

BRIEF COMMUNICATION

Perceptual and Memory Inhibition Deficits in Clinically Healthy Older Adults Are Associated With Region-Specific, Doubly Dissociable Patterns of Cortical Thinning

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Converging evidence suggests that the cognitive control processes that enable the inhibition of irrelevant information on a perceptual versus a memorial basis are qualitatively different and are underlain by unique neural systems that may be affected differentially in aging. In the current study, we investigated whether individual differences in performance on these 2 types of inhibitory processes were attributable to region-specific patterns of cortical thinning. Clinically healthy older adults completed a pair of behavioral memory and perceptual inhibition tasks and then underwent structural brain imaging. We found that worse memory inhibition was associated with reduced cortical thickness in the left ventral lateral prefrontal cortex (VLPFC), an area that has been functionally associated with memory inhibition, but not in either the right or left superior parietal lobule (SPL), areas that have been functionally associated with perceptual inhibition. On the contrary, while impaired perceptual inhibition was associated with cortical thinning in the right SPL, it was not associated with cortical thickness in either the left VLPFC or SPL. These results suggest a double dissociation between performance on 2 types of inhibitory control tasks and cortical thinning in specific brain areas, previously shown to be uniquely associated with functional activation of each these 2 types of cognitive tasks.

Keywords: aging, inhibition, cortical thickness, neuromorphology, individual differences

Individual differences in cognitive trajectories across the life span have been proposed to stem, at least in part, from variation in neuro-morphological changes that occur with age (Fjell et al., 2006). Age-related changes to mental processes occur across a host of different cognitive abilities ranging from fluid reasoning to perceptual speed (Braver & West, 2008; Craik & Byrd, 1982; Stern et al., 2014). Though many studies have investigated changes to brain structure across the life span (de Leon et al., 1997; Fischl & Dale, 2000; Fjell et al., 2006; Jack et al., 1997; Salat et al., 2004), and a number of studies have investigated the relationship between volumetric mea-

asures of brain integrity and cognition (see Kaup, Mirzakhania, Jeste, & Eyler, 2011, for a recent review), relatively few studies have explored the relationship between cortical thickness and cognitive decline (cf., Razlighi et al., 2016; Sun et al., 2016; Westlye, Grydeland, Walhovd, & Fjell, 2011), despite the fact that thickness is thought to be a better marker of neurodegenerative pathology than gray matter volume (Winkler et al., 2010).

Of all cognitive changes that accompany normal aging, memory decline remains one of the primary complaints of older adults (Hertzog & Dixon, 1994), and is a near ubiquitous finding within the field of cognitive aging (Craik, 1994; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). According to a growing body of literature, however, a deficit in inhibitory control processes, which guide and regulate how information enters and leaves memory, may underlie these memory impairments (Anderson, Reinholz, Kuhl, & Mayr, 2011; Hasher & Zacks, 1988; Hasher & Zacks, 2007). For example, when previously learned information (an old password, or last year's student's names) interferes with new memories (a new password, or this year's student's names), retrieval failures may ensue: a phenomenon known as proactive interference. Inhibitory processes in this context serve to rid memory of the once relevant, but now irrelevant information, which may reduce interference and aid memory for the new information (Anderson & Neely, 1996).

Several studies, using variants of a classic Sternberg item-recognition task (Sternberg, 1969), have shown that the inhibitory processes that act in memory are dissociable from those processes

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involved in the inhibition of irrelevant perceptual information at the time of encoding (Ahmari, Eich, Cebenoyan, Smith, & Blair Simpson, 2014; Eich et al., 2016; Nee & Jonides, 2008b; Smith, Eich, Cebenoyan, & Malapani, 2011). In these studies, participants had to inhibit irrelevant words based on a cue that occurred either before, or after, the words entered working memory, fostering memorial and perceptual inhibitory processes, respectively. Aging affects these two types of inhibitory processes differentially; although older adults were shown to have reductions in both perceptual and memorial inhibition relative to younger adults, the deficits were particularly pronounced for memory inhibition, and performance across the two types of task was not correlated (Eich et al., 2016).

The dissociation of these two types of inhibitory processes extends to their neural substrates. Activity in the left VLPFC has been shown across several functional MRI (fMRI) studies to be uniquely associated with inhibiting irrelevant information in memory (Nee & Jonides, 2008b; Nee, Jonides, & Berman, 2007; Nee, Wager, & Jonides, 2007) and to mediate the role of interference-resolution during memory retrieval (Eich, Nee, Insel, Malapani, & Smith, 2014). On the contrary, top-down control originating in both left and right SPL has been shown to be associated with the down-regulation of visual representations of irrelevant information in early visual cortex, which was shown to predict successful perceptual inhibition (Nee & Jonides, 2008a, 2008b). Although aging is associated with global changes in patterns of cortical thinning, disproportionately pronounced reductions in the frontal cortices (Raz & Rodrigue, 2006; Salat et al., 2004; cf., Persson et al., 2014; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010) and lateral parietal cortices (Bakkour, Morris, Wolk, & Dickerson, 2013; McGinnis, Brickhouse, Pascual, & Dickerson, 2011) have been reported. Critically, these areas overlap with those implicated in perceptual and memory inhibitory processes, respectively.

Taken together, these different lines of research suggest that individual differences in memory inhibition and perceptual inhibition abilities may be associated with distinct, region-specific patterns of cortical thinning in healthy elders. To test this hypothesis, we examined the relationship between cortical thickness in brain areas that have previously been functionally associated with memory inhibition on the one hand (the left VLPFC) and perceptual inhibition on the other hand (left and right SPL), and behavioral measures of memory and perceptual inhibition.

Method

Participants

Twenty-one clinically healthy older adults ($M_{\text{age}} = 67.29$, $SD = 3.95$, range 61–76, 10 female/11 male, M years education = 16.24, $SD = 1.33$) who had previously completed two behavioral tasks targeting memory inhibition and perceptual inhibition (Eich et al., 2016) underwent structural brain imaging. One additional participant who completed the tasks did not have structural brain data. Participants were screened for dementia using the Mattis Dementia Rating Scale (Mattis, 1988). Only those participants with a score ≥ 135 were tested. The average number of days between testing and structural brain image acquisition was 282.33 ($SD = 318.71$; range 1–1,086). Written informed consent was obtained for all participants as per the ethical standards of the Columbia University Institutional Review Board and American Psychological Association.

MRI Acquisition

Structural MRI data for each participant was acquired on a 3.0 Tesla (T) Philips Achieva Magnet (Philips Health care, Best, the Netherlands). Total acquisition time was 4 min 47 s. A scout, T1-weighted image was acquired to determine participant position. Participants then received a magnetization prepared rapid gradient echo (MPRAGE) scan with the following pulse sequence parameters: echo time = 3 ms; repetition time = 6.5 ms; flip angle = 8°; in-plane resolution = 256×256 voxels; field of view = 25.6×25.6 cm; slices = 165–180 in axial direction with slice-thickness/ gap of 1/0 mm.

Morphometric Analysis

FreeSurfer software (v5.1.0; Fischl et al., 2002; Fischl et al., 2004) was used to calculate cortical thickness. 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). Using a validated automated labeling system (Fischl et al., 2004) FreeSurfer divides the cortex into 33 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). To account for differences due to head size, cortical thickness measures were adjusted for total intracranial volume (ICV), producing an unstandardized residual for each parcellation. BrainWash (<https://www.nitrc.org/projects/art>) was used to compute ICV (Ardekani, Braun, Hutton, Kanno, & Iida, 1995).

Memory and Perceptual Inhibition Tasks

As is reported in (Eich et al., 2016), participants were tested individually on two item-recognition working memory tasks using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA). In both tasks, a word set containing four colored words, two in red and two in blue, was presented, followed by a test probe. In the perceptual inhibition task, a cue telling participants which color words to remember appeared *before* the word set, fostering perceptual inhibition of the irrelevant words (Figure 1A). In the memory inhibition task, the cue came *after* the word set, fostering inhibitory processes in memory (see Figure 1B). Participants were instructed to respond positively to the test probe by pressing the "1" key if it matched either of the words that had been cued (i.e., words in the cued-color; "valid" trial), and to respond negatively by pressing the "0" key otherwise. Half of the negative responses were probes that should have been inhibited, either perceptually or in memory (i.e., words in the noncued color; "lures"), and the other half were words that had not been part of the word set ("controls"). Words were four-letter nouns, drawn from a set of 80. memory and perceptual inhibition task blocks alternated, with the order counterbalanced across participants. Participants completed between

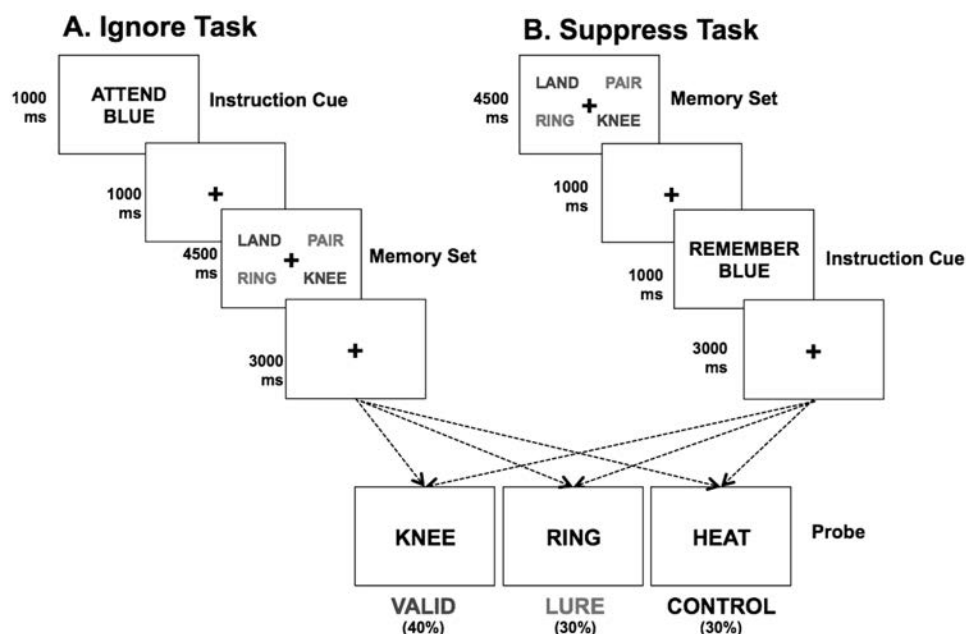


Figure 1. Schematic of the two inhibition tasks, showing the three possible probe types. On each trial, only one type of probe was given. Valid probes required a positive response. Lure and control trials required a negative response. See the online article for the color version of this figure.

eight and 16 trials of each task with feedback before beginning the experiment. Participants received eight total blocks of trials, with 25 trials per block, including, on average, 10 valid trials, 7.5 control trials, and 7.5 lure trials. Feedback was not given on experimental trials.

Statistical Analysis

Statistical analyses were performed using SPSS (v.22; SPSS, Chicago, Illinois). The data of major interest were (a) neuromorphological residuals in three brain ROIs shown previously in fMRI activation studies to be uniquely activated by and associated with memory inhibition (the left VLPFC; Figure 2A) or perceptual inhibition (left SPL; not shown, and the right SPL; Figure 2B), and (b) the behavioral inhibition indexes on the two inhibition tasks (accuracy, and normalized reaction times [RTs] for correct trials, calculated as the average RT for each condition divided by the average RT across conditions, within participants). The inhibition index was operationalized as the difference score between the two kinds of negative probes (lure-control). All trials on which RTs were two standard deviations from their individual mean in each condition were excluded. In the perceptual inhibition task, a smaller (closer to zero) inhibition index was indicative of greater inhibitory impairment (see Eich et al., 2016; Nee & Jonides, 2008a, 2008b; for a discussion). In the memory inhibition task, a larger inhibition index was reflective of inhibitory dysfunction (see Monsell, 1978; Smith & Jonides, 1998; for a discussion). Table 1 shows accuracy and RT performance across trial type. Repeated-measures analysis of variance (ANOVA), *t* tests and bivariate Pearson correlations were used to investigate differences in behavioral performance on the two tasks. Multiple regression models were used to assess the relationship between cortical thickness and

behavioral inhibition, adjusting for age, gender, and years of education. Nominally significant *p* values were defined as $p \leq .05$.

Results

We began by comparing accuracy performance on the two inhibitory tasks. A repeated-measures ANOVA with perceptual and memory inhibition index as within-subjects factors revealed no significant difference between accuracy between the two tasks ($F(1, 20) = 2.23, p = .15$). The correlation between accuracy on perceptual and memory inhibition indexes was not significant ($r = .23, p = .32$). For RT, however, there was a significant main effect of task ($F(1, 20) = 101.28, p < .001, \eta_p^2 = .84$), such that RTs were larger for the memory relative to the perceptual inhibition task. Post hoc *t* tests further revealed that while the memory inhibition index was significantly greater than zero ($t(20) = 11.16, p < .001, 95\% \text{ CI } [.217, .316]$) the perceptual inhibition index was not ($t(20) = -0.70, p = .49$). The correlation between RTs for the two inhibition tasks was not significant ($r = .15, p = .52$). Because performance differences were found only for RT, we limited subsequent analyses to this dependent variable. We then turned our attention to the main question of interest: the relationship between memory and perceptual inhibition and cortical thickness in the three ROIs. Two multiple regression models were created, the first for perceptual inhibition, and the second for memory inhibition. In both models, the inhibition index was z-transformed, and served as the dependence variable, and predictors included age, gender, years of education and residual measures of the three ROIs.

For perceptual inhibition, there was no effect of age ($B = .035, p = .578$), gender ($B = .857, p = .059$) or years of education ($B = -.075, p = .641$). However, as is illustrated in Figure 2C, there was a significant relationship between the perceptual inhibi-

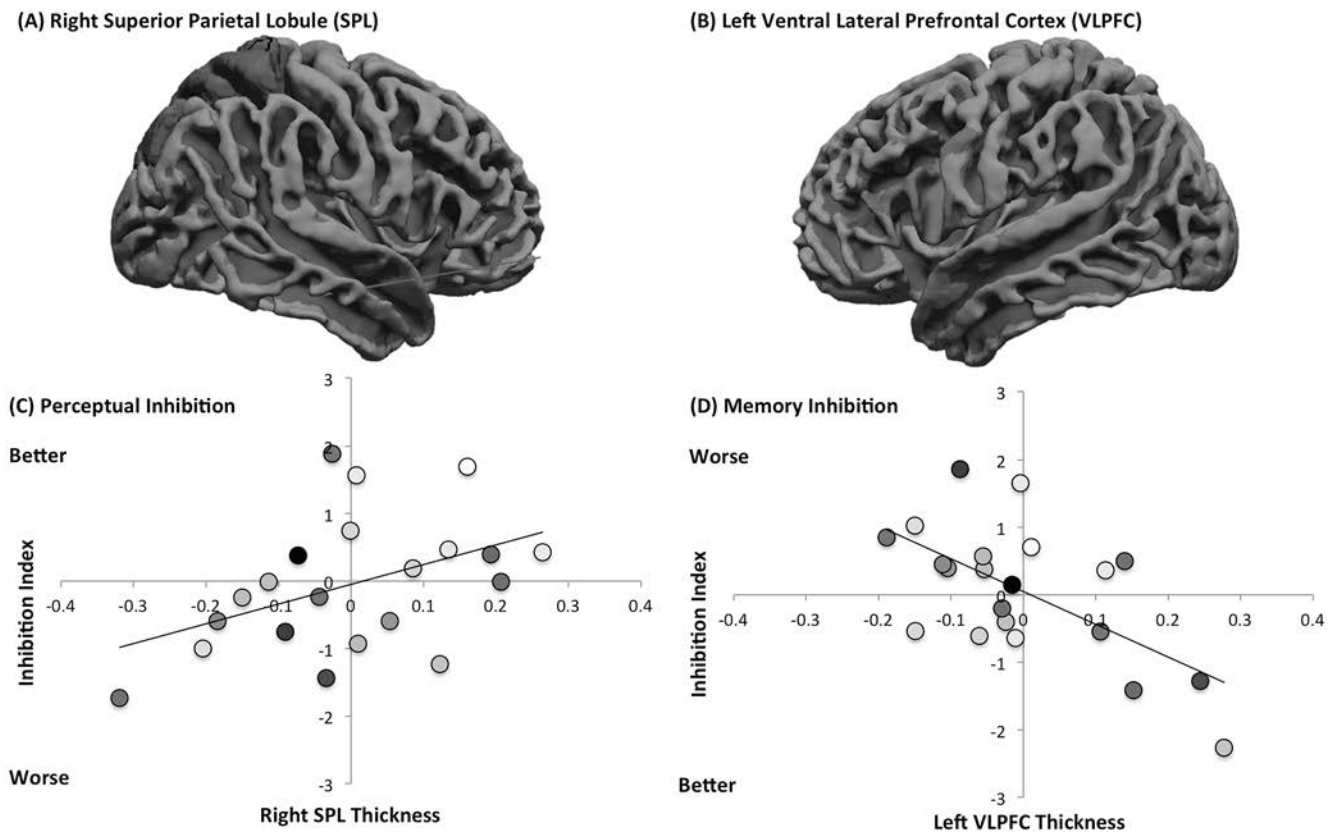


Figure 2. (A) The right superior parietal lobule (SPL), shown in green. (B) The left ventral lateral prefrontal cortex (VLPFC), shown in red. (C) The correlation between residualized thickness in the right SPL and the z-transformed inhibition index (normalized RTs for correct lure-control probe trials) for the perceptual inhibition task, where higher scores are indicative of better inhibition. (D) The correlation between residualized thickness in the left VLPFC and z-transformed inhibition index for the memory inhibition task, where higher scores indicate worse inhibitory control. See the online article for the color version of this figure.

tion index and thickness in the right SPL ($B = 3.90$, $p = .025$), such that a higher (better) inhibition index was associated with a thicker cortex. Critically, there was no relationship between perceptual inhibition latencies and cortical thickness in either the left SPL ($B = -.575$, $p = .698$) or the left VLPFC ($B = -2.048$, $p = .287$). Similarly, the degree of memory inhibition was not predicted by age ($B = .091$, $p = .125$), gender ($B = -.016$, $p = .967$), or years of education ($B = -.295$, $p = .057$). Neither was it predicted by thickness in the left ($B = 1.628$, $p = .237$) or right ($B = .795$, $p = .583$) SPL. However, as can be seen in Figure 2D, memory inhibition was associated with thickness in the left VLPFC ($B = -4.009$, $p = .032$), such that thinner cortex was associated with worse performance. These results point to a double dissociation between the type of behavioral inhibitory impairment and patterns of cortical thinning in brain areas previously shown to be associated with memory and perceptual inhibition.

Discussion

We previously showed deficits in the ability of older adults to inhibit irrelevant information compared with education-matched younger adults; in that study, older adults showed deficits in both perceptual and memorial inhibition, but dysfunction in memory

inhibition was more pronounced, and performance across the two tasks was uncorrelated, both within each age group, and across the whole sample (Eich et al., 2016). The current study provides evidence for a neuromorphological mechanism contributing to these behavioral effects: individual differences in patterns of cortical thinning in the frontal and parietal lobes are associated with different inhibitory deficits in clinically healthy older adults. More specifically, while deficits in memory inhibition were associated with thinning in the left VLPFC, they were not related to cortical thickness in either the left or right SPL. On the contrary, reduced perceptual inhibition correlated with thinning in the right SPL, but not in the left VLPFC or left SPL. Both findings were above and beyond the effects of age, gender, and years of education.

Cortical thinning 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). Indeed, cortical thickness has been shown to be an index of normal brain development, proceeding in a “last in, first out” manner, such that areas that are late to develop are also early to be lost (McGinnis et al., 2011). The “brain maintenance” theory posits that individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related

Table 1

Accuracy (Proportion Correct) and Normalized RTs for Correct Trials, Where the Average RT for Each Condition is Divided by the Average RT Across Tasks, Within Participants, Across the Three Probe Types (Control, Lure, Valid) in Each Inhibition Task

Measure	Perceptual inhibition			Memory inhibition		
	Control	Lure	Valid	Control	Lure	Valid
Accuracy						
Mean	.985	.963	.951	.933	.855	.914
Median	1.000	.970	.972	1.000	.903	.946
SD	.023	.050	.065	.149	.154	.104
SIR	.017	.018	.038	.019	.062	.054
Normalized RTs						
Mean	.910	.920	.941	.983	1.249	1.014
Median	.911	.925	.955	.985	1.262	.987
SD	.078	.079	.082	.062	.098	.092
SIR	.050	.054	.061	.020	.053	.065

Note. RT = reaction time; SD = standard deviation; SIR = semi-interquartile range.

cognitive decline” (Nyberg et al., 2012, p. 295). Sun and colleagues (2016) recently reported that “superagers”—those older adults “with memory performance abilities equal to or better than those of people 20–30 years younger” (p. 9659) had reduced cortical thinning relative to age-matched “normal” older adults in several key large-scale intrinsic brain networks that support memory processes, which correlated with memory performance. In the current data, the finding of a double dissociation between different measures of cortical thickness and types of inhibition, which were not significantly associated with each other, suggests that there may be distinct trajectories of cortical thinning that predict individual differences in cognitive morbidity across subtly different cognitive tasks, even in clinically healthy older adults.

Several limitations of the current study should be noted. First, the sample size was small. However, the finding of a double dissociation—often considered a key metric in cognitive neuroscience research (Fischl et al., 2004)—between patterns of cortical thinning and behavioral performance on two inhibition tasks within the same individuals, helps to mitigate concerns over the small sample size. Second, a younger adult group was not included. However, cortical thinning, as opposed to volumetric changes, have been documented to occur in a linear pattern across the life span (Fjell et al., 2009; Westlye et al., 2010). Given this, individual differences in inhibitory performance as mediated by changes in cortical thickness would not be predicted in a younger adult sample, although future work could empirically test this idea.

Deficits in cognitive functioning are considered one of the most debilitating aspects of aging, and prevent older adults from leading productive and meaningful lives (Bayles & Kaszniak, 1987). The results of this study help to shed light on the neuromorphologic changes that occur in healthy aging and are associated with subtle differences in cognitive functioning. One of the ultimate goals of neuroscientific research is to identify targets for intervention to improve cognitive functioning and mitigate cognitive decline. The targets identified here, in the future, may guide individualized interventions aimed at improving age-related dysregulation in inhibitory processes and their downstream cognitive and behavioral effects.

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