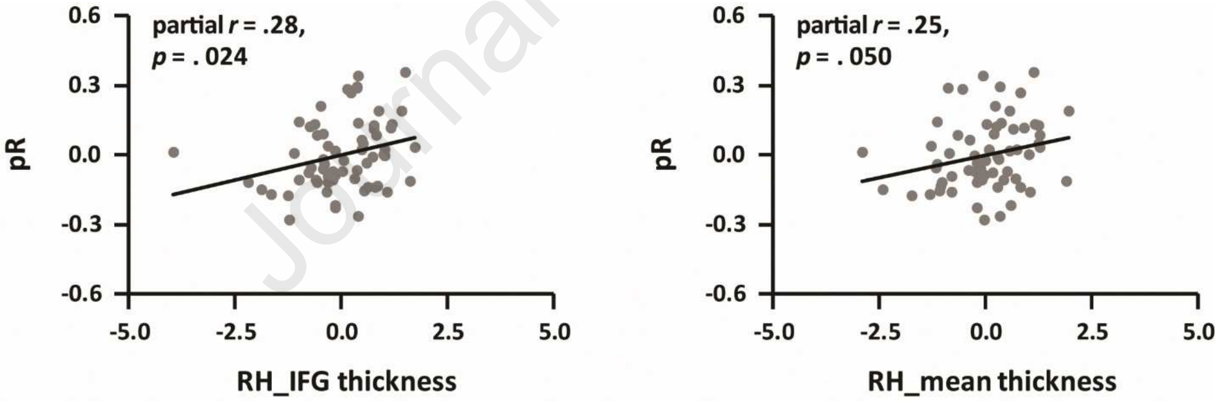

Figure 2. Scatter plots of the relationship between thickness of right IFG (left) and the right hemisphere (right) and pR, after controlling for age.

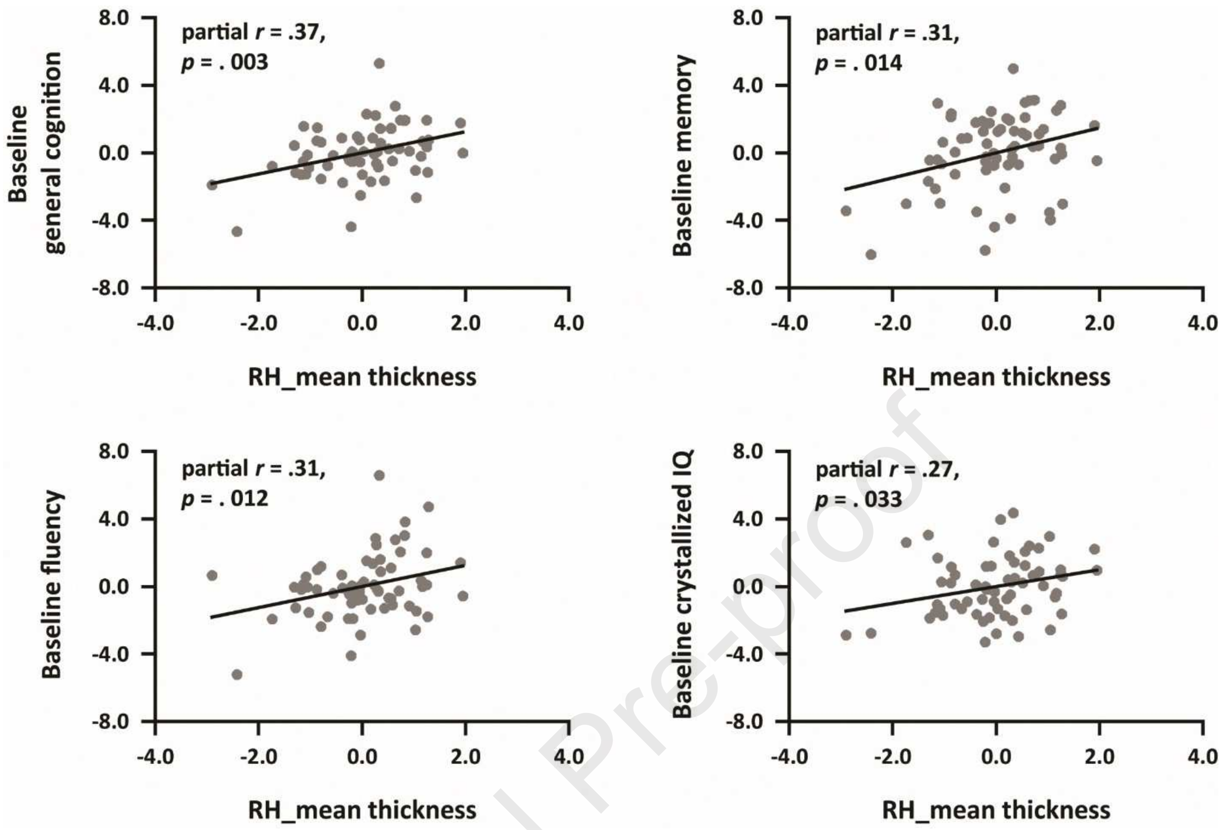

Figure 3. Scatter plots of the relationship between mean cortical thickness of the right hemisphere and baseline component scores for general cognition and individual cognitive domains, after controlling for age.

3.4 Association between IFG thickness and longitudinal cognitive change

Based on the general model described in the Materials and Methods section (see ‘statistical analyses’), a series of linear mixed effects models were constructed to examine whether thickness of the left or right IFG or left or right hemisphere was predictive of longitudinal change in general cognition or each individual cognitive domains. For each model, we were interested in: 1) the thickness term, which reflects the strength of the relationship between thickness and mean cognitive performance averaged over baseline and session 3, and 2) the thickness × session interaction term, which indexes the relationship between the thickness measure and cognitive change.

Results of the models using IFG thickness to predict mean performance and change in general cognition are shown in Table 5. Right IFG thickness (Model 2) significantly predicted general cognitive performance, consistent with the results reported in Table 3 and Figure 1. However, the interactions between left or right IFG thickness and session were both non-significant.

Table 5. Linear mixed effects regression results for IFG thickness predicting performance and change in general cognition.

General cognition				
Parameter	B (SE)	df	*t*	*p*
		Model 1		
Intercept	5.99 (4.29)	50	1.40	.168
Age	-.09 (.06)	50	-1.37	.177
LH_IFG	.31 (.24)	57	1.29	.204
Session	-.16 (.12)	51	-1.34	.185
LH_IFG × Session	-.03 (.12)	51	-.29	.776
		Model 2		
Intercept	4.18 (4.06)	50	1.03	.308
Age	-.06 (.06)	50	-1.00	.322
RH_IFG	**.57 (.23)**	**57**	**2.49**	**.016**
Session	-.16 (.11)	51	-1.38	.173
RH_IFG × Session	.20 (.12)	51	1.74	.088

Note. LH_IFG: left IFG thickness; RH_IFG: right IFG thickness.

The outcomes of the linear mixed effects models employing IFG thickness to predict mean performance and change in each individual cognitive domain are shown in Table 6. In the case of memory, IFG thickness failed to predict mean memory scores averaged across baseline and session 3. However, there was a significant interaction between right IFG thickness and test session (Model 4), indicative of an inverse relationship between thickness and longitudinal memory decline (see Figure 4 for plots illustrating this relationship).

Consistent with the findings reported above for the baseline scores, right IFG thickness was a significant predictor of fluency. Neither left nor right IFG thickness predicted longitudinal change in fluency scores, however. Finally, a significant relationship was identified between right IFG thickness and crystallized IQ.

Table 6. Linear mixed effects regression results for IFG thickness predicting performance and change in individual cognitive domains.

Memory				
Parameter	B (SE)	df	*t*	*p*
Model 3				
Intercept	8.82 (6.36)	50	1.39	.172
Age	-.13 (.09)	50	-1.37	.177
LH_IFG	.19 (.36)	57	.53	.597
Session	-.21 (.18)	51	-1.14	.258
LH_IFG × Session	-.01 (.19)	51	-.08	.937
Model 4				
Intercept	7.02 (6.27)	50	1.12	.269
Age	-.10 (.09)	50	-1.10	.276
RH_IFG	.40 (.35)	57	1.15	.257
Session	-.21 (.17)	51	-1.20	.237
RH_IFG × Session	**.39 (.18)**	**51**	**2.22**	**.031**
Fluency				
Parameter	B (SE)	df	*t*	*p*
Model 5				
Intercept	8.16 (4.84)	50	1.68	.099
Age	-.12 (.07)	50	-1.65	.105
LH_IFG	.51 (.28)	60	1.85	.070
Session	-.21 (.16)	51	-1.27	.208
LH_IFG × Session	-.14 (.17)	51	-.81	.421
Model 6				
Intercept	6.08 (4.57)	50	1.33	.189
Age	-.09 (.07)	50	-1.30	.200
RH_IFG	**.81 (.26)**	**61**	**3.12**	**.003**
Session	-.21 (.17)	51	-1.27	.211
RH_IFG × Session	.02 (.17)	51	.10	.918
Crystallized IQ				
Parameter	B (SE)	df	*t*	*p*
Model 7				
Intercept	1.00 (4.33)	50	.23	.818
Age	-.01 (.06)	50	-.21	.837
LH_IFG	.23 (.355)	56	.93	.355
Session	-.05 (.11)	51	-.48	.632

LH_IFG × Session	.05 (.11)	51	.45	.657
		Model 8		
Intercept	-.57 (4.18)	50	-.14	.892
Age	.01 (.06)	50	.16	.871
RH_IFG	**.48 (.23)**	**56**	**2.05**	**.045**
Session	-.05 (.11)	51	-.50	.621
RH_IFG × Session	.20 (.11)	51	1.84	.072

Note. LH_IFG: left IFG thickness; RH_IFG: left IFG thickness.

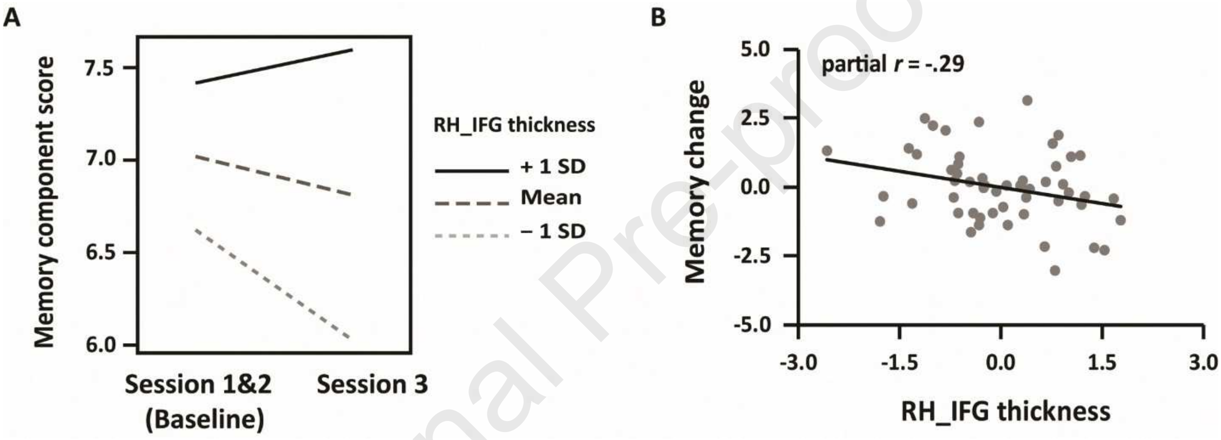

Figure 4. A: Right IFG thickness × session interaction visualized with simple slopes (mean ±1SD). B: scatter plot depicting the relationship between memory change scores (baseline minus session 3) and right IFG thickness, controlling for age and baseline scores.

To examine whether the relationships identified with general cognition were specific to the right IFG, we employed a follow-up linear mixed effects model in which extra-IFG thickness (i.e. extra-IFG) of the right hemisphere, and the extra-IFG × session interaction term were included as additional predictors. As is evident from the first panel of Table 7, after controlling for these variables, right IFG thickness did not significantly predict general cognition.

In a series of models following up the relationships identified between right IFG thickness and individual component scores documented in Table 7, we added extra-IFG thickness, mean performance across the other two cognitive domains and their interactions with test session as predictors. As is evident from the table, with the inclusion of these additional predictors, the right IFG thickness × session interaction term no longer predicted memory change.

Right IFG thickness continued to predict fluency after controlling for the average of the memory and crystallized IQ scores. This relationship did not persist, however, when extra-IFG thickness and the extra-IFG × session interaction terms were included as additional predictors. The previously identified relationship between right IFG thickness and crystallized IQ was also non-significant after controlling for the additional covariates.

Table 7. Linear mixed effects regression results for IFG thickness predicting cognitive performance and change, before and after controlling for variance shared with other cognitive domains and thickness of extra-IFG regions (*p* values in the parentheses).

RH_IFG predicting ***general cognition***

	Intercept	Age	TK	Se	TK × Se	extra-IFG	extra-IFG × Se	$M_{OTH\text{-}COG}$	$M_{OTH\text{-}COG}$ × Se
Model 2	4.18 (.308)	-.06 (.322)	**.57 (.016)**	-.16 (.173)	.20 (.088)				
+ extra-IFG	2.46 (.566)	-.03 (.586)	.34 (.289)	-.16 (.174)	.10 (.558)	.33 (.329)	.14 (.399)		

RH_IFG predicting ***memory***

	Intercept	Age	TK	Se	TK × Se	extra-IFG	extra-IFG × Se	$M_{OTH\text{-}COG}$	$M_{OTH\text{-}COG}$ × Se
Model 4	7.02 (.269)	-.10 (.276)	.40 (.257)	-.21 (.237)	**.39 (.031)**				
+ extra-IFG	3.79 (.566)	-.05 (.577)	-.00 (.993)	-.21 (.235)	.18 (.479)	.61 (.241)	.29 (.254)		
+ $M_{OTH\text{-}COG}$	4.69 (.387)	-.07 (.386)	-.13 (.689)	-.10 (.514)	.28 (.115)			**.82 (< .001)**	.03 (.755)
+ extra-IFG & $M_{OTH\text{-}COG}$	2.30 (.685)	-.03 (.685)	-.42 (.329)	-.10 (.508)	.12 (.596)	.46 (.308)	.23 (.303)	**.81 (< .001)**	.02 (.862)

RH_IFG predicting ***fluency***

	Intercept	Age	TK	Se	TK × Se	extra-IFG	extra-IFG × Se	$M_{OTH\text{-}COG}$	$M_{OTH\text{-}COG}$ × Se
Model 6	6.08 (.189)	-.09 (.200)	**.81 (.003)**	-.21 (.211)	.02 (.918)				
+ extra-IFG	5.07 (.302)	-.07 (.317)	.66 (.082)	-.21 (.216)	.00 (.998)	.23 (.564)	.02 (.926)		
+ $M_{OTH\text{-}COG}$	4.10 (.276)	-.06 (.287)	**.58 (.011)**	-.14 (.370)	-.22 (.189)			**.55 (< .001)**	.10 (.289)
+ extra-IFG & $M_{OTH\text{-}COG}$	4.32 (.282)	-.06 (.292)	.56 (.076)	-.14 (.374)	-.12 (.597)	.02 (.954)	-.15 (.500)	**.55 (< .001)**	.11 (.241)

RH_IFG predicting ***crystallized IQ***

	Intercept	Age	TK	Se	TK × Se	extra-	extra-	$M_{OTH\text{-}}$	$M_{OTH\text{-}COG}$

						IFG	IFG × Se	$_{COG}$	× Se
Model 8	-.57 (.892)	.01 (.871)	**.48** **(.045)**	-.05 (.621)	.20 (.072)				
+ extra-IFG	-1.47 (.742)	.02 (.723)	.37 (.269)	-.05 (.623)	.12 (.436)	.16 (.650)	.10 (.506)		
+ $M_{OTH\text{-}COG}$	-3.10 (.396)	.05 (.387)	.22 (.298)	.03 (.755)	.18 (.111)			**.42** **(< .001)**	-.07 (.193)
+ extra-IFG & $M_{OTH\text{-}COG}$	-3.17 (.414)	.05 (.406)	.23 (.422)	.03 (.760)	.12 (.427)	-.02 (.940)	.09 (.535)	**.42** **(< .001)**	-.08 (.162)

Note. TK: left or right IFG thickness; Se: Session.

3.5 Association between cortical thickness of each hemisphere and longitudinal cognitive change

We also constructed a series of linear mixed effects models to examine whether thickness of the left or right hemisphere was predictive of longitudinal change in general cognition and in each of the individual cognitive domains. The outcomes of these models are shown in Table 8. Mean thickness of the right hemisphere (Model 10) was a significant predictor of performance in general cognition, consistent with the results reported in Table 4 and Figure 3. However, neither left nor right hemisphere thickness significantly interacted with test session.

Table 8. Linear mixed effects regression results for hemisphere thickness predicting performance and change in general cognition.

		General cognition		
Parameter	B (SE)	df	*t*	*p*
		Model 9		
Intercept	2.91 (4.53)	50	.64	.524
Age	-.04 (.07)	50	-.61	.542
LH_mean	.40 (.25)	56	1.62	.110
Session	-.16 (.11)	51	-1.38	.174
LH_mean × Session	.19 (.12)	51	1.63	.109
		Model 10		
Intercept	1.71 (4.16)	50	.41	.683
Age	-.02 (.06)	50	-.38	.706
RH_mean	**.67 (.23)**	**57**	**2.86**	**.006**
Session	-.16 (.11)	51	-1.38	.174
RH_mean × Session	.19 (.12)	51	1.66	.102

Note. LH_mean: mean cortical thickness of the left hemisphere; RH_mean: mean cortical thickness of the right hemisphere.

The outcomes of the linear mixed effects models employing thickness of left or right hemisphere to predict mean performance and change in the individual cognitive domains are shown in Table 9. Consistent with the results reported in Table 4 and illustrated in Figure 3, right hemisphere thickness was positively, albeit non-significantly, correlated with mean memory performance (Model 12). As is also evident from Models 11 and 12, there were marginally significant interactions between the thickness measures and test session, indicative of a weak inverse relationship with longitudinal memory decline.

As is shown in Models 13 and 14, and consistent with the findings reported for the baseline scores above, both left and right hemisphere thickness significantly predicted fluency scores, although in neither case was there a significant interaction with session. Finally, no relationship was identified between either thickness measure and crystallized IQ.

Table 9. Linear mixed effects regression results for mean cortical thickness predicting performance and change in individual cognitive domains.

		Memory		
Parameter	B (SE)	df	*t*	*p*
		Model 11		
Intercept	5.10 (6.75)	50	.76	.454
Age	-.07 (.10)	50	-.74	.463
LH_mean	.39 (.38)	56	1.04	.303
Session	-.21 (.18)	51	-1.18	.243
LH_mean × Session	.33 (.18)	51	1.86	.069
		Model 12		
Intercept	3.70 (6.38)	50	.58	.564
Age	-.05 (.09)	50	-.56	.575
RH_mean	.68 (.36)	57	1.91	.061
Session	-.21 (.18)	51	-1.19	.242
RH_mean × Session	.35 (.18)	51	1.96	.055
		Fluency		
Parameter	B (SE)	df	*t*	*p*
		Model 13		
Intercept	4.60 (5.15)	50	.89	.376

Age	-.07 (.08)	50	-.86	.392
LH_mean	**.59 (.29)**	**59**	**2.03**	**.047**
Session	-.21 (.17)	51	-1.27	.211
LH_mean × Session	.04 (.17)	51	.22	.830
Model 14				
Intercept	3.51 (4.77)	50	.74	.465
Age	-.05 (.07)	50	-.70	.485
RH_mean	**.84 (.27)**	**61**	**3.10**	**.003**
Session	-.21 (.17)	51	-1.27	.211
RH_mean × Session	.06 (.17)	51	.33	.743
Crystallized IQ				
Parameter	B (SE)	df	*t*	*p*
Model 15				
Intercept	-.99 (4.66)	50	-.21	.832
Age	.02 (.07)	50	.24	.814
LH_ mean	.24 (.26)	55	.94	.349
Session	-.05 (.11)	51	-.50	.621
LH_ mean × Session	.20 (.11)	51	1.85	.070
Model 16				
Intercept	-2.10 (4.41)	50	-.48	.635
Age	.03 (.06)	50	.50	.617
RH_ mean	.48 (.25)	55	1.96	.055
Session	-.05 (.11)	51	-.49	.625
RH_ mean × Session	.17 (.11)	51	1.59	.118

Note. LH_mean: mean cortical thickness of the left hemisphere; RH_mean: mean cortical thickness of the right hemisphere.

To examine whether the relationships identified in Models 13 and 14 were specific to the fluency component, follow-up models were constructed with the mean of the memory and crystallized IQ component scores (i.e. $M_{OTH\text{-}COG}$) and the $M_{OTH\text{-}COG}$ × session interaction term as additional predictors. As is evident from Table 10, even with the inclusion of these additional variables, right hemisphere thickness remained a significant predictor of fluency scores.

Table 10. Linear mixed effects regression results for left and right hemisphere thickness predicting cognitive performance and change in fluency, before and after controlling for variance shared with other cognitive domains (*p* values in the parentheses).

LH_thickness predicting ***fluency***							
	Intercept	Age	TK	Se	TK × Se	$M_{OTH-COG}$	$M_{OTH-COG}$ × Se
Model 13	4.60 (.376)	-.07 (.392)	**.59 (.047)**	-.21 (.211)	.04 (.830)		
+ $M_{OTH-COG}$	3.29 (.423)	-.05 (.437)	.41 (.088)	-.13 (.389)	-.17 (.301)	**.58 (< .001)**	.08 (.369)
RH_thickness predicting ***fluency***							
	Intercept	Age	TK	Se	TK × Se	$M_{OTH-COG}$	$M_{OTH-COG}$ × Se
Model 14	3.51 (.465)	-.05 (.485)	**.84 (.003)**	-.21 (.211)	.06 (.743)		
+ $M_{OTH-COG}$	2.99 (.449)	-.04 (.464)	**.53 (.028)**	-.14 (.369)	-.17 (.329)	**.54 (< .001)**	.10 (.313)

Note. TK: mean cortical thickness of left or right hemisphere; Se: Session.

4. Discussion

The present study examined the relationships in older adults between the thickness of the left and right IFG, cortical thickness of the entire left and right hemispheres, and cognitive performance and longitudinal cognitive change over three years. Thickness of the right IFG and mean cortical thickness across the entire right hemisphere correlated with baseline general cognition and performance in individual cognitive domains. Additionally, right IFG thickness was predictive of longitudinal memory change. Of importance, none of the relationships identified between right IFG thickness and cognition persisted after controlling for the thickness of the remaining ipsilateral cortex. Furthermore, most of the associations between thickness measures and the component scores for individual cognitive domains did not persist after controlling for the variance shared with other cognitive domains.

In the present study, we adopted a burst measurement design to mitigate the re-test and regression to the mean effects that are inherent to longitudinal studies of cognitive performance. The benefits of this approach, along with more general issues concerning re-test effects, are discussed in detail in Hou et al. (2020). We note, however, that our main findings in respect of relationships between cortical thickness and baseline performance, and of the relationships between thickness and memory change, were largely unaffected when either session 1 or session 2 scores alone comprised the estimates of baseline performance (see Supplementary materials).

However, when session 2 alone acted as the baseline, additional relationships were evident between thickness and longitudinal change in the crystallized IQ component scores. These relationships are however almost certainly artifactual. They reflect the combination of the robust correlation that existed between session 1 crystallized IQ and cortical thickness (see Supplemental Tables 14 and 15), and the patterning of the correlations between the session scores and change scores across sessions, which is strongly suggestive of the influence of regression to the mean [session 1 baseline scores were inversely correlated with session 2 – session 1 change (r = -.34, p = .010), while session 2 scores were positively correlated with session 2 – session 3 change (r = .28, p = .042)]. These findings exemplify the benefit of estimating baseline cognitive performance from multiple test sessions.

The present investigation was motivated by prior fMRI findings linking IFG subsequent associative recognition effects to in-scanner associative memory performance (pR) in older adults (de Chastelaine et al., 2011, 2016a), as well as by findings that older individuals demonstrate bilateral rather than left-lateralized IFG subsequent memory effects (de Chastelaine et al., 2016a; see also Duverne et al., 2009). Seemingly in accord with these fMRI findings, we identified a positive correlation between right IFG thickness and pR. This correspondence is more apparent than real, however. First, the correlations across participants between the magnitudes of their IFG subsequent associative recognition effects (de Chastelaine et al., 2016a) and IFG thickness were small and far from significant (r = .10, p = .955, and r = .14, p = .268, for left and right IFG respectively; see Hou et al., 2020, for highly analogous findings for functional and structural measures derived from the hippocampus). Second, in a multiple regression model employing right IFG thickness and IFG subsequent memory effects (collapsed over hemisphere) as predictors of pR, the structural and functional effects explained unique proportions of the variance in pR [adjusted R^2 = .137, p = .005; B = .04, t(59) = 2.25, p = .028, and B = .08, t(59) = 2.27, p = .027, for the structural and functional measures respectively]. Third, as is discussed in more detail below, right IFG thickness did not predict pR after controlling for the thickness of the remaining right hemisphere regions and, indeed, thickness of the entire right hemisphere predicted pR with a very similar effect size to that for the IFG alone (r = .25 vs. r = .28 for the entire hemisphere and IFG respectively). Together, these findings suggest that the structural and functional measures derived from the IFG reflect independent contributions to the efficacy of associative encoding and, in the case of the structural measure, it seems likely that these contributions do not reflect functions supported specifically by that cortical region.

As was just noted, thickness of the right IFG and the entire right hemisphere were similarly correlated with pR. Strikingly, with the exception mentioned below, this finding also held for general cognition, and for the component scores in each of the three cognitive domains derived from the neuropsychological test battery. Of equal importance, these relationships between right IFG thickness and cognitive performance were no longer reliable when mean thickness of all other right hemisphere cortical regions was included as a covariate. These findings suggest that while thickness of the right IFG might have acted as a sensitive predictor of baseline cognitive performance, it did not explain unique variance in these cognitive measures. Rather, it appears to have acted as a proxy for the structural integrity of the right cerebral cortex as a whole. It is also worth noting that, with the exception of the fluency component, neither right IFG nor right hemisphere thickness accounted for unique variance in performance in any individual cognitive domain. Together, these findings are highly reminiscent of those reported by Salthouse et al. (2015) and add to the evidence that seemingly unique relationships between regional thickness and domain-specific cognitive performance are strongly reflective of a more general association between cortical thickness and cognition.

Relatedly, we note that, in general, a statistically significant relationship between a particular regional brain structural measure and a specific cognitive domain is not necessarily indicative of a unique brain-behavior association. Whether a brain-behavior relationship is statistically significant is a different question from whether the relationship is a specific one. A significant relationship between a regional measure and cognitive performance indicates that the measure explains a numerically higher proportion of the variance in performance than it does in regions where the relationship is non-significant. It does not, however, license the conclusion that the region accounts for a *significantly* larger proportion of the variance than other regions. This latter conclusion depends on the outcome of a direct contrast of the strength of the respective relationships (see the discussion of hemisphere differences, below, and see Jernigan et al., 2003 for a similar argument applied to voxel-wise analysis of fMRI data).

The only specific brain-behavior relationship that we identified in the present study was that between right hemisphere thickness and fluency component scores (see Table 10). However, this finding should be treated with caution, given that we could only identify the relationship in the context of a linear mixed effects model: the partial correlations between right hemisphere thickness and baseline fluency were not significant in either the full group or the longitudinal subgroup after controlling for performance in the other cognitive domains (Table 4 and Supplementary Materials). Thus, while the finding for fluency identified by the linear mixed effects analysis is consistent with the possibility that cortical thickness accounts for variance unique to this cognitive domain, the lack of converging evidence from the alternative analyses described above dictates that this finding should be treated as highly provisional.

In addition to predicting baseline cognitive performance, right IFG thickness was also predictive of longitudinal memory change. This relationship did not survive, however, when the mean thickness of the remaining ipsilateral cortical regions and its interaction with test session were included as additional predictors in the relevant mixed effects model (Table 7). Furthermore, a similar relationship with memory change was evident for the thickness of the entire right hemisphere, although this just failed to achieve statistical significance (Model 12 in Table 9). Nonetheless, the two effect sizes were highly comparable (partial r = -.29 vs partial r = -.25 for the right IFG and right hemisphere respectively). Thus, as in the case of baseline cognitive scores, the thickness of the whole hemisphere was essentially as predictive of memory change as was thickness of the right IFG alone. Moreover, the findings are ambiguous with respect to whether these structural measures explained variance in change scores that was unique to the memory component. After controlling for the variance shared with other cognitive domains, neither thickness measure reliably predicted memory change [for right IFG thickness, see Table 7; for right hemisphere thickness, B = .22, $t(50) = 1.26$, $p = .213$]. On the other hand, though, nor was there a significant relationship between the thickness measures and change either in general cognition or in the other domain-specific component scores. Further research employing more highly powered designs will be necessary to establish more precisely the specificity with which right IFG thickness predicts longitudinal memory change.

In contrast to the findings for the right hemisphere, we did not identify significant relationships between any left hemisphere thickness measure and cognitive performance. In follow-up analyses, we employed Steiger’s z tests to directly contrast the size of the thickness-cognition correlations in the left vs. the right hemisphere (see Supplementary materials). In brief, the correlation with memory change was significantly greater for right than for left IFG thickness.

In addition, correlations were significantly higher for right than for left whole hemisphere thickness for the general cognition, memory and crystallized IQ baseline scores. These findings are striking given that our neuropsychological test battery was heavily weighted in favor of verbal cognition, which one would assume to be more heavily dependent on left- than right-lateralized processing. A speculative explanation for these asymmetric effects is that they reflect individual differences in the contribution of compensatory processes supported by the right hemisphere in the face of declining structural integrity of the left hemisphere. By this argument, individuals in whom the right hemisphere has maintained a relatively high level of structural integrity might be better able to compensate for the failure of left hemisphere cortical regions to fully support cognitive performance (see Cabeza et al., 2018, for discussion of the concepts of brain maintenance and compensation, and their possible inter-relationships). Alternatively, rather than reflecting the contribution of compensatory processes to performance, these asymmetric effects might indicate that the structural integrity of the right hemisphere becomes increasingly relevant to cognition with advancing age, perhaps as a consequence of a weakening of hemispheric specialization (a possible example of age-related dedifferentiation; see Koen & Rugg, 2019 for review). Future research will be needed to arbitrate between these and other potential accounts.

The present study has a number of limitations. First, the sample size is modest, limiting our ability to detect brain-behavior relationships with small effect sizes. This limitation means that considerable caution is required before accepting the null findings reported above; for example, while we can be confident that including a generic thickness measure as a covariate markedly reduces the amount of variance in cognitive performance explained by the more specific measure of right IFG thickness, it remains to be seen whether a more highly powered study would identify a small but unique contribution of this measure. A second limitation of the study is that we employed only a single, relatively short follow-up period (three years), and therefore were not able examine relationships between cortical thickness and long-term cognitive change or to estimate the trajectory of change. Third, since we only acquired thickness measures at baseline, we were unable to examine change-change relationships between cortical thickness and cognition. Finally, we did not examine performance across a very wide range of cognitive domains and, in particular, we did not employ tests of spatial cognition or visual memory. Thus, future research would benefit from the employment of larger samples, a longer follow-up period, longitudinal measurement of cortical thickness, and a more extensive test battery.

These limitations notwithstanding, our main findings are clear. The relationships identified between the thickness of a specific cortical region, here, the right IFG, and performance in three different cognitive domains (and, perhaps, longitudinal memory change) were largely accounted for by a more generic relationship between the thickness of the entire right hemisphere and an across-domain measure of cognitive performance. Together with previous reports (e.g. Salthouse et al., 2015), the findings highlight the importance of adopting analysis approaches that control for such generic relationships when examining hypotheses about relationships between regionally specific brain structural measures and domain-specific cognition.

Funding

This work was supported by the National Institute on Aging (grant number 1RF1AG039103).

Acknowledgements

We gratefully acknowledge the contributions of Hannah Stanton and Kay Moolenijzer for their assistance with participant recruitment and neuropsychological data collection. We thank the staff of the UTSW Advanced Imaging Center for their assistance with MRI data collection.

Declarations of Interest: None

Reference

Agelink van Rentergem, J. A., de Vent, N. R., Schmand, B. A., Murre, J. M. J., Staaks, J. P. C., Huizenga, H. M., 2020. The Factor Structure of Cognitive Functioning in Cognitively Healthy Participants: a Meta-Analysis and Meta-Analysis of Individual Participant Data. Neuropsychol. Rev, 30, 51–96.

Badre, D., Wagner, A.D., 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia, 45, 2883–2901.

Bland, J. M., Altman, D. G. 1994. Regression towards the mean. Br Med J, 308, 1499.

Braver, T.S., West, R., 2008. Working memory, executive control, and aging. In: Craik, F.I.M., Salthouse, T.A. (Eds.), The Handbook of Aging and Cognition, third ed. Psychology Press, Hove, UK, pp. 311–372.

Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S. C., Lindenberger, U., Heekeren, H.R., 2012. Cortical thickness is linked to executive functioning in adulthood and aging. Hum Brain Mapp, 33, 1607–1620.

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., Rajah, M.N., 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat Rev Neurosci, 19, 701–710.

Carroll, J.B., 1993. Human cognitive abilities: A survey of factor-analytic studies. New York, NY: Cambridge University Press.

Costafreda, S.G., Fu, C.H.Y., Lee, L., Everitt, B., Brammer, M.J., David, A.S., 2006. A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. Hum Brain Mapp, 27, 799–810.

de Chastelaine, M., Donley, B.E., Kennedy, K.M., Rugg, M.D., 2019. Age moderates the relationship between cortical thickness and cognitive performance. Neuropsychologia, 132, 107136.

de Chastelaine, M., Mattson J.T., Wang, T.H., Donley B.E., Rugg, M.D., 2016a. The relationships between age, associative memory performance, and the neural correlates of successful associative memory encoding. Neurobiol Aging, 42, 163-176.

de Chastelaine, M., Mattson, J.T., Wang, T.H., Donley, B.E., Rugg, M.D., 2015. Sensitivity of negative subsequent memory and task-negative effects to age and associative memory performance. Brain Res, 1612, 16–29.

de Chastelaine, M., Mattson, J.T., Wang, T.H., Donley, B.E., Rugg, M.D., 2016b. The neural correlates of recollection and retrieval monitoring: Relationships with age and recollection performance. Neuroimage, 138, 164-175.

de Chastelaine, M., Wang, T.H., Minton, B., Muftuler, L.T., Rugg, M.D., 2011. The effects of age, memory performance, and callosal integrity on the neural correlates of successful associative encoding. Cereb Cortex, 21, 2166–2176.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 2000. California Verbal Learning Test, 2nd ed. San Antonio, TX: The Psychological Corporation.

Destrieux, C., Fischl, B., Dale, A., Halgren, E., 2010. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage, 53, 1-15.

Duverne, S., Motamedinia, S., Rugg, M.D., 2009. The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex, 19, 733–744.

Ecker, C., Stahl, D., Daly, E., Johnston, P., Thomson, A., Murphy, D.G.M., 2009. Is there a common underlying mechanism for age-related decline in cortical thickness? NeuroReport, 20, 1155–1160.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the humanCereb Cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A, 97, 11050–11055.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron, 33, 341–355.

Fjell, A.M., Amlien, I.K., Westlye, L.T., Stenset, V., Fladby, T., Skinningsrud, A., Eilsertsen, D.E., Bjørnerud. A., Walhovd, K.B., 2010. CSF biomarker pathology correlates with a medial temporo-parietal network affected by very mild to moderate Alzheimer's disease but not a fronto-striatal network affected by healthy aging. NeuroImage, 49, 1820-1830.

Fjell, A.M., Walhovd, K.B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B.T., Fischl, B., Dale, A.M., 2006. Selective increase of cortical thickness in high-performing elderly - Structural indices of optimal cognitive aging. NeuroImage, 29, 984–994.

Fjell, A.M., Westlye, L.T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D.H., Greve, D.N., Fischl, B., Dale, A.M., Walhovd, K.B., 2009. High consistency of regional cortical thinning in aging across multiple samples. Cereb Cortex, 19, 2001–2012.

Fjell, A.M., Westlye, L.T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Dale, A.M., Walhovd, K.B., 2014. Accelerating cortical thinning: Unique to dementia or universal in aging? Cereb Cortex, 24, 919–934.

Geerligs, L., Tsvetanov, K.A., Henson, R.N., 2017. Challenges in measuring individual differences in functional connectivity using fMRI: the case of healthy aging. Hum Brain Mapp, 38, 4125–4156.

Hedden, T., Schultz, A.P., Rieckmann, A., Mormino, E.C., Johnson, K.A., Sperling, R.A., Buckner, R.L., 2016. Multiple Brain Markers are Linked to Age-Related Variation in Cognition. Cereb Cortex, 26, 1388–1400.

Hildebrandt, A., Wilhelm, O., Schmiedek, F., Herzmann, G., Sommer, W., 2011. On the Specificity of Face Cognition Compared With General Cognitive Functioning Across Adult Age. Psychol Aging, 26, 701–715.

Hou, M., de Chastelaine, M., Jayakumar, M., Donley, B.E., Rugg, M.D., 2020. Recollection-related hippocampal fMRI effects predict longitudinal memory change in healthy older adults. Neuropsychologia, 107537.

Jernigan, T.L., Gamst, A.C., Fennema-Notestine, C., Ostergaard, A.L., 2003. More “mapping” in brain mapping: statistical comparison of effects. Hum Brain Mapp, 19, 90–95.

Kaup, A.R., Mirzakhanian, H., Jeste, D.V., Eyler, L.T., 2011. A Review of the Brain Structure Correlates of Successful Cognitive Aging. J Neuropsychiatry, 23, 6–15.

Knopman, D.S., Lundt, E.S., Therneau, T.M., Vemuri, P., Lowe, V.J., Kantarci, K., Gunter, J.L., Senjem, M.L., Mielke, M.M., Machulda, M.M., Roberts, R.O., Boeve, B.F., Jones, D.T., Petersen, R.C., Jack, C.R., 2018. Joint associations of β-amyloidosis and cortical thickness with cognition. Neurobiol Aging, 65, 121–131.

Koen, J.D., Hauck, N., Rugg, M.D., 2019. The relationship between age, neural differentiation, and memory performance. J Neurosci, 39, 149–162.

Koen, J.D., Rugg, M.D., 2019. Neural dedifferentiation in the aging brain. Trends Cogn Sci, 23, 547–559.

Kranz, M.B., Voss, M.W., Cooke, G.E., Banducci, S.E., Burzynska, A.Z., Kramer, A.F., 2018. The cortical structure of functional networks associated with age-related cognitive abilities in older adults. PLoS ONE, 13, 1–26.

Lee, S., Habeck, C., Razlighi, Q., Salthouse, T., Stern, Y., 2016. Selective association between cortical thickness and reference abilities in normal aging. NeuroImage, 142, 293–300.

Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: Nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol Aging, 33, 617.e1-617.

MacPherson, S.E., Cox, S.R., Dickie, D.A., Karama, S., Starr, J.M., Evans, A.C., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2017. Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. Cortex, 95, 92–103.

McGinnis, S.M., Brickhouse, M., Pascual, B., Dickerson, B.C., 2011. Age-Related changes in the thickness of cortical zones in humans. Brain Topogr, 24, 279–291.

Moss, H.E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., Tyler, L.K., 2005. Selecting among competing alternatives: Selection and retrieval in the left inferior frontal gyrus. Cereb Cortex, 15, 1723–1735.

Murphy, E.A., Holland, D., Donohue, M., McEvoy, L.K., Hagler, D.J., Dale, A.M., Brewer, J.B., 2010. Six-month atrophy in MTL structures is associated with subsequent memory decline in elderly controls. NeuroImage, 53, 1310–1317.

Nyberg, L., Pudas, S., 2019. Successful Memory Aging. Annu Rev Psychol. 70, 219–243.

Oschwald, J., Guye, S., Liem, F., Rast, P., Willis, S., Röcke, C., Jäncke, L., Martin, M., Mérillat, S., 2019. Brain structure and cognitive ability in healthy aging: A review on longitudinal correlated change. Rev Neurosci, 31, 1–57.

Pacheco, J., Goh, J.O., Kraut, M.A., Ferrucci, L., Resnick, S.M., 2015. Greater cortical thinning in normal older adults predicts later cognitive impairment. Neurobiol Aging, 36, 903–908.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage, 59, 2142–2154.

Rast, P., Kennedy, K.M., Rodrigue, K.M., Robinson, P.R.A.W., Gross, A.L., McLaren, D.G., Grabowski, T., Schaie, K.W., Willis, S.L., 2018. APOEε4 Genotype and Hypertension Modify 8-year Cortical Thinning: Five Occasion Evidence from the Seattle Longitudinal Study. Cereb Cortex, 28, 1934–1945.

Reitan, R.M., Wolfson, D., 1985. The Halstead–Reitan neuropsychologican test battery. Tucson, AZ: Neuropsychological Press.

Reuter, M., Tisdall, M.D., Qureshi, A., Buckner, R.L., van der Kouwe, A.J., Fischl, B., 2015. Head motion during MRI acquisition reduces gray matter volume and thickness estimates. Neuroimage, 107, 107–115.

Sala-Llonch, R., Idland, A.V., Borza, T., Watne, L.O., Wyller, T.B., Brækhus, A., Zetterberg, H., Blennow, K., Walhovd, K.B., Fjell, A.M., 2017. Inflammation, Amyloid, and Atrophy in the Aging Brain: Relationships with Longitudinal Changes in Cognition. J Alzheimers Dis, 58, 829–840.

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S.R., Busa, E., Morris, J.C., Dale, A.M., Fischl, B., 2004. Thinning of theCereb Cortex in aging. Cereb Cortex, 14, 721–730.

Salthouse, T.A., 2009. When does age-related cognitive decline begin? Neurobiol Aging, 30, 507–514.

Salthouse, T.A., Davis, H.P., 2006. Organization of cognitive abilities and neuropsychological variables across the lifespan. Dev Rev, 26, 31–54.

Salthouse, T.A., Habeck, C., Razlighi, Q., Barulli, D., Gazes, Y., Stern, Y., 2015. Breadth and age-dependency of relations between cortical thickness and cognition. Neurobiol Aging, 36, 3020–3028.

Salthouse, T.A., Madden, D.J., 2007. Information processing speed and aging. In: Deluca J, Kalmar J, editors. Information processing speed in clinical populations. New York: Psychology Press; p. 221–241.

Salthouse, T.A., Tucker-Drob, E.M., 2008. Implications of Short-Term Retest Effects for the Interpretation of Longitudinal Change. Neuropsychology, 22, 800–811.

Savalia, N.K., Agres, P.F., Chan, M.Y., Feczko, E.J., Kennedy, K.M., Wig, G.S., 2017. Motion□related artifacts in structural brain images revealed with independent estimates of in□scanner head motion. Hum. Brain Mapp, 38, 472–492.

Spearman, C.E., 1927. The abilities of man. New York: MacMillan.

Spreen, O., Benton, A.L., 1977. Neurosensory center comprehensive examination for aphasia. Victoria, BC, Canada: Neuropsychology Laboratory.

Sun, F.W., Stepanovic, M.R., Andreano, J., Barrett, L.F., Touroutoglou, A., Dickerson, B.C., 2016. Youthful brains in older adults: Preserved neuroanatomy in the default mode and salience networks contributes to youthful memory in superaging. J Neurosci, 36, 9659–9668.

Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J.L., Resnick, S.M., 2010. Longitudinal changes in cortical thickness associated with normal aging. NeuroImage. 52, 1215–1223.

Tsapanou, A., Habeck, C., Gazes, Y., Razlighi, Q., Sakhardande, J., Stern, Y., Salthouse, T.A., 2019. Brain biomarkers and cognition across adulthood. Hum Brain Mapp, 40, 3832–3842.

van Velsen, E.F.S., Vernooij, M.W., Vrooman, H.A., van der Lugt, A., Breteler, M.M.B., Hofman, A., Niessen, W.J., Ikram, M.A., 2013. Brain cortical thickness in the general elderly population: The Rotterdam Scan Study. Neurosci Lett, 550, 189–194.

Vinke, E.J., de Groot, M., Venkatraghavan, V., Klein, S., Niessen, W.J., Ikram, M.A., Vernooij, M.W., 2018. Trajectories of imaging markers in brain aging: the Rotterdam Study. Neurobiol Aging, 71, 32–40.

Vonk, J.M.J., Rizvi, B., Lao, P.J., Budge, M., Manly, J.J., Mayeux, R., Brickman, A.M., 2019. Letter and Category Fluency Performance Correlates with Distinct Patterns of Cortical Thickness in Older Adults. Cereb Cortex, 29, 2694–2700.

Wager, T.D., Lindquist, M.A., Nichols, T.E., Kober, H., Van Snellenberg, J.X., 2009. Evaluating the consistency and specificity of neuroimaging data using meta-analysis. Neuroimage, 45, 210–221.

Wechsler, D. 2001. Wechsler Test of Adult Reading. San Antonio, TX: The Psychological Corporation.

Wechsler, D. 2009. Wechsler Memory Scale–Fourth Edition. San Antonio, TX: Pearson.

Westlye, L.T., Grydeland, H., Walhovd, K.B., Fjell, A.M., 2011. Associations between regional cortical thickness and attentional networks as measured by the attention network test. Cereb Cortex, 21, 345–356.

Zhao, L., Matloff, W., Ning, K., Kim, H., Dinov, I.D., Toga, A.W., 2019. Age-Related Differences in Brain Morphology and the Modifiers in Middle-Aged and Older Adults. Cereb Cortex, 29, 4169–4193.

- Cortical thickness of the right IFG and right hemisphere were positively correlated with general and domain-specific cognitive performance
- Right IFG thickness was predictive of longitudinal memory change
- The relationships between right IFG thickness and cognition did not persist after controlling for thickness of other ipsilateral cortical regions
- Most relationships between thickness and individual cognitive domains were non-significant after controlling for the variance shared with other cognitive domains

Verification

1. No declarations of interest.

2. This work was supported by the National Institute on Aging (grant number 1RF1AG039103).

3. The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

4. Experimental procedures were approved by the Institutional Review Boards of The University of Texas at Dallas and The University of Texas Southwestern Medical School.

5. All authors have reviewed the contents of the manuscript being submitted, approve of its contents, and validate the accuracy of the data.