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Cortical Thickness is Linked to Executive Functioning in Adulthood and Aging

Agnieszka Z. Burzynska,[1]* **Irene E. Nagel,**[2] **Claudia Preuschhof,**[2]
Sebastian Gluth,[1] **Lars Bäckman,**[1,3] **Shu-Chen Li,**[1] **Ulman Lindenberger,**[1]
and Hauke R. Heekeren[1,2,4]

[1]*The Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany*
[2]*Department of Educational Science and Psychology, Freie Universität Berlin, 14195 Berlin, Germany*
[3]*Aging Research Center, Karolinska Institute, Gävlegatan 16, 11330, Stockholm, Sweden*
[4]*Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstraße 1a, 04103 Leipzig, Germany*

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Abstract: Executive functions that are dependent upon the frontal-parietal network decline considerably during the course of normal aging. To delineate neuroanatomical correlates of age-related executive impairment, we investigated the relation between cortical thickness and executive functioning in 73 younger (20–32 years) and 56 older (60–71 years) healthy adults. Executive functioning was assessed using the Wisconsin Card Sorting Test (WCST). Cortical thickness was measured at each location of the cortical mantle using surface-based segmentation procedures on high-resolution T1-weighted magnetic resonance images. For regions involved in WCST performance, such as the lateral prefrontal and parietal cortices, we found that thicker cortex was related to higher accuracy. Follow-up ROI-based analyses revealed that these associations were stronger in older than in younger adults. Moreover, among older adults, high and low performers differed in cortical thickness within regions generally linked to WCST performance. Our results indicate that the structural cortical correlates of executive functioning largely overlap with previously identified functional patterns. We conclude that structural preservation of relevant brain regions is associated with higher levels of executive performance in old age, and underscore the need to consider the heterogeneity of brain aging in relation to cognitive functioning. *Hum Brain Mapp 33:1607–1620, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: WCST; right DLPFC; prefrontal cortex; parietal cortex; fronto-parietal network; structure-function relationship; performance level; lifespan; healthy aging

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*Correspondence to: Agnieszka Z. Burzynska, Max Planck Institute for Human Development, Lentzeallee 94, D-14195 Berlin, Germany. E-mail: burzynska@mpib-berlin.mpg.de

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INTRODUCTION

Normal aging is accompanied by decline in many cognitive domains, especially those related to fluid abilities [Baltes, 1987; Cattell, 1971; Horn, 1968; Lindenberger, 2001], such as reasoning and executive functioning [Bäckman et al., 2000; Li et al., 2004; Rhodes, 2004; West, 1996]. Executive functions comprise several cognitive abilities, such as working memory, selective attention, inhibition, set shifting, and task switching [Miyake et al., 2000; Teuber 1972]. Conjointly, these functions enable flexible and goal-directed behavior in a changing environment. Age-related decline in executive functioning may impose difficulties in everyday situations, such as social contacts, street traffic, and diet or drug compliance.

To assess executive functioning, we administered the Wisconsin Card Sorting Test (WCST), a standard neuropsychological test, which requires attention, feedback-based updating of information in working memory, inhibition of prepotent responses, and shifting of mental set [Grant and Berg 1948; Heaton et al., 1993]. In healthy adults, performing the WCST results in increased functional brain activity within a distributed fronto-parietal network [see Buchsbaum et al., 2005; Nyhus and Barcelo, 2009, for reviews]. The right prefrontal (PFC) and parietal cortices are most consistently recruited during the WCST, with less consistent findings regarding activation of the temporal and occipital lobe, as well as subcortical gray matter [Buchsbaum et al., 2005; Nyhus and Barcelo, 2009].

Parallel to cognitive decline, advancing age is related to a structural degeneration of the cerebral cortex as indicated by widespread reductions in cortical thickness [Fjell et al., 2009; Hutton et al., 2009; Salat et al., 2004], gray matter density [Sowell et al., 2003], and gray matter volume [Courchesne et al., 2000; Good et al., 2001; Raz et al., 1997, 2000, 2005; Walhovd et al., 2009]. So far, attempts at linking age-related structural alterations to executive functioning have yielded mixed results. Fjell et al. [2006], Ziegler et al. [2010], and Van Petten et al. [2004] reported no correlation between cortical thickness and composite scores of various executive measures, whereas Kochunov et al. [2009] found that thicker cortex in many regions was related to better executive performance in adults between 30 and 90 years, but not in adults between 19 and 26 years. These correlations, however, were no longer significant after controlling for age [Kochunov et al., 2009]. In 87 participants aged 20 to 77 years, Raz et al. [2008] observed that, after accounting for the effects of age, sex, and vascular risk factors, the orbitofrontal cortex and the prefrontal white-matter volumes as well as the 5-year change in entorhinal cortex volume predicted fluid intelligence level, assessed by Cattell Culture Fair Intelligence and Letter Sets tests. Hartberg et al. [2010] found that thicker cortex in superior temporal, superior frontal, and inferior frontal gyri was related to fewer perseverative errors in the WCST among schizophrenic patients and healthy adults 20–56 years old. Elderkin-Thompson et al. [2008] found both positive and negative correlations between volume of the frontal lobe gyri and various executive function scores in adults aged 61–88 years. Specifically, greater anterior cingulate volume was associated with less time needed to complete the Stroop Inhibition Task, whereas larger orbitofrontal volumes were associated with poorer verbal fluency. Other studies show that, in older adults, smaller PFC gray-matter volume [Gunning-Dixon and Raz, 2003] and smaller right frontal-lobe volume [Hanninen et al., 1997] were related to a higher number of perseverative errors in the WCST, and that larger frontal-lobe volume was positively linked to the number of completed WCST categories [Schretlen et al., 2000].

At least some of the above findings suggest that structure-function relationships are more pronounced in late than in early adulthood. A healthy mature brain may function above a critical threshold despite some inter-individual variability in brain structure. Conversely, in the presence of biological constraints on information processing mechanisms (i.e., when decline in biological resources reaches a certain threshold), such as during aging, the extent of decline in brain structure may be more predictive of cognitive performance [Almeida et al., 2008; Li et al., 2004; Lindenberger et al., 2008; Nagel et al., 2008; Sullivan and Pfefferbaum, 2006].

Despite the associations described above, many studies using the WCST have reported negative results. This might reflect relatively small sample sizes, Elderkin-Thompson et al., 2008, $n = 23$; Gur et al., 1998, $n = 17$; Sanfilipo et al., 2002, $n = 27$, or stem from combining the WCST with other tests, whose neural substrates may not be overlapping [Van Petten et al., 2004]. In addition to issues regarding sample size and use of composite scores of executive functioning, the studies reporting negative results are affected by at least one of the following limitations: (a) use of volumetric measures, which confound cortical thickness, surface area, and folding [Im et al., 2006a,b]; a direct comparison of volumetric measures based on voxel-based morphometry and cortical thickness measures in 48 healthy adults aged 22–60 years revealed that volumetric measures were less sensitive, had lower signal-to-noise ratio, lower T-scores, and were more confounded by overall brain size than thickness measures [Hutton et al. 2009]; (b) gross definition of frontal volume or frontal gyri, pooling together functionally dissociable areas, such as the dorsal and ventrolateral PFC, the orbitofrontal cortex, and premotor areas; and (c) investigation of frontal-lobe volume only, although the WCST is no longer considered a specific test of prefrontal function [Nyhus and Barcelo, 2009].

In this study, we investigated the structural correlates of executive functioning in the adult human brain. Specifically, our goal was twofold: (a) to better characterize the relations between cortical thickness of brain regions associated with the WCST (as defined in previous functional neuroimaging studies) [Buschbaum et al., 2005; Nyhus and Barcelo, 2009] and executive functioning and (b) to investigate the effects of age and performance level in modulating this relation.

To accomplish these goals, in a sample of 73 younger and 56 older healthy adults, we (a) measured cortical thickness, a clearly defined anatomical property (distance between the gray/white matter boundary and the cortical surface) [Fischl and Dale, 2000; MacDonald et al., 2000] that better reflects the surface-based organization of the cortex than gray-matter density or gyral/lobar volume [Hutton et al., 2009; Im et al., 2006a,b]; (b) used higher spatial precision of the measurement by calculating cortical thickness at each location of the cortical mantle [Fischl and Dale, 2000], using procedures that have been validated against histological [Rosas et al., 2002] and manual [Kuperberg et al., 2003; Salat et al., 2004] measurements; (c) applied a hypothesis-free search of the entire cerebrum, known to be more sensitive to focal effects than averaging a brain measure over a large region [e.g., Barrick et al., 2010; Voormolen et al., 2010; Ziegler et al., 2010]; and (d) used a single standardized test, WCST, which allows direct comparison to previous functional neuroimaging studies [Buchsbaum et al., 2005; Nyhus and Barcelo, 2009]. The study was guided by two main hypotheses. First, we expected that cortical thickness in regions most robustly activated during the WCST, namely (right) lateral prefrontal and parietal cortices, and is positively correlated with WCST performance. Second, we predicted that the association between individual differences in cortical thickness and individual differences in task performance is stronger in older than in younger adults.

MATERIALS AND METHODS

Participants

Seventy-three younger adults (32 women) between 20 and 32 years of age ($M = 25.6 \pm 3.1$) and 56 older adults (27 women) between 60 and 71 years of age ($M = 64.8 \pm 2.6$) participated. All subjects had received at least eight years of education, were right-handed, and had no history of psychiatric or neurological disease. Age groups did not differ with respect to schooling ($M_{\text{younger}} = 16.8 \pm 3.3$ years; $M_{\text{older}} = 16.3 \pm 3.9$ years, $P = 0.38$). For 50 of the 56 older adults, we have information about vascular risk factors: 19 participants (38%) reported arterial hypertension (defined as blood pressure constantly above 140/90 mm Hg), 7 of the 19 hypertensive participants took anti-hypertensive medication, 4 (8%) had type 2 diabetes, all of whom took medication but only one was insulin-dependent, and 5 (10%) reported hypercholesterolemia (two of whom were taking medication).

One of the authors (A.Z.B) evaluated the presence of age-related WM hyperintensities (WMH) on fluid attenuated inversion recovery (FLAIR) images using the rating scale described by Wahlund et al. [2001]. The presence of moderate WMHs is typical for a normally aged population [Baloh and Vinters, 1995]. We estimated WMH volume using a semi-automated procedure based on FMRIB's Automated Segmentation Tool [FAST 4.1, Zhang et al., 2001], described in more detail in Burzynska et al. [2010]. All younger and 20 older participants had Grade 0 (no lesions), 24 older adults had Grade 1 (a single to several focal WM lesions, $M_{\text{WMH volume}} = 916.9 \pm 700.4$ voxels, range 117–2615 voxels), and 12 older participants had Grade 2 (beginning confluence of lesions, $M_{\text{WMH volume}} = 5767.8 \pm 2729.9$ voxels, range 3094–13021 voxels). A neuroradiologist examined the structural images of participants with WMH Grade 2 and classified all of them as within the normal range for their age.

Older adults showed deficits in processing speed, as measured by Digit-Symbol Substitution ($M_{\text{younger}} = 63.5 \pm 10.2$, $M_{\text{older}} = 48.8 \pm 12.6$, $P < 0.001$) but higher verbal knowledge, as measured by the Spot-a-Word task ($M_{\text{younger}} = 18.6 \pm 5.2$, $M_{\text{older}} = 22.8 \pm 5.8$, $P < 0.001$). This pattern of age differences is consistent with the literature on cognitive aging [e.g., Li et al., 2004].

The ethics committee of the Charité University Medicine Berlin and the Max Planck Institute for Human Development approved the study, and written informed consent was obtained from all participants prior to the examination. Participants received financial reimbursement.

Wisconsin Card Sorting Test

We administered a computerized version of the standard 128-cards WCST [Heaton et al., 1993]. Four reference cards were presented at the top of the screen and a single response card was shown at the bottom centre of the screen. We asked participants to sort the response card to one of the cards presented in the upper half of the screen by pressing one of the four corresponding buttons with the index finger of the right hand. We instructed the participants to perform as quickly and accurately as possible; however, there was no time limit to provide a response. Once a button was pressed, the response could be cancelled within 1550 ms, followed by, again, unlimited time to give an alternative answer. Finally, feedback on the correctness of the answer was communicated visually ("correct" or "false" presented on the screen for 1500 ms) and verbally (spoken via headphones).

This feedback was the only guidance about the sorting rules. In general, the cards could be matched based on three dimensions: color, form, and number. The first sorting principle was color, followed by form and then number. When a person attained 10 consecutive correct responses for a specific category, the sorting principle changed. Because no indication was given about the change, participants were required to make a shift of category to receive positive feedback again. The test either ended after a participant had completed six categories or sorted a set of 128 cards.

We evaluated WCST performance by applying the standard scoring parameters [Heaton et al., 1993], which include the number of categories completed, and the total number of trials needed to complete the first category. Percentage of correct responses and perseverative errors were calculated by dividing absolute values of correct responses and perseverative errors, respectively, by the total number of responses for each participant. Reaction time for correct responses was measured as the time between the presentation of a new key card and the button press of its final (i.e., correct) assignment. Reaction times below 600 ms and above 25 s were considered as error trials and were excluded from the analyses. Statistical analyses were performed using SPSS (v.16, SPSS, Chicago, IL).

MR Acquisition

High-resolution structural MR scans were acquired using a 3D gradient-echo T1-weighted (Fast Low Angle Shot) sequence (TR = 20 ms; TE = 5 ms; flip angle = 30°; matrix = 256 × 256; FOV = 256; 180 slices; resolution = 1 × 1 × 1 mm) on a 1.5 Tesla MR Siemens Magnetom Vision scanner (Siemens, Erlangen, Germany) with a conventional head coil. FLAIR images were acquired on a 1.5 T Siemens Sonata with 40 mT/m gradients and 200 T/m/sec slew rates (Siemens, Erlangen, Germany). All images were obtained parallel to the anterior-posterior commissure plane with no interslice gap. FLAIR images consisted of 24 five-mm-thick slices with an in-plane resolution of 1.3 × 0.9 mm (240 × 256 matrix, TR/TE/TI = 7500/118/2200 ms). To minimize head movement, we stabilized the head with a vacuum pillow.

Cortical Thickness Analysis

Automated brain tissue segmentation and reconstruction of cortical models was performed on T1-weighted images using the Freesurfer software, version 4.4 (http://surfer.nmr.mgh.harvard.edu/). In brief, individual T1-weighted images underwent non-brain tissue removal, Talairach transformation, creation of representations of the gray/white matter boundaries [Dale et al., 1999; Dale and Sereno, 1993], and calculation of the cortical thickness as the distance between the gray/white matter boundary and the pial surface at each point across the cortical mantle [Fischl and Dale, 2000]. We screened surface reconstructions to evaluate the success and plausibility of the automatically processed results, as recommended by the software developers. Next, cortical thickness maps were inflated [Fischl et al., 1999a], smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of 10 mm, and registered to a spherical atlas to match individual cortical folding patterns across subjects [Fischl et al., 1999b].

Statistical Analysis

Whole-brain analyses

First, we compared cortical thickness between younger and older adults. Next, we investigated associations between cortical thickness and executive performance in the total sample, controlling for age. Here, we computed a general linear model to assess the relationships among age, cortical thickness at each vertex (measurement point at the cortical mantle), and executive performance. As the index of executive functioning, we selected the percentage of correct responses because its values exhibited the largest variance, the distribution was least skewed in both age groups, and the effect size of the age-related difference was the largest. All results are shown on inflated standard cortical surface maps with a P-value ranging from $P < 0.001$ to $P < 0.000001$ (see Fig. 1) or $P < 0.05$ to $P < 0.005$ (Figs. 2 and 3), uncorrected, which is common in surface-based group analysis of cortical thickness [e.g., Espeseth et al., 2008; Fjell et al., 2006; Walhovd et al., 2006].

Post-hoc region-of-interest analyses

Region-of-interest (ROI) analyses were used to illustrate characteristics of the positive structure-performance correlations within the fronto-parietal network. By using the ROI manual drawing tool in Freesurfer, we manually delineated regions with $P < 0.005$, which occupied a surface area larger than 30 mm^2 in the standard spherical space. Next, the ROIs created in the standard spherical space were mapped onto each participant's surface representations. Finally, mean values of cortical thickness and ROI surface were extracted for each participant in individual space.

First we checked the reliability of variances of cortical thickness and behavioral measures in the ROI analyses in younger and older adults using MPlus software (Muthen & Muthen,Version 5, 2008, Los Angeles, CA). All variances differed significantly from zero ($P_{\text{younger, older}} < 0.001$), indicating that there was enough variance in the data to assess and interpret the correlations.

To test the hypothesis that cortical thickness of the ROIs is related to WCST performance after controlling for age, we performed linear hierarchical regression analyses, where WCST performance was the dependent variable, age was entered as the main independent variable and cortical thickness as the second independent variable. Factorial ANOVAs were calculated per ROI to test for age group × cortical thickness interactions, that is, whether cortical thickness was more predictive of WCST performance in older than in younger adults. To illustrate these findings, we plotted WCST performance against cortical thickness and fitted the regression lines separately for younger and older adults (Fig. 2B).

In addition, we investigated relationships between cortical thickness and WCST accuracy separately within the two age groups (see Supporting Information). Finally, we calculated the mean thickness across the cortical gray matter for every participant, separately for each hemisphere.

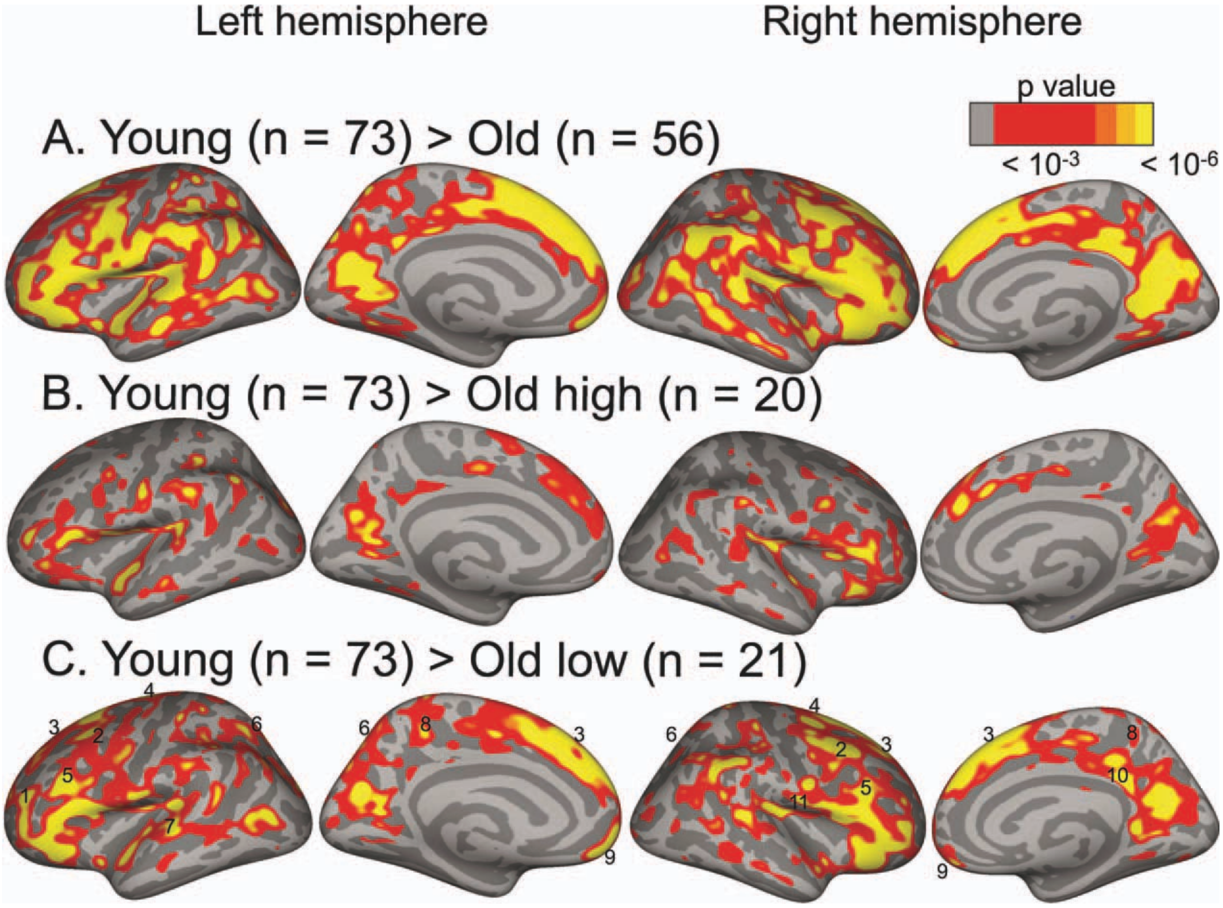

Figure 1.

Age-group comparisons show a strong and spatially distributed negative effect of age on cortical thickness. Red to yellow: regions where cortex was thicker in younger than in (**A**) older adults, (**B**) high-performing older adults, and (**C**) low-performing older adults. In (C) numbers indicate, 1: left frontal pole (BA 10), 2: caudal part of the MFG (BA 6/8), 3: lateral superior frontal gyrus (BA 6/8/9), 4: precentral gyrus (BA 4), 5: rostral part of the MFG (BA9/46), 6: posterior parietal cortex (BA 7), 7: left caudal superior temporal gyrus (BA 22), 8: medial postcentral gyrus (BA 5), 9: orbitofrontal cortex (BA 11), and 10: right isthmus cingulate cortex (BA 23).

RESULTS

WCST Performance

Older adults showed lower performance on the WCST than younger adults; they needed more trials to complete the first category ($M_{\text{younger}} = 14.0 \pm 6.4$, $M_{\text{older}} = 33.5 \pm 36.5$, $P < 0.001$) and therefore completed less sorting categories altogether ($M_{\text{younger}} = 6.0 \pm 0.1$, $M_{\text{older}} = 4.7 \pm 1.7$, $P < 0.001$), made more perseverative errors ($M_{\text{younger}} = 9.8\% \pm 3.6$, $M_{\text{older}} = 21.0\% \pm 10.5$, $P < 0.001$), had a lower percentage of correct answers ($M_{\text{younger}} = 80.7\% \pm 6.9$, $M_{\text{older}} = 62.2\% \pm 15.0$ $P < 0.001$), and had longer response times for correct trials ($M_{\text{younger}} = 2855$ ms $\pm$ 539, $M_{\text{older}} = 4412$ ms $\pm$ 1322 $P < 0.001$).

Within each age group, age was normally distributed (Kolmogorov-Smirnov test, $P > 0.05$). WCST scores were reliably correlated with age in older adults ($r_{\text{percent correct}} = -0.28$, $P = 0.04$; $r_{\text{first category}} = 0.24$, $P = 0.08$; $r_{\text{categories}} = -0.27$, $P = 0.04$; $r_{\text{perseverative errors}} = 0.23$, $P = 0.09$; $r_{\text{reaction time}} = 0.32$, $P = 0.02$), but not in younger adults ($r_{\text{percent correct}} = 0.01$, $P = 0.96$; $r_{\text{first category}} = 0.04$, $P = 0.73$; $r_{\text{categories}} = -0.09$, $P = 0.43$; $r_{\text{perseverative errors}} = 0.09$, $P = 0.45$; $r_{\text{reaction time}} = -0.03$, $P = 0.79$).

Associations Between Age Group and Cortical Thickness

The average cortical thickness values were $M_{\text{younger RH}} = 2.59 \pm 0.09$, $M_{\text{younger LH}} = 2.59 \pm 0.09$, $M_{\text{older RH}} = 2.44 \pm 0.09$, and $M_{\text{older LH}} = 2.44 \pm 0.10$. As mean cortical thickness was highly correlated between the two hemispheres ($r_{\text{younger RH-LH}} = 0.94$ $P < 0.001$, $r_{\text{older RH-LH}} = 0.89$

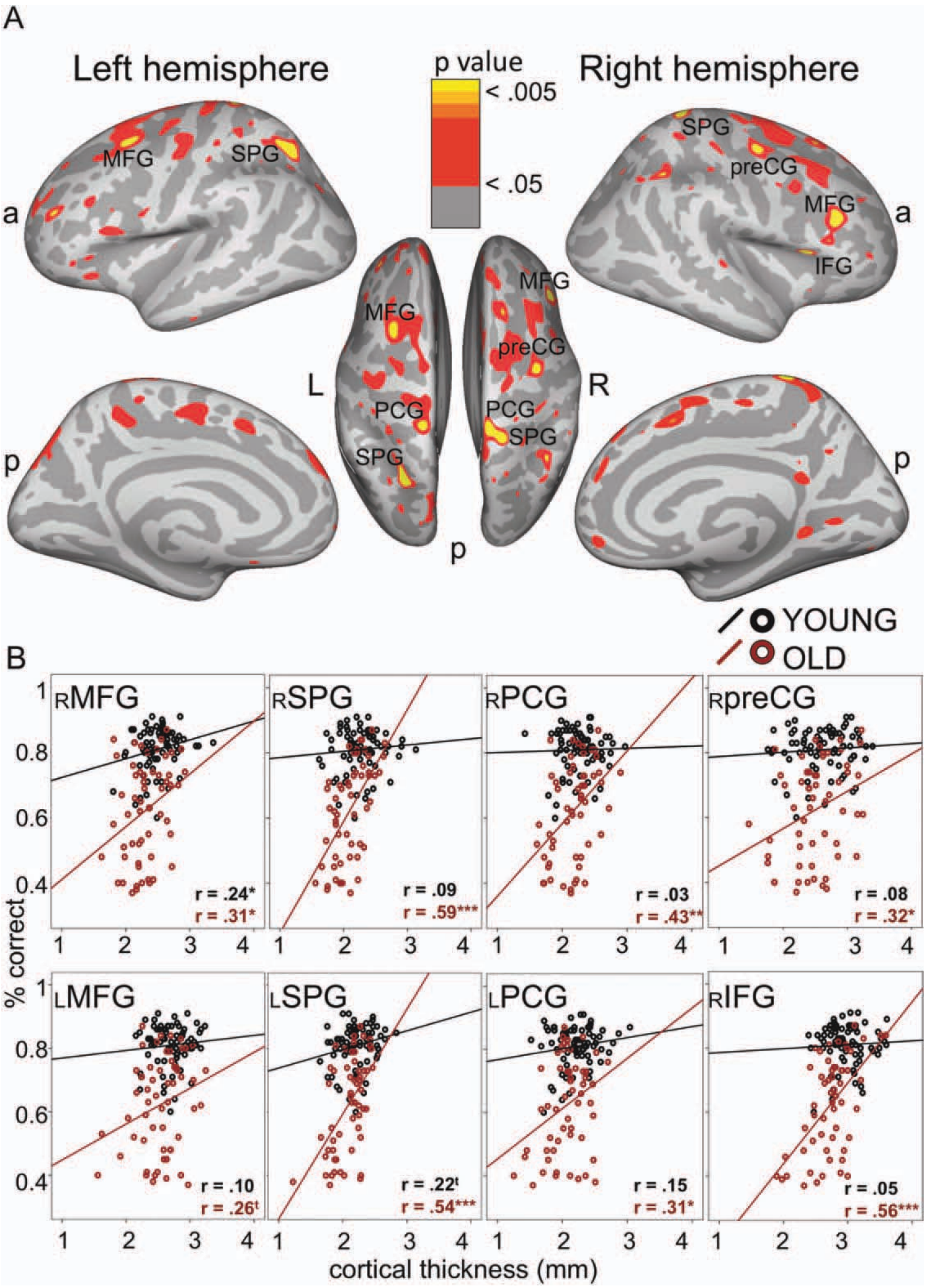

Figure 2.

Relationship between cortical thickness and executive performance. **A**: Thicker cortical mantle was associated with better WCST performance (red-yellow) in the total sample (corrected for age), and **B**: Mean cortical thickness from regions at $P < 0.005$ larger than 30 mm^2 in panel A regressed on WCST accuracy. *x*-axis: cortical thickness in mm, *y*-axis: WCST accuracy (% correct responses); *r*: Pearson's correlation coefficients, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, ^{t}trend ($0.07 > P > 0.05$). MFG: middle frontal gyrus, IFG: inferior frontal gyrus, SPG: superior parietal gyrus, preCG: precentral gyrus, PCG: post-central gyrus. a: anterior, p: posterior, L: left, and R: right. This figure only displays positive correlations. A few areas with significant negative correlations were found in the temporal lobes (see Supporting Information Fig. S2), which are outside the fronto-parietal WCST network as described in Nyhus and Barcelo, [2009]; Buchsbaum et al., [2005].

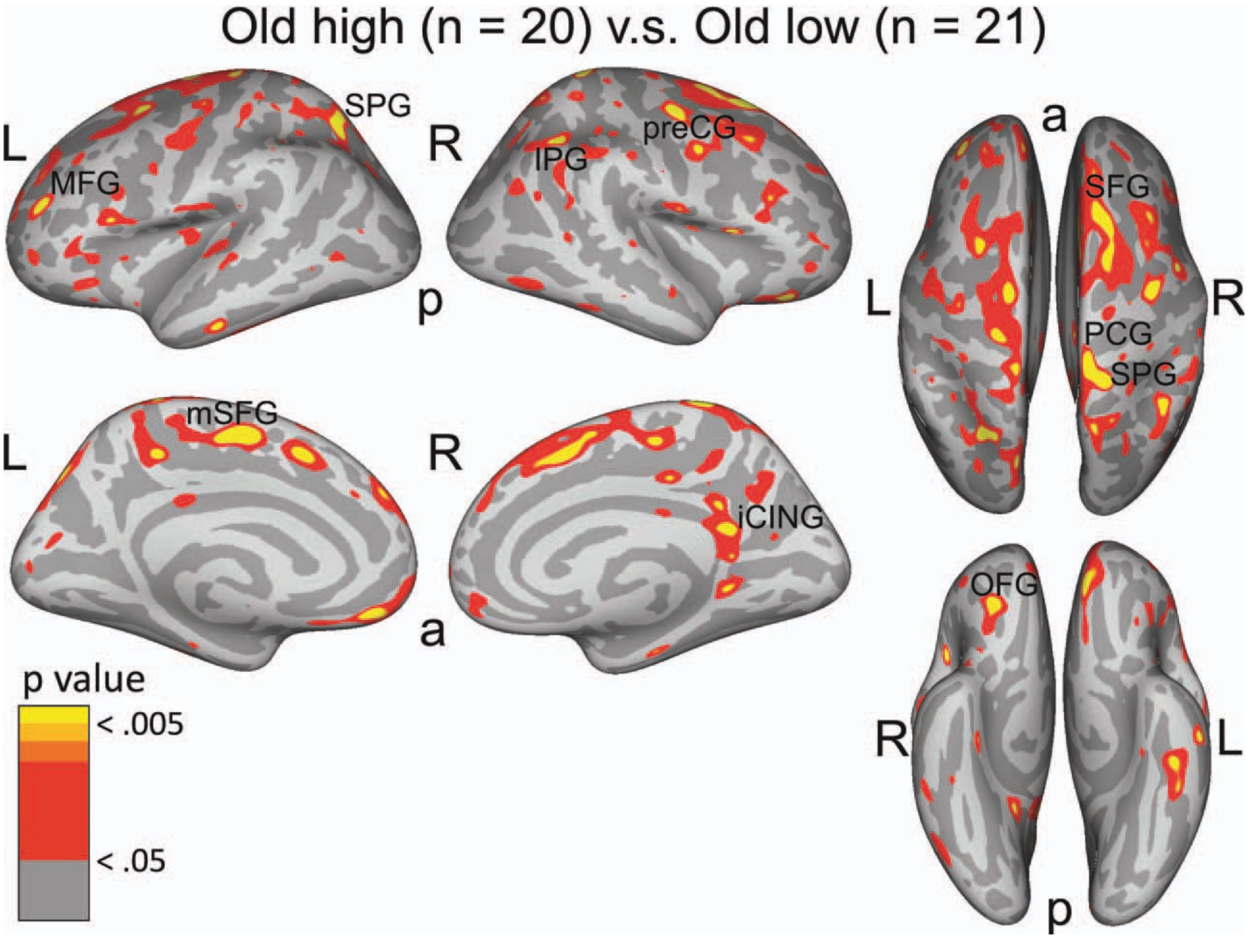

Figure 3.

Cortical thickness of high- versus low-performing older adults. In red-yellow: regions where cortical thickness of high-performing older adults was thicker than in low-performing adults. The most highly significant regions (larger than 30 mm^2 at $P < 0.005$ and including vertices at $P < 0.001$, see Table III) were: MFG: middle frontal gyrus, SPG: superior parietal gyrus, mSFG: medial superior frontal gyrus, IPG: inferior parietal gyrus, preCG: precentral gyrus, iCING: isthmus cingulate gyrus, OFG: orbitofrontal gyrus. a: anterior, p: posterior, L: left, and R: right.

$P < 0.001$), we averaged the thickness of both hemispheres in subsequent analyses ($M_{\text{younger}} = 2.59 \pm 0.09$, $M_{\text{older}} = 2.44 \pm 0.09$). Older adults had thinner cortex than younger adults ($P < 0.001$). This observation was confirmed by a vertex-wise whole-brain comparison of cortical thickness: There was a strong and spatially distributed negative effect of age group on cortical thickness, regardless of performance level. We observed the strongest effects in the bilateral frontal cortex (superior, middle, inferior, orbital, and ventral precentral gyri), parietal cortex (inferior parietal and supramarginal gyri), posterior cingulate gyrus, and temporal cortex (superior and middle temporal gyri), as well as the medial part of the precuneus (Fig. 1A). None of the examined cortical regions showed significantly thicker cortex in older than in younger adults.

Associations Between Cortical Thickness and WCST Performance

We correlated cortical thickness with percent correct responses on the WCST in all 129 participants, controlling for chronological age. As shown in Figure 2A, a thicker cortical mantle in the fronto-parietal network, including frontal cortex (bilateral middle frontal gyrus (MFG), as well as right inferior frontal gyrus (IFG), precentral gyrus (preCG), postcentral gyrus (PCG), and superior parietal gyrus (SPG), was related to better WCST performance. The only significant negative correlations (i.e., where thinner cortex was related to better performance on WCST; see Figure S3 in the Supporting Information) were located in the temporal lobes, outside the fronto-parietal WCST network [Buchsbaum et al., 2005; Nyhus and Barcelo, 2009], and therefore were not addressed in the following analyses.

To illustrate the pattern of the positive correlations separately in younger and older adults, we regressed mean cortical thickness on percent correct WCST responses separately for each region larger than 30 mm^2 (Fig. 2B). Table I summarizes the anatomical and functional definitions, as well as the coordinates, of the ROIs.

We performed multiple hierarchical regression analyses using age and cortical thickness as factors to test whether variance in WCST accuracy is accounted for by cortical thickness in addition to age. The change statistics were significant in all ROIs: right MFG ($R^2_{\mathrm{change}} = 0.041$, F_{change} (1/126) = 9.82, $P < 0.01$), left SPG ($R^2_{\mathrm{change}} = 0.084$, F_{change} (1/126) = 21.80, $P < 0.001$), right PCG ($R^2_{\mathrm{change}} = 0.04$, F_{change} (1/126) = 9.51, $P < 0.01$), right IFG ($R^2_{\mathrm{change}} = 0.085$, F_{change} (1/126) = 22.03, $P < 0.001$), right SPG ($R^2_{\mathrm{change}} = 0.069$, F_{change} (1/126) = 17.40, $P < 0.001$), left MFG ($R^2_{\mathrm{change}} = 0.024$, F_{change} (1/126) = 5.52, $P < 0.01$), left PCG ($R^2_{\mathrm{change}} = 0.036$, F_{change} (1/126) = 8.43, $P < 0.01$), and right preCG ($R^2_{\mathrm{change}} = 0.028$, F_{change} (1/126) = 6.40, $P = 0.01$). These findings indicate that, beyond age, cortical thickness is an important predictor of WCST performance.

A repeated-measures ANOVA testing the age group x cortical thickness interaction revealed significant interactions in most of the regions: left SPG [F(1,125) = 14.74; $P < 0.001$; $\eta^2 = 0.076$], right IFG [F(1,125) = 18.36; $P < 0.001$; $\eta^2 = 0.095$], right PCG [F(1,125) = 11.08; $P < 0.01$; $\eta^2 = 0.065$], right preCG [F(1,125) = 4.76; $P = 0.03$; $\eta^2 = 0.031$], and right SPG [F(1,125) = 26.83; $P < 0.001$; $\eta^2 = 0.119$], reflecting stronger positive associations between cortical thickness and WCST performance in older than in younger adults. In the right MFG the interaction was not reliable [F(1,125) = 2.37; $P = 0.13$; $\eta^2 = 0.017$], as thicker cortex was linked to better performance in both younger and older adults. In the left MFG and PCG, the relationships between cortical thickness and performance were significant in older adults and at trend levels in younger adults; hence the interactions were not reliable {left MFG [F(1,125) = 1.90, $P = 0.17$; $\eta^2 = 0.014$]; left PCG [(F(1,125) = 3.64, $P = 0.06$, $\eta^2 = 0.025$], respectively}. Correlation coefficients for younger and older adults for all ROIs are depicted in Figure 2B. For whole-brain correlations between cortical thickness and WCST accuracy separately within the younger and older and age groups, see Supporting Information.

To check the specificity of our findings for WCST, we also examined the relationship of cortical thickness to processing speed (Digit Symbol) and vocabulary (Spot-a-Word). Cortical thickness within the eight ROIs was not a significant predictor of processing speed or vocabulary, when entered into the model after age, except for processing speed in the left PCG ($R^2_{\mathrm{change}} = 0.029$, F_{change} (1/126) = 4.70, $P = 0.03$). The age × cortical thickness interaction was not reliable for left PCG, suggesting that the age groups did not differ with respect to cortical thickness-processing speed associations in this region.

TABLE I. Thicker cortex predicts higher WCST accuracy (after controlling for age, $n = 129$): most significant ROIs from Figure 2 ($P < 0.005$ across > 30 mm^2)

ROI	Gyrus	BA	Anatomical definition	Talairach coordinates	Peak P-value	ROI size (mm^2) on standard surface	Mean ROI size (mm^2) at $P < 0.005$
Left SPG	Superior parietal	7	Somatosensory association cortex	−25, −56, 47	0.00008	128.4	170 ± 59
Right MFG	Rostral middle frontal	9/46	Dorsolateral PFC	43, 27, 22	0.001	91.6	103 ± 29
Right PCG	Dorsal postcentral	2	Primary somatosensory cortex	9, −34, 71	0.0002	83.6	61 ± 13
Right SPG	Superior parietal	5	Somatosensory association cortex	17, −38, 63	0.0002	81.6	98 ± 30
Left MFG	Caudal middle frontal	8/9	Dorsolateral PFC	−27, 9, 46	0.002	71.4	83 ± 26
Right pre-CG	Pre-central, lateral	4/6	Primary motor/premotor cortex	38, −5, 53	0.002	43.7	45 ± 14
Right IFG	Inferior frontal, pars opercularis	44	Ventrolateral PFC	42, 15, 7	0.0002	40.6	49 ± 12
Left PCG	Dorsal postcentral	2	Primary somatosensory cortex	−13, −32, 71	0.001	36.6	33 ± 8

TABLE II. Differences in cortical thickness among younger, older high-performing, and older low-performing adults in WCST-relevant regions (see Fig. 2 and Table I)

	Cortical thickness			*P*-values	
ROI	Younger $n = 73$	Older high $n = 20$	Older low $n = 21$	Younger vs. older High	Older low vs. older High
Left SPG	2.2 ± 0.2	2.2 ± 0.2	1.9 ± 0.3	0.856	<0.001
Right MFG	2.5 ± 0.3	2.4 ± 0.3	2.2 ± 0.3	0.195	0.027
Right PCG	2.3 ± 0.3	2.3 ± 0.3	2.0 ± 0.3	0.580	0.002
Right SPG	2.3 ± 0.3	2.3 ± 0.2	2.0 ± 0.2	0.532	<0.001
Left MFG	2.7 ± 0.3	2.7 ± 0.3	2.4 ± 0.4	0.661	0.020
Right pre-CG	2.6 ± 0.4	2.7 ± 0.4	2.4 ± 0.4	0.734	0.015
Right IFG	3.0 ± 0.3	2.9 ± 0.3	2.5 ± 0.3	0.271	0.001
Left PCG	2.1 ± 0.3	2.1 ± 0.2	1.9 ± 0.3	0.307	0.028

Whole-brain analysis revealed that thickness of regions related to Digit Symbol (bilateral supramarginal gyrus, fusiform gyrus, and left postcentral gyrus, Supporting Information Fig. S4) or Spot-a-Word (left pre- and post-central, and medial orbitofrontal gyri, parietal, inferior and medial temporal regions, and right medial paracentral gyrus, Supporting Information Fig. S5) were outside the fronto-parietal network identified for WCST.

Low- vs. High-performing Older Adults

Behavioral characteristics

As shown in Figure 2B, some older adults performed similarly to younger adults, whereas others showed much lower performance. To investigate potential structural differences between these subgroups, we took the 20 older adults with the lowest ($n = 21$; the highest accuracy score in this group was shared by two participants) and the 20 older adults with the highest accuracy score on the WCST ($n = 20$). Older high and low performers did not differ with respect to age ($M_{\text{older high}} = 64.2 \pm 2.1$, $M_{\text{older low}} = 65.6 \pm 3.3$, $P = 0.10$), years of education ($M_{\text{older high}} = 16.4 \pm 3.7$, $M_{\text{older low}} = 15.5 \pm 4.4$, $P = 0.45$), performance on Digit Symbol ($M_{\text{older high}} = 51.8 \pm 15.4$, $M_{\text{older low}} = 47.5 \pm 11.2$, $P = 0.37$), but they differed, of course, significantly with respect to WCST accuracy ($M_{\text{older high}} = 0.78 \pm 0.05$, $M_{\text{older low}} = 0.45 \pm 0.06$, $P < 0.001$), number of categories completed ($M_{\text{older high}} = 6.00 \pm 0.00$, $M_{\text{older low}} = 2.86 \pm 1.49$, $P < 0.001$), trials to complete first category ($M_{\text{older high}} = 21.05 \pm 13.73$, $M_{\text{older low}} = 55.24 \pm 51.05$, $P = 0.01$), percent perseverative errors ($M_{\text{older high}} = 11.54 \pm 3.22$, $M_{\text{older low}} = 31.81 \pm 7.76$, $P < 0.001$), and WCST reaction time ($M_{\text{older high}} = 3895.6 \pm 731.2$ ms, $M_{\text{older low}} = 5072.0 \pm 1704.1$ ms, $P = 0.01$). Old high and low performers in the WCST also differed in vocabulary ($M_{\text{older high}} = 25.65 \pm 2.81$, $M_{\text{older low}} = 21.19 \pm 6.76$, $P = 0.01$). As expected, older low performers, but not older high performers, had lower WCST accuracy than younger adults ($P < 0.001$ and $P = 0.07$, respectively). Neither older high nor low performers differed from younger adults with respect to years of education. Both older subgroups were, however, slower on the WCST ($P_{\text{older high}}$, $P_{\text{older low}} < 0.001$), scored significantly lower on Digit Symbol ($P_{\text{older high}}$, $P_{\text{older low}} < 0.001$), and had a higher number of correct responses in Spot-a-Word than younger adults ($P_{\text{older high}} < 0.001$, $P_{\text{older low}} = 0.06$).

Taken together, both older adults subgroups showed the expected age-related decline in processing speed along with superior vocabulary. Critically, older high and older low performers differed specifically with respect to the WCST, but not in processing speed (Digit Symbol).

Structural characteristics

First, older high performers showed thinner global cortical thickness than younger adults ($M_{\text{older high}} = 2.47 \pm 0.07$, $P < 0.001$), and older low performers had thinner cortex than older high performers ($M_{\text{older low}} = 2.40 \pm 0.11$, $P = 0.03$). Next, we performed the same comparisons within the regions involved in WCST (as described in Fig. 2). In all regions, older high performers did not differ in cortical thickness from younger adults, but older low performers had thinner cortex than older high performers (Table II).

We also compared the variances of cortical thickness between younger, older high- and older low-performing persons. The variances did not differ between the groups except for the left MFG, where older low performers displayed larger variance than younger and older high performers (Chi-square distribution, $P < 0.05$), and the right SPG, where younger adults had higher variance than both older high and low performers (Chi-square test, $P < 0.01$).

Next, we performed a whole-brain comparison of the three groups with respect to cortical thickness. Figure 1B shows the comparison between younger and older high-performing adults, and Figure 1C shows the comparison between younger and older low-performing adults. Both older groups had a thinner cortical mantle than younger adults in multiple regions. In certain regions, however, cortex in older low performers, but not in older high

TABLE III. Thicker cortex in high - than in low-performing older adults: most significant ROIs ($P < 0.005$ across > 30 mm^2 and including vertices at $P < 0.001$, see Fig. 2)

ROI	Gyrus	BA	Anatomical definition	Talairach coordinates	Peak *P*-value	ROI size on average surface (mm^2)
Right SFG	Superior frontal	6/8	Premotor cortex	20, 19, 51	0.0002	196.7
Right SPG	Superior parietal	5/7	Somatosensory associatation cortex	17, −38, 63	0.0001	138.6
Right PCG	Poscentral	1/2/3	Primary somatosensory cortex	9, −33, 71	0.0002	136.3
Right preCG	Precentral	4	Primary Motor Cortex	39, −5, 52	0.0003	99.9
Right IPG	Inferior parietal	7	Somatosensory associatation cortex	42, −49, 41	0.0006	84.9
Right OBF	Orbitofrontal	45/47/11	Orbitofrontal cortex	24, 30, −10	0.0004	64.1
Right iCING	Isthmus cingulated	23/30	Posterior cingulate cortex	7, −49, 18	0.0009	43.1
Left mSFG	Medial superior frontal	6	Supplementary motor cortex	−7, −5, 50	0.0002	184.9
Left SPG	Superior parietal	7	Somatosensory associatation cortex	−26, −58, 46	0.0002	169.0
Left MFG	Middle frontal	46	Dorsolateral PFC	−26, 47, 1	0.0009	77.1

performers, was thinner than in younger adults. These regions were mainly located in prefrontal and parietal cortex. As portrayed in Figure 1C, they include: left frontal pole (BA 10), left PPG (BA 7), left caudal SPG (BA 22), left medial PCG (BA 5), caudal part of the MFG (BA 6/8), rostral MFG (BA9/46), lateral superior frontal gyrus (SFG, BA 6/8/9), preCG (BA 4), orbitofrontal cortex (OFG, BA 11), and the right isthmus cingulate gyrus (iCING, BA 23). It is also apparent that the difference in cortical thickness in the lateral dorsal and ventral PFC was larger between younger adults and low-performing older adults than between younger adults and high-performing older adults. We then compared older low and high performers directly. Here, we used a less stringent *P*-threshold in visualizing the data ($P < 0.005$ instead of $P < 0.001$), as we expected more subtle differences than in the comparison with younger adults (see Fig. 3 and Table III). Older high performers had thicker cortex than older low performers in left MFG (BA 46/10), left SPG (BA 7), left OFG (BA 11), left medial SFG (BA 6), right SFG (BA 8/9), preCG (BA 4), inferior parietal gyrus (IPG, BA 7), SPG (BA 5/7), PCG (BA 5), and iCING (BA 23/30).

DISCUSSION

The aim of this study was to characterize the link between cortical thickness and executive functioning in younger and older adults. The key results are that: (a) thicker cortex in specific frontal and parietal regions was related to better executive performance, irrespective of age; (b) this association was stronger in later than in earlier adulthood; and (c) cortical thickness in specific regions involved in executive functioning differed between groups that differed with respect to WCST accuracy (low-performing vs. high-performing older adults), but did not differ between similarly performing groups (younger adults versus high-performing older adults).

Cortical Thickness Decreases and Executive Performance Deteriorates With Normal Aging

Younger adults clearly outperformed older adults on the WCST for both accuracy and response speed, and the size of the age-related differences observed is in agreement with a meta-analysis of studies on the WCST and aging [Rhodes, 2004]. Similarly, we observed age-related cortical thinning of the entire frontal cortex, the parietal cortex (supramarginal and posterior parietal), the occipital cortex (pericalcarine), and the superior temporal cortex. The largest age difference was seen in the superior and inferior frontal and superior temporal gyri. There was relative sparing of thickness in aging for the interior, medial temporal, and cingulate cortex. These results confirm previous findings regarding patterns of age-related cortical thinning across different brain regions [Fjell et al., 2009; Hutton et al., 2009; Salat et al., 2004].

Regions Where Thicker Cortex is Related to Better Performance Correspond to Functional Networks Activated During WCST Performance

We showed that thicker cortex in the lateral prefrontal and parietal regions is related to higher WCST performance. These regions resemble closely the "distributed frontoparietal activation pattern" identified in a meta-analysis of functional imaging studies on the WCST [Buchsbaum et al., 2005]. The observed pattern is also in line with the assertion based on lesion and functional imaging studies that the WCST does not exclusively depend on prefrontal regions. Rather, similar to other executive tasks, WCST performance draws on widespread neuronal networks [Nyhus and Barcelo, 2009]. More specifically, regions consistently activated during WCST performance include inferior frontal and middle gyri, parietal cortex, and the postcentral gyrus, but also subcortical gray matter, cerebellum, and the occipital lobe [Buchsbaum et al., 2005]. Two specific cognitive components are thought to be important to successful WCST performance: set shifting and inhibitory control [Buchsbaum et al., 2005]. A conjunction of meta-analyses of the WCST and two other tasks (task-switching and go/no-go) restricted the task-related activations to the bilateral middle and inferior frontal, bilateral inferior parietal, and right medial frontal gyrus, with the largest overlapping region in the right MFG. Interestingly, these patterns were replicated in a later fMRI study decomposing the cognitive constituents of the WCST regarding their neural underpinnings [Lie et al., 2006]. This study linked activations in certain regions to different cognitive operations: right dorsolateral prefrontal cortex (DLPFC) to executive operations; right ventrolateral PFC/superior parietal cortex to working memory; and anterior cingulate/temporo-parietal regions to error detection. In addition, we showed that (a) cortical thickness in the aforementioned regions predicted performance only in the WCST, but not on tasks assessing processing speed and vocabulary, and (b) regions where thicker cortex predicted faster processing speed or vocabulary did not overlap with regions associated with WCST performance. These results suggest that the structure-function relationships we observed are specific to executive functions.

The fact that our results mimic the patterns of task-related activations described in Buchsbaum et al. [2005] and Lie et al. [2006] has two important implications: First, it suggests that structural characteristics (i.e., cortical thickness) of regions functionally involved in the WCST are predictive of performance. Second, the results confirm the notion that WCST is not a pure prefrontal test, but rather relies on a distributed neuronal network.

The Association Between Cortical Thickness and WCST Performance was Stronger in Older than in Younger Adults

The link between cortical thickness and WCST was stronger in older than in younger adults for all regions examined, and the age group x cortical thickness interaction was significant for bilateral SPG, right IFG, PCG, and preCG. Previous studies also reported stronger structure-function or structure-cognition relationships in older than in younger adults. Specifically, thickness in temporoparietal areas correlated with electrophysiological responses in older but not in younger adults, and these relationships mediated executive functions [Fjell et al., 2007]. Also, Kochunov et al. [2009] found that thicker cortex in many brain regions was related to better executive performance in adults between 30 and 90 years, but not in adults between 19 and 26 years. Importantly, we showed that the weak structure-performance correlations in younger adults were not because of to insufficient variance in cortical thickness, although the variance in WCST accuracy was larger in older than in younger adults. Thus, the restricted range of performance scores may partly explain the lower correlation between cortical thickness and performance observed in younger adults.

Further, the age-differential relationships are in line with previous findings on age-related increases in cognitive heterogeneity [Ardila, 2007; De Frias et al., 2007]. This increasing heterogeneity is most likely due to age-related deterioration of biological resources [Lindenberger et al., 2008; Nagel et al., 2008], in the present case age-related cortical thinning. Rarefaction of dendritic arbors, spines and synapses, cell shrinkage, and cortical myelin loss are thought to underlie nonpathological age-related alterations in cortical thickness, density, and volume [Burke and Barnes, 2006; Morrison and Hof, 1997].

The threshold concept invoked in the introduction suggests that between-person variations are more likely to result in functional impairments if cortical thickness falls below a certain level. In accordance with this notion, we observed that younger adults with thinner cortex performed similarly to those with thicker cortex. By contrast, older adults with thinner cortex performed worse than those with thicker cortex, likely because age-related thinning had moved the older low-performing adults below a certain threshold.

Consequently, it is noteworthy that the cortical thickness-WCST correlation did not differ reliably between younger and older adults in the right MFG. This finding indicates that the structure of specific cortical regions (i.e., right DLPFC) may influence performance even if biological resources are superior. Toward this end, the importance of the right DLPFC for WCST performance in younger adults was demonstrated in a recent repetitive transcranial stimulation study, showing that stimulation of the right DLPFC during feedback hampers WCST performance in adults aged 19–33 years [Ko et al., 2008].

In sum, the association strength between cortical thickness and executive performance differs by age and brain region. Specifically, in the most task-relevant cortical regions such as the right DLPFC, individual variations in structure predicted behavior even in young age, whereas in other areas of the network, the cortical mantle may need to undergo structural decline below a certain threshold to influence performance.

Cortical Thickness Differentiates Between Older High and Low Performers on the WCST

Whole-brain comparison of older high and low performers showed that low-performing older adults had thinner cortex in prefrontal and parietal regions. Specifically, for regions where thicker cortex predicted higher WCST accuracy in addition to age in the whole sample, thinner cortex distinguished older low- from older high-performing adults, but there was no difference between older high and younger adults. This pattern suggests that structural integrity of regions involved in performing the WCST is important to preservation of high function in late adulthood. In line with these assertions, in recent fMRI research we found that older adults with a more “youth-like” load-dependent modulation of the BOLD signal during working memory attained higher levels of performance [Nagel et al., 2009, 2010].

Due to its cross-sectional design, this study did not directly assess the neural mechanisms underlying mean changes in cortical thickness, individual differences in these changes, and their relations to individual differences in cognitive change. However, our finding that the associations between cortical thickness and executive performance increase from early to late adulthood renders it likely that individual differences in rates of cortical change do in fact exist. Common genetic polymorphisms may contribute to this aging-induced increase in structural heterogeneity [cf. Lindenberger et al., 2008]. For instance, in healthy older adults, individual differences in cortical thickness, in particular in the PFC, are associated with apolipoprotein E [Fan et al., 2010] and catechol-O-methyltransferase [Cerasa et al., 2010] genetic polymorphisms. Future longitudinal studies need to determine why certain individuals reach old age with a "youth-like" cortical mantle, whereas others do not.

CONCLUSIONS

This study revealed that inter-individual variation in regional cortical thickness in the fronto-parietal network is related to executive functioning in younger and older adults. Importantly, these effects were specific to WCST, as similar associations were not observed for measures of processing speed and vocabulary. The key brain regions involved in the structure-performance link resemble closely those identified in functional neuroimaging studies on the WCST. This suggests that microscopic gray-matter properties, such as dendritic arborization and spine or glial density reflected macroscopically by cortical thickness, may contribute to variation in functional activation patterns. For most of the identified regions, the cortical thickness-performance association was stronger in older adults, lending support to the threshold concept. In both age groups, however, thicker cortex especially in the right DLPFC was associated with higher WCST accuracy, pointing to the important role of this region in executive functioning. In addition, our data suggest that the degree of structural integrity of regions involved in performing the WCST in old age differentiates high- from low-performing individuals. Future research needs to further delineate and explain the mechanisms contributing to individual differences in brain aging and their relations to cognitive stability and decline.

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