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Cortical thickness in the right inferior frontal gyrus mediates age-related performance differences on an item-method directed forgetting task

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ABSTRACT

Evidence suggests that older adults have difficulty relative to younger adults in forgetting irrelevant information. Here we sought to understand the physical basis of this deficit by investigating the relationship between cortical thickness and intentional forgetting, using an item-method directed forgetting task. We tested younger (n = 44) and older (n = 54) adults' memories for words that they were instructed to either remember or to forget, and then extracted cortical thickness values from brain regions previously shown, using functional neuroimaging, to be associated with memory suppression, including the right inferior frontal gyrus, the right postcentral gyrus and the left superior/middle frontal gyrus. Results from a parallel mediation model indicated that variations in cortical thickness in the right inferior frontal gyrus, but not the right postcentral gyrus or left superior/middle frontal gyrus, partially explained age-related differences in directed forgetting: older adults with thinner cortices in this area showed worse forgetting ability. This is the first study to explore how neuromorphological differences affect the ability to intentionally suppress items in memory. The results suggest that age-related differences in directed forgetting may be partly driven by cortical thickness in a brain structure known to be functionally involved in directed forgetting, and inhibitory control more broadly, supporting a contribution of deficient inhibition to this phenomenon.

1. Introduction

While failing to be able to remember is, by nearly all accounts, one of the most negative aspects of aging (Schacter, 1999), forgetting may also serve a critical, adaptive function for memorial processes (Bjork, 1989). According to William James (1890), "If we remembered everything, we should on most occasions be as ill off as if we remembered nothing". This is because, given unlimited memory storage, if we had the ability to also recall all memories, the act of recalling any one specific event (where you parked your car *today*) would result in the recall of all related events (where you parked *yesterday* or *the day before yesterday* or *the day before that)*. Retrieval competition (between memories for all places that you have *ever* parked your car) would have to be resolved in order for you to finally find your car in the lot. As Robert Bjork aptly said, this would be "a mess" (Bjork, 2012, p.12).

In the lab, one of the tasks frequently used to explore the ability to actively control the contents of memory is the directed forgetting (DF) paradigm (see (Anderson & Hanslmayr, 2014) for a review). In the item-method version of this task, participants are presented with a series of words, one at a time, and told after the presentation of each whether the word is to be remembered (TBR) for a later memory test, or to be forgotten (TBF). Memory is then probed for all items, including words that participants should have forgotten. Younger adults typically show poorer memory for

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the TBF items relative to the TBR items, often indexed by the size of difference score between TBR and TBF items and called the DF effect. A 2010 meta-analysis of the DF effect in older adults revealed that while older adults show a DF effect, the DF effect is "reliably smaller in older adults than in younger adults, even after controlling for age differences in baseline recall" (Titz & Verhaeghen, 2010).

What is the origin of reduced directed forgetting in aging? Two main cognitive mechanisms have been proposed to underlie item-method DF effects: the differential encoding/selective rehearsal account posits that TBR items are rehearsed and elaborated on, which results in memory for these items being strengthened. TBF items, on the other hand, simply decay, passively, over time (see Bjork, 1972; MacLeod, 1998). The second mechanism posits that TBF items are actively inhibited at encoding through higher order control processes. Hasher and colleagues' seminal theory of inhibition (Hasher & Zacks, 2006; Hasher et al., 2007), based on and supported by a multitude of experimental manipulations (Anderson, Reinholz, Kuhl, & Mayr, 2011; Eich et al., 2017, 2018; Hartman & Hasher, 1991; Hasher, Quig, & May, 1997; Hasher & Zacks, 1988; Morrone, Declercq, Novella, & Besche, 2010; Zacks, Hasher, & Li, 2000) proposed that the cognitive process involved in being able to rid memory of irrelevant information accounts "for much of the variation in cognitive performance" and indeed may even to be a "fundamental determinant" of cognitive health in normal aging (Hasher, Lustig, & Zacks, 2007). That is, it is not merely the case that memory *per se* is impaired in aging. Rather, the process allowing an individual to forget or filter out irrelevant information is impaired. To wit, they argue that the smaller DF effect found for older adults stems precisely from this failure to inhibit the irrelevant information in response to the forget instruction, which leads older adults to inappropriately recall more TBF words during a later recall test (Zacks, Radvansky, & Hasher, 1996).

Compelling behavioral and neural data favor a contribution of active inhibition processes to the item-method DF effect. On a behavioral level, evidence for an active forgetting process comes from both a meta-analysis (Murayama et al., 2014) as well as a study in which predictions about each potential mechanism were directly tested (Fawcett & Taylor, 2008). In this study, participants were given a secondary task to complete after each TBF or TBR memory cue. If, according to the differential encoding account, effortful processing enhances memory for TBR items and TBF items decay passively, then performance on the secondary task should be worse for TBR cues relative to TBF cues, as cognitive resources should be occupied with processes that enhance memory for TBR items at the expense of completing the secondary task. On the other hand, if active inhibitory processes are engaged to suppress the encoding of TBF items, then performance on the secondary task should be impaired following the TBF cues. This later result was observed: reaction times were slower following TBF cues relative to TBR cues, suggesting that participants were actively engaging cognitive resources to forget the TBF items. On a neural level, recent evidence from intracranial recordings in both the prefrontal cortex and the hippocampus establish a top-down influence of the right prefrontal cortex on hippocampal processing in response to the forget instruction, consistent with an active process that suppresses hippocampal encoding (Oehrn et al., 2018; see Anderson & Hulbert, 2021, for a discussion).

As the foregoing intracranial findings suggest, the neural mechanisms of DF have been largely attributed to prefrontal control mechanisms (Anderson & Hanslmayr, 2014; Bastin et al., 2012; Fawcett & Taylor, 2008; Hauswald, Schulz, Iordanov, & Kissler, 2011; Paz-Caballero, Menor, & Jiménez, 2004; Wylie, Foxe, & Taylor, 2008; Yang et al., 2013). Relatively few functional neuroimaging study have explored memory suppression using the DF paradigm, and we are aware of only one study that has examined age-related differences in brain activity during the task (Rizio & Dennis, 2014). In this study, intentional forgetting was measured by comparing brain activity for items that were supposed to be forgotten and subsequently were, versus items that were supposed to be remembered and subsequently were (TBF-Forgotten > TBR-Remembered). This contrast revealed greater activity for younger adults relative to older adults in the right middle frontal and superior frontal gyri, as well as the paracentral lobule. This study also examined the difference between intentional and unintentional forgetting by comparing brain activity elicited for words that were supposed to be forgotten, and those that were supposed to be remembered but instead were forgotten incidentally (TBF-F > TBR-F). This contrast revealed greater activity for younger relative to older adults in similar areas. However, a contrast specially focused on active versus passive forgetting (e.g., the difference between items that were supposed to be forgotten and were, versus those that were supposed to be forgotten and weren't) was not reported in this study. Wylie, Foxe and Taylor (2008), however, in a sample of younger adults, did directly contrast intentional versus unintentional forgetting by comparing activation for TBF trials that later resulted in successful forgetting, as compared to TBF trials that were later remembered (TBF-F>TBF-R). Activity in three main brain areas emerged from their analysis: the left superior/middle frontal gyrus (BA 10), the right inferior frontal gyrus and, to a lesser extent, the right postcentral gyrus (PCG, BA 4). These areas have been associated with several functions that may contribute to different aspects of intentional forgetting. The superior/middle frontal gyrus has been associated with prospective memory (Burgess et al., 2011), relational integration (Bunge et al., 2009; Smith et al., 2007) and episodic memory retrieval (Düzel et al., 2001). Broadman area 4 of the postcentral gyrus, located in the lateral parietal lobe, on the other hand, encompasses the primary motor cortex. Critically, the right inferior frontal gyrus region identified by Wylie and colleagues is widely regarded as an origin of inhibitory control signals involved in motor response stopping, and perhaps inhibitory control more broadly (Aron et al, 2014).

While the neural correlates of directed forgetting have previously been explored using functional imaging, it is not yet known whether structural indices of brain health are related to impairments in the ability to intentionally forget information. A reduction in cortical thickness, which is thought to be a proxy for the number of neurons, dendritic arborization and spines, synapses, and glial cells at each cortical vertex (la Fougère et al., 2011), has been shown, using longitudinal designs, to begin in middle-age (defined as individuals with a mean age of 48.6, range 41–57 years) (Salat et al., 2004), with frontal areas showing greater degeneration with age than other brain areas (Raz et al., 1997). Further, the rates of age-related cortical thinning within the PFC are not homogeneous. Declines in several regions within the PFC, including the pars opercularis and pars triangularis –subparts of the inferior frontal gyrus – are more vulnerable to age-related atrophy, even amongst healthy elders. Thus, based on the previous functional imaging work which revealed several key brain areas to associated with the ability to actively forget information, the current study was designed to directly test whether the age-related DF is attributable to cortical thickness in these same brain areas. We were particularity interested in whether age-related differences would be explained by thickness in the right inferior frontal gyrus, which is known to be involved in inhibitory control more broadly (Aron et al., 2014). To this end, we used parallel mediation analyses to simultaneously model the effects of thickness in the right inferior frontal gyrus along with the other two areas reported by Wylie et al, which have been associated with other cognitive func-

tions including memory and motor actions, to allow us to test for the specificity of the role of an inhibitory mechanism underlying the DF effect in aging.

2. Materials and Methods

2.1. Participants

One hundred participants who were either 40 or under or 65 or older when they had a structural T1-weighted MRI scan completed were recruited to the present study, called the SOFIA study (Study of the Factor-structure of Inhibition in Aging), which focused on age-related changed to inhibitory control processes. SOFIA study participants were recruited from two larger ongoing studies in the Cognitive Neuroscience Division at Columbia University, the RANN (Reference Ability Neural Network) and the CR (Cognitive Reserve) studies. To be eligible to participate in RANN or CR, participants were required to be right-handed English speakers with at least a fourth-grade reading level. All participants were screened for current neurological or psychiatric diagnoses, and medication use. Older adults were additionally screened for dementia via the Dementia Rating Scale (Mattis, 1988), and any participant with a score below 135 was not eligible to participate. Informed consent, as approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, was obtained prior to study participation. Before completing the DF task, all participants completed an instruction manipulation check (IMC) modeled after (Oppenheimer, Meyvis, & Davidenko, 2009), in which participants had to carefully read a set of instructions and press an indicated key to advance. Two participants were excluded prior to analysis for requiring more than 10 attempts to pass the IMC, leaving a final sample of forty-four younger adults (M age 34.00, SD 3.9, 71% Female; M years of education 16.41, SD 2.21) and fifty-four older adults (M age 72.89, SD 4.32, 48% Female; M years of education 16.65, SD 2.24).

2.2. Directed forgetting task

Participants completed a computerized, item-method DF task (Bjork, 1972). In the study phase, participants were presented, one at a time, with words that were either to be remembered (TBR) or to be forgotten (TBF). Each word was presented for 2500 ms, followed by a 500 ms delay and then a memory cue, presented for 1500 ms. The TBR memory cue consisted of four green R's (for Remember), and the TBF cue consisted of four red F's (for Forget). Six additional unscored buffer trials were presented as the first and last three trials of the experiment, to minimize primacy and recency effects. Before beginning the study phase, participants were instructed that they should remember the TBR words for a later memory test, and that forgetting the TBF words would help them remember all of the TBR words. Each trial was separated by a 1000 ms inter-trial interval. Following the presentation of the study items, participants were given a recognition test, consisting of the 36 study words and 36 foils (new words). Before the recognition test began, participants were instructed to indicate whether or not the word had been presented to them before at any point during the experiment. If the word had been presented, they should press the Y key on the keyboard (for Yes). If the word had not been presented, they should press the N key (for No). They were further instructed that they should press the Y key for TBF words, even though they were told to forget these words previously, because these words had been presented. Thus, the correct response for both TBR and TBF items was "Y", whereas the correct response for New items was "N". Each test word appeared on the screen for 20,000 ms, or until the participant responded, whichever occurred first.

Stimuli were drawn from a pool of 72 highly unrelated and unambiguous concrete nouns, ranging in length from three to eight letters. Participants received 36 study words and 72 test words in one of four stimuli lists, which were pseudo randomly assigned. In all lists, each of the 36 items was pre-assigned to be in one of 6 study blocks. Within each block, half the items were TBR items and the other half were TBF items. Both the order of the 6 study blocks and the order of the items within each study block were randomized. Test words consisted of all 36 of the studied words, plus an additional 36 new words. The 72 test items were pre-assigned to be in one of 6 test blocks, each containing 12 items: 3 TBR items, 3 TBF items, and 6 new items. The order of the items within each test block, and the order of the 6 test blocks, was randomized. Items within each of the 4 study and test lists were counterbalanced across participants: The items that were TBR in list 1 became TBF items in list 2 (and likewise for lists 3 and 4), and New test items in list 1 and 2 became either TBR or TBF items in lists 3 and 4.

2.3. Structural imaging data acquisition

Participants underwent a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scan, acquired on a 3.0 Tesla Philips Achieva MRI scanner. These scans were acquired with TE/TR of 3/6.5 ms and Flip Angle of 8 degrees, in-plane resolution of 256 × 256, field of view of 25.4 × 25.4 cm, and 165–180 slices in axial direction with slice-thickness/gap of 1/0 mm.

2.4. Structural image data processing

The T1-weighted MPRAGE scans were reconstructed using FreeSurfer (v5.1.0) (http://surfer.nmr.mgh.harvard.edu/) an automated segmentation and cortical parcellation software package (Fischl, 2012; Fischl et al., 2002; Fischl, van der Kouwe, et al., 2004). Using each participant's T1-weighted MPRAGE image, the gray/white matter boundary (Dale, Fischl, & Sereno, 1999) was reconstructed at the cortical surfaces, and then the distances between these surfaces at each point across the cortical mantle was calculated. Although the thickness estimation procedure is automated, the accuracy of the spatial registration and the white/gray matter segmentations were manually checked following the analytic procedures outlined in Fjell et al (2009), and were also visually inspected. When necessary, manual editing to ensure accuracy was conducted per the FreeSurfer manual editing guidelines (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction) by a single technician who was blind to participant demographics. The borders of the parcellated cortical and sub-cortical regions were then overlayed on top of the original input structural image by a second technician in a second round of quality control. Using a validated automated labeling system (Fischl, Salat, et al., 2004) FreeSurfer divides the cortex into 34 different gyral-based regions of interest (ROIs) per hemisphere according to the Desikan-Killiany atlas (Desikan et al., 2006) and calculates the mean thickness in each area (Hagler, Saygin, & Sereno, 2006). The maps produced are capable of detecting submillimeter differences in cortical thickness between individuals (Fischl & Dale, 2000). The results of this gyral-based cortical parcellation were used for cortical parcellation and regional identification of clusters.

2.5. A priori regions of interest

Wylie, Foxe and Taylor (2008) previously used event-related fMRI to isolate brain activity associated with actively –and not passively– forgetting information during an item-method Direct Forgetting task, by contrasting brain activity resulting from TBF trials that later resulted in successful forgetting, as opposed TBF trials that were later remembered (TBF-Forget > TBF-Remember). The ROIs for the current study were created by averaging cortical thickness values from this contrast: Left superior/middle frontal gyrus was created by averaging left hemisphere values derived from the FreeSurfer parcellation for superior frontal and medial orbitofrontal areas, and right inferior frontal gyrus was created by averaging right hemisphere values across its three subgyri: the pars opercularis, pars orbitalis and pars triangularis (Greenlee et al., 2007). Thickness values for the right postcentral gyrus were among the 34 parcellations automatically generated by FreeSurfer's parcellation algorithm.

2.6. Statistical analysis

A repeated measures ANOVA including both age group and sex as between-subjects factors and trial type (TBR, TBF and new items) as within-subjects factors was used to assess trial level behavioral performance on the task. The main behavioral variable of interest, the DF effect, was investigated using an ANOVA, in which both age group and sex were included as fixed factors, followed by post-doc two-tailed t-tests of these differences within each age and sex-group. The DR effect was calculated by subtracting performance on TBF items from TBR items. If TBF items are inhibited, accuracy for these items relative to TBR items should be worse, as these forgotten items will appear to be new, making the TBF-TBR difference score larger. Thus, by an inhibition account, a larger DF score partially reflects inhibition ability, and the smaller difference score in aging arises from increased recognition of words that should have been forgotten by inhibition. JASP (2020, Version 0.14.1) was used to conduct these analyses. To explore the role of brain morphometry in the age-behavioral relationship, we conducted a parallel mediation model using Hayes' PROCESS macro in SPSS (Hayes, 2017) to test whether DF scores were attributable to age-related differences in cortical thickness. In a secondary analysis, we entered sex as a covariate in the model.

To test a mediation effect in the historical, causal steps approach, first, there must be a direct effect between the exposure (e.g., age) and the outcome (e.g., DF)(Baron & Kenny, 1986). Second, there must be a direct effect between the exposure (e.g., age) and the mediator (e.g., cortical thickness), as well as an adjusted effect between the mediator (e.g., cortical thickness) and the outcome (e.g., DF) after accounting for the exposure-mediator relationship. However, more recent approaches suggest that the lack of a direct effect should not preclude the investigation of hypothesis-driven mediation effects, particularly in small samples and in the presence of competing mediation effects. Parallel mediation extends the typical mediation analysis by testing several mediators simultaneously within a single model.

Mediation results can be broken down into two components: the direct effect between exposure and outcome (e.g., older age is related to lower DF; C in Fig. 1) and the indirect effect from exposure to mediator to outcome (e.g., older age is related to thinner cortex in particular ROIs ($a_{1\text{-}3}$ in Fig. 1), which is in turn, related to lower DF ($b_{1\text{-}3}$ in Fig. 1). Complete mediation occurs when the entirety of the effect of the exposure on the outcome can be attributed to the mediator(s) (i.e., the direct effect after accounting for the mediation effect, C', is not significant, but the indirect effect through the mediator, a*b, is significant). Partial mediation occurs when part of the effect of the exposure on the outcome can be attributed to the mediator(s) (i.e., the direct effect after accounting for the mediation effect, C', is significant, and the indirect effect through the mediator, a*b, is significant). Finally, no mediation occurs when the effect of the exposure on the outcome cannot be attributed to the mediator(s) (i.e., the direct effect after accounting for the mediation effect, C', is significant, but the indirect effect through the mediator, a*b, is not significant). We used bootstrapping to calculate confidence intervals for the indirect effects of the three ROIs. Confidence intervals that do not include zero indicate a significant mediation model where age indirectly affects DF score via the specified ROI.

Table 1
Participant demographics, performance on the three different trial types (To Be Remembered (TBR) words; To Be Forgotten (TBF) words; New words) and cortical thickness values for the 3 regions of interest by age group

	Younger	Older
N	44	54
Age @ MRI (SD)*	31.09 (4.55)	70.48 (4.22)
Age @ DF Test (SD)*	34 (3.93)	72.89 (4.32)
% Female*	71	48
Years Education (SD)	16.41 (2.21)	16.65 (2.24)
TBR % Correct (SD)	83.21 (14.30)	78.49 (17.62)
TBF % Correct (SD)*	53.66 (24.64)	63.07 (20.54)
New % Correct (SD)	86.86 (15.34)	86.69 (15.65)
TBR - TBF % (SD)*	29.55 (24.25)	15.43 (17.62)
Left superior/middle FG Thickness (SD)*	2.75 (.14)	2.57 (.15)
Right Inferior Frontal Gyrus Thickness (SD)*	2.79 (.15)	2.57 (.16)
Right Postcentral Thickness (SD)*	2.19 (.13)	2.12 (.13)

* indicates a significant ($p < .05$) difference between age-groups.

3. Results

3.1. Sample characteristics

There were no significant differences between either the level of education of the younger and older adults (t(96) = -0.528, $p = 0.598$), or the lag time between MRI and DF testing (t(96) = 1.460, $p = 0.147$). However there were significantly more women in the younger relative to the older adult groups (t(96) = 2.262, $p = 0.026$).

3.2. Directed forgetting performance

The mean and standard deviation (SD) of the accuracy for younger and older adults in each of the 3 conditions (TBR, TBF and new items) as well as the DF effect (TBR-TBF) are shown in Table 1. A repeated measures ANOVA including both age group and sex as between-subjects factors and trial type (TBR, TBF and new items) as within-subjects factors revealed a main effect of trial type (f(2, 188) 73.389, $p = 0.001$, $n^2 = 3.08$) and a significant interaction between trial type and age group (f(2, 188) 5.835, $p = 0.003$, $n^2 = 0.024$). The main effects of age group and sex were not significant ($p > 0.2$), nor was the interaction between trial type and sex ($p = 0.084$) or trial type, age group and sex ($p = 0.270$). Post-hoc Bonferroni corrected t-tests based on the results of this ANOVA revealed that the sample as a whole exhibited control over memory encoding, and recognized more TBR than TBF items (t(43 = 11.518, $p < 0.001$, (95% CI = 0.306, 0.242), an effect which was also found within each age group (for younger adults, t(43) = -8.080, $p < 0.001$, (95% CI = -0.369, -0.222); for older adults, t(53) = -6.4357, $p < 0.001$, (95% CI = -0.202, -0.106)). Independent samples t-test were then used to compare performance between younger and older adults on all four measures. Older and younger adults did not reliably differ in accuracy for TBR words,

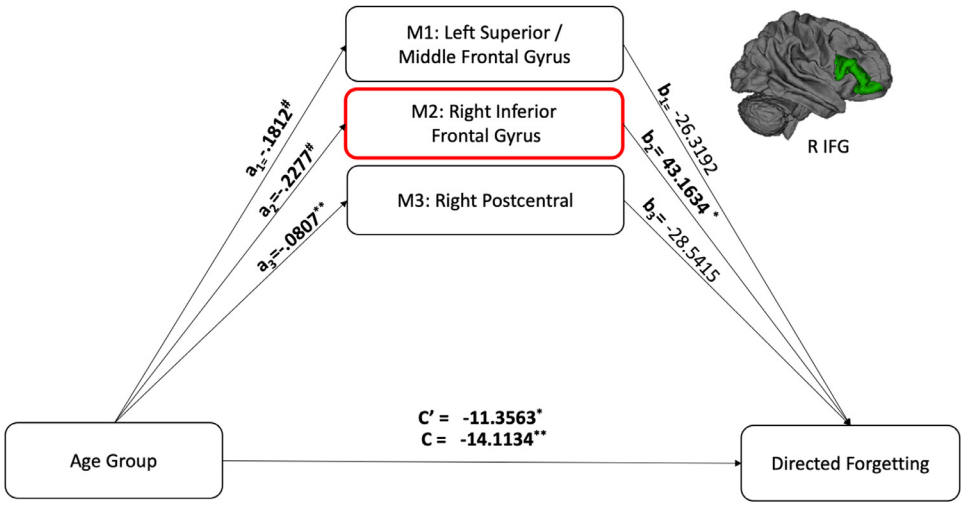

Fig. 1. The mediating effect of cortical thickness (CT) from 3 regions of interest (ROI) associated with Intentional Forgetting (from the contrast of TBF-Forgotten - TBF-Remembered from Wylie, Foxe and Taylor, 2008) in the relationship between Age Group and Directed Forgetting (DF). Notes: $^{*}p < .05$, $^{**}p < .01$, $\#p < .001$; All presented effects are unstandardized; a_n is effect of age on CT ROIs, Young are coded as 0 and Old as 1; b_n is effect of CT ROIs on DF; c is the total effect and c′ is the direct effect of Age Group on DF

t(96) = 1.425, $p = 0.157$, (95% CI = -0.018, 0.112), or for New words, t(96) = 0.033, $p = 0.974$, (95% CI= -0.062, 0.064). However, older adults did identify more TBF words as "old" than did younger adults, t(96) = 2.0618, $p = 0.042$, (95% CI =- 0.185, - 0.003), indicating that older adults did not forget these words, and instead remembered words that they were told to forget to a greater extent than did younger adults. An ANOVA on the DF score replicated previous findings, revealing a main effect of age-group (f(1, 94) = 15.417, $p = 0.001$, $n^2 = 0.133$), with younger adults showing significantly larger DF scores than older adults. Sex was also significant (f(1, 94) = 5.614, $p = 0.020$, $n^2 = 0.048$). Post hoc t-tests revealed that women overall had smaller DF scores than did men. The interaction between age and sex was not significant (f<1).

3.3. Age-brain-behavior mediation model

As is shown in Figure 1, results from the parallel mediation analysis indicated that Age is indirectly related to DF through its relationship with cortical thickness in the right inferior frontal gyrus, but not the left superior/middle frontal or right postcentral gyrus. Not surprisingly, all three ROIs were thinner in the older relative to younger adults ($a_{1,2,3}$ and see Table 1). When sex was included in secondary analyses due to the greater proportion of females to males in the younger adult group, it was not significantly related to thickness in any of the areas. However, critically, thickness in the right inferior frontal gyrus was subsequently related (positively) to the DF score (b1 = 43.163, $p = 0.0195$), suggesting a localized and specific role of this area in active forgetting. A 95% bias-corrected confidence interval based on 10,000 bootstrap samples indicated that the indirect effect through right inferior frontal gyrus thickness (a2b2 = 43.1634), holding the other mediators constant, was entirely below zero (-18.3463 to -1.4402). After controlling for sex, this finding was slightly attenuated, but still significant ($a2b2^{sex} = 38.8620$, $p = 0.0335$). In contrast, the indirect effects through both left middle/superior frontal gyrus and right postcentral gyrus were not different than zero (−1.9696 to 12.1928 and -.7959 to 6.4953, respectively; see Figure 1 for the effects associated with these pathways), including after controlling for sex. Finally, the direct effect ($c' = -11.3563$, $p = 0.0344$) was still significant, but reduced by inclusion of the CT variables, indicating that CT in all three of the ROIs partially mediates the relationship between Age and DF. This result was unchanged when sex was included in the model, (c′sex = -13.2789, $p = 0.0140$).

4. Discussion

Although many cognitive changes occur in the normal course of aging, memory loss is perhaps the most well recognized, both within the research community and by the public at large (Daselaar, Dennis, & Cabeza, 2007; Zacks et al., 2000). The ability to inhibit irrelevant information has been proposed to serve a critical function in efficient memory processes, aiding memory retrieval by reducing interference, thus freeing up limited-resources needed to access relevant information (Hasher & Zacks, 2006; Hasher et al., 2007). Whereas a number of studies have examined the functional neural basis of intentional memory suppression in younger adults, and one study to date has investigated age-related differences in task-related brain activity, no study has investigated whether cortical morphology plays a role in age-related differences in the ability to consciously control the contents of memory through inhibitory mechanisms. To fill this gap in the literature, we used parallel mediation analyses to test whether cortical thickness in brain areas previously found to be functionally associated with intentional forgetting in an item-method directed forgetting paradigm mediates the relationship between age and the ability to successfully suppress specific items from memory.

Our results robustly replicate previous behavioral findings of a diminished DF effect in older adults relative to younger adults. In the current study, this age-related difference appeared to derive primarily from a reduced ability to forget TBF items successfully. Performance on TBR items was not impaired in older relative to younger adults, suggesting that our older adult sample did not have measurable difficulty with encoding verbal items. Instead, the difference in the size of the DF effect across age groups stemmed from older adults recognizing a higher proportion of TBF items, which in turn reduced the DF difference score. The selectivity of the age effect to the forget condition is consistent with an age-related deficit in active forgetting of the TBF items, and in line with an inhibitory deficit account of cognitive aging. On the other hand, the preservation of high accuracy in the remember condition was

not predicted, insofar as a failure to inhibit irrelevant items should tax resources needed to maintain relevant information, and thus impair performance on these (TBR) items. It is possible that, because we used a recognition test rather than free recall, the upper limits of memory load were not reached even for the older adults. Indeed, accuracy for TBR items was high across both groups. Future studies that either use a harder task or that employ a free recall test could be used to determine the conditions under which such a tradeoff, in which inhibitory deficits cause irrelevant information to be retained at the expense of relevant information, does or does not occur.

Our main interest, however, centered on the brain basis of the observed age-related deficit in intentional forgetting, and specifically cortical morphometry, whose relation to age-related changes in behavior have thus far not been explored. As expected, older adults showed significantly thinner cortex in all of our *a priori* chosen regions of interest, which were derived from past functional neuroimaging work that directly assessed active versus passive forgetting using the directed forgetting paradigm: the right inferior frontal gyrus, the right precentral gyrus, and the left middle/superior frontal gyrus. While there was a lag between when structural neuroimaging scans and directed-forgetting testing occurred (see Table 1), in our sample, brain scans always occurred before testing. Because of this, cortical thickness of the older adults is most likely overestimated, and thus one limitation of the current study is that we may be underestimating the influence of cortical thickness on intentional forgetting.

Critically, we found that only thickness in the right inferior frontal gyrus mediated the detrimental effect of age on the ability to intentionally forget. Notably, the right inferior frontal gyrus is known to play a causal role in implementing inhibitory control over motor action (Aron et al., 2014; Aron et al., 2003), as well as in the suppression of memory retrieval (Guo et al. 2018). Our findings are consistent with the possibility that the age-related structural loss in the right inferior frontal gyrus contributes to dysfunction in the ability to activity inhibit episodic encoding, and future studies exploring the relation between brain morphometry and these other inhibitory tasks could directly address this possibility.

The current findings should not be taken to indicate that right inferior frontal gyrus is the sole mechanism mediating successful inhibition in the item-method forgetting procedure. Indeed, in this study, we restricted our analysis to a small set of *a priori* regions motivated by prior imaging work, and so it is possible, even likely, that additional regions contribute to successful implementation of this ability. Future studies that take a bottom-up approach to investigating the full context of the effect being measured and that test the role of cortical thickness across the full set of cortical structural regions on age-related directed forgetting abilities, rather than restricting analyses to a smaller set of regions chosen based on extant literature or theory, could determine whether or not this is the case. They do, however, illustrate how not all regions revealed by functional neuroimaging to be associated with directed forgetting are causally necessary to successful forgetting. The failure to observe relationships between age-related decline in directed forgetting and cortical thickness in the left superior/middle frontal gyrus and the post-central gyrus suggest that the structural integrity of these regions can be perturbed without substantially affecting successful memory inhibition. However, the functional contribution of these regions to directed forgetting remains to be understood.

Although our findings indicate the structural changes in the right inferior frontal gyrus mediate age-related changes in intentional forgetting, this mediation effect was only partial. Even after considering cortical thickness in the inferior frontal gyrus, a significant relationship between age and directed forgetting remained in our mediation analysis. This suggests that additional causes of age-related directed forgetting effects apart from those due to structural deficits in right inferior frontal gyrus remain to be identified. Several possibilities exist. First, in addition to structural changes to the inferior frontal gyrus measurable with cortical thickness analysis, age may also alter other aspects of the functioning of the right inferior frontal gyrus not detectable with this method, including changes in neurochemistry, vascular changes, or white matter connectivity necessary to implement inhibitory control over memory. Second, the residual deficit may arise from age-related changes to elaborative encoding. However, elaborative encoding would be expected to benefit memory for the TBR items, and thus any such differences would be expected to affect memory for these items in particular, which in the current study, was not found to be the case. Further, a recent study by (Amlien et al., 2019), used graph theory to explore the relative contribution of different brain regions to successful episodic retrieval as a function of the depth at which memory targets were encoded, and reported that, of 42 regions tested, the right middle frontal gyrus was one of three areas found to be positively related to semantic elaboration during encoding. In our study, a mediating effect of the right middle frontal gyrus on the relationship between age and directed forgetting was not found. Combined, these results suggest that elaborative encoding may not be contributing to age-related differences in active forgetting. Finally, the residual deficit may reflect deficits in cognitive functions such as task-set maintenance that may not rely on our *a priori* defined ROIs. For example, task switching has been associated with activation in Broadman Areas 9, 46, 44, and 45, along with the inferior frontal gyrus in younger adults (Richter & Yeung, 2014), with increased activity in these areas as well as the right precentral and postcentral gyri being associated with a greater switch cost in older adults (Nashiro et al., 2018). These brain regions represent fruitful targets for future imaging research into DF effects.

The present findings add to the body of research suggesting that age-related declines in mnemonic function may derive, in part, from deficits in inhibitory control, consistent with the inhibitory deficit hypothesis of cognitive aging (Hasher & Zacks, 2006; Hasher et al., 2007). The selectivity of the deficit to performance on TBF items, and the selective coupling of this deficit to a prefrontal region widely known to be instrumental to inhibitory control in a variety of functional contexts suggests that age-related changes in directed forgetting are unlikely to derive solely from deficient elaborative encoding. If so, then morphological changes in the right inferior frontal gyrus may rob older adults of the important ability to forget unwelcome experiences in life. Future studies that investigate the consequences of such failures, to both other cognitive abilities, and activities of daily living, are urgently needed.

Disclosure statement

I certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on me or on any organization with which I am associated AND, if applicable, I certify that all financial and material support for this research (eg, NIH or NHS grants) and work are clearly identified in the title page of the manuscript.

Declaration and verification

The work described has not been published previously and is not under consideration for publication elsewhere. All authors

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CRediT authorship contribution statement

Teal S. Eich: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Patrick Lao:** Formal analysis, Writing – review & editing. **Michael C. Anderson:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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