Cognitive, Affective, & Behavioral Neuroscience
2005, 5 (2), 246-251

Structural brain variation, age, and response time

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Response time (RT) generally slows with aging, but the contribution of structural brain changes to this slowing is unknown. We used voxel-based morphometry (VBM) to determine gray matter (GM) and white matter (WM) brain volumes in 9 middle-aged adults (38–58 years old) and 9 seniors (66–82 years old). We correlated brain volumes with RT assessed in both a simple visual stimulus–response task and a visual continuous recognition memory task. No GM correlations with simple RT were significant; there was one WM correlation in the right fusiform gyrus. In the memory task, faster RT was correlated ($p < .05$, corrected) with *less* GM in the globus pallidus, the parahippocampus, and the thalamus for both groups. Several Brodmann areas (BA) differed between the groups such that in each area, less GM was correlated with slower RTs in the middle-aged group but with *faster* RTs in the senior group (BAs 19, 37, 46, 9, 8, 6, 13, 10, 41, and 7). The results suggest that individual differences in specific brain structure volumes should be considered as potential moderating factors in cognitive brain imaging studies.

Structural brain imaging studies with magnetic resonance imaging (MRI) reveal large individual differences in brain size and morphometry in normal subjects (Allen, Damasio, & Grabowski, 2002; Good et al., 2001). A number of studies have examined some morphometric differences as they relate to performance on cognitive tasks, but little is known about morphometric differences as they relate to individual differences in speed-of-processing measures such as response time (RT). One study used region-of-interest (ROI) methods and reported that increased volume of the thalamus was correlated with faster performance on speeded neuropsychological tests (measured in seconds) in young and middle-aged adults, but not in older subjects (Van der Werf et al., 2001). A similar ROI study found no age-independent relationships between speeded neuropsychological test performance and volumes of the hippocampus, parahippocampus, or total brain volume (Tisserand, Visser, van Boxtel, & Jolles, 2000). We are aware of only one study that examined correlations between brain morphometry in several ROIs and RT performance, finding correlations (uncorrected for multiple comparisons) limited to cerebellum measures and variability in RT in a choice RT task (Kamitani, Kuroiwa, Li, Ikegami, & Matsubara, 2003).

Voxel-based morphometry (VBM) is a newer technique with several advantages over the ROI technique, including automated algorithms to distinguish both gray and white matter regional differences across the entire brain (Ashburner & Friston, 2001; Good et al., 2002; Richardson et al., 1997). VBM was used in one study to determine that the posterior hippocampi in London taxi drivers were larger than those of controls (Maguire et al., 2000). A subsequent study of drivers without taxi experience showed no association between the size of hippocampi and navigation expertise, suggesting that structural differences in the human hippocampus may depend on use rather than reflect innate ability (Maguire et al., 2003). However, a review of 33 studies showing a relationship between hippocampus size and memory noted little evidence to support the "bigger is better hypothesis"; in fact there is evidence that smaller volume predicts better memory for younger subjects (Van Petten, 2004).

Given the paucity of information about the relationship between regional brain structure and RT, we undertook this exploratory VBM study to determine whether regional gray matter (GM) and white matter (WM) volumes are related to speed of processing. Since RT measures generally show age-related slowing and since there are well-known age-related changes in regional brain structures (Tisserand & Jolles, 2003; Van Petten et al., 2004), we examined both middle-aged and senior adults. Only the thalamus, hippocampus, and parahippocampus have been studied in previous research designed to link neuropsychological test speed to ROI morphometry (Tisserand et al., 2000; Van der Werf et al., 2001); however, use of VBM assesses the entire brain. We hypothesized (1) that RT in a memory task would correlate with GM or WM volumes in areas previously associated with memory

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(Cabeza & Nyberg, 2000; Tisserand & Jolles, 2003; Van Petten et al., 2004) and (2) volume in these areas would not be related to RT in a simple stimulus–response task. More GM (or WM) may result in faster RT if more tissue is associated with more resources available to process information for a faster result. Alternatively, more GM (or WM) tissue might also result in slower RT if greater volume is associated with the need for more synapses to fire before a response is made. Given that there are a number of reports of inverse correlations between GM volume and memory performance in older adults (Salat, Kaye, & Janowsky, 2002; Van Petten et al., 2004) and given that many functional imaging studies show inverse as well as positive correlations between cognitive performance and brain activity (Alkire, Haier, Fallon, & Cahill, 1998; Daselaar, Prince, & Cabeza, 2004; Gur et al., 2000; Haier & Benbow, 1995; Haier et al., 1992; Haier et al., 1988; Landau, Schumacher, Garavan, Druzgal, & D'Esposito, 2004; Rypma, Berger, & D'Esposito, 2002; Shaywitz et al., 2001), there is no clear empirical basis for predicting the direction of any correlations between RT and specific regional brain volumes. This would be especially true if any such relationships are age dependent, as are other memory performance/brain structure relationships (Rypma, Prabhakaran, Desmond, & Gabrieli, 2001; Tisserand & Jolles, 2003; Van Petten et al., 2004).

METHOD

All procedures were in accord with the University of California, Irvine, Human Subjects Committee's review and approval; the subjects gave their informed consent. We used a data set from 18 normal right-handed volunteers in good health who had been selected as control subjects for another study (Haier, Alkire, et al., 2003). All subjects with a complete data set including MRI and RT testing were used in this study. There were 10 men and 8 women (mean age = 60.6; *SD* = 14.7; range, 38–82). These subjects were originally selected in two groups: middle-aged (n = 9, mean age = 47.3; *SD* = 6.7; range, 38–58) and seniors (n = 9; mean age = 73.8; *SD* = 4.7; range, 66–82). Subjects were screened and were included only if they had no medical history of head injury or psychiatric disorder and no indication of dementia or mild cognitive impairment at the time of cognitive testing.

Each subject was tested on two computer-based cognitive tests used previously for a study of neuropharmacological effects on cognition (Polich & Gloria, 2001). After a tutorial on each test, the subject completed a practice series and then completed the actual experimental trials. The first test was a simple stimulus–response task: After a random delay of 500 to 1,500 msec, a cross stimulus was presented in the center of a computer screen for 750 msec or until the subject responded by pressing a button. There were 22 trials. The second test was more difficult: a memory-loaded, continuous recognition test. The stimuli consisted of words, nonsense words, numbers, letters, geometrical shapes, outline drawings of common objects, or human faces from high school year books. During the test, one of these stimuli was presented in the center of the screen and the subject pressed the left arrow key if it had not been presented previously at any time during the foregoing trials and the right arrow key if it had been presented previously. The stimulus was removed with the response. After a 1,000-msec delay, a new stimulus appeared. There were 75 trials; the number of stimuli between two presentations of the same stimulus was random. No stimulus was repeated more than twice, and each category of stimulus had an equal probability of appearing. On average, 37 stimuli separated the presentation of any two identical stimuli. All subjects completed the test in less than 4 min.

Structural MRIs were obtained with a 1.5T clinical Philips Eclipse scanner (Philips Medical Systems, Bothell, WA) on a separate occasion. We used T_1-weighted, volumetric spoiled gradient recalled acquisition (SPGR) MRI scans (FOV = 24 cm, flip angle = 40, TR = 24, TE = 5). The images consisted of 120 contiguous 1.2-mm thick axial slices, each with an in-plane image matrix of 256 × 256 image elements. All images were visually inspected to ensure image quality.

We used voxel-based morphometry (VBM) to identify brain areas where GM and WM volumes were correlated with median RTs in both RT tasks. We used Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, University College London) to create a study-specific template and then applied the optimized VBM protocol using the methods of Ashburner and Friston (2000) and Good et al. (2001). To preserve the amount of tissue in any given anatomical region after spatial normalization, the optimal GM, WM, and CSF partitions were multiplied by the Jacobian determinants of their respective spatial transformation matrix. This modulation step was performed so that the final VBM statistics would reflect local deviations in the absolute amount (volume) of tissue in different regions of the brain (Ashburner & Friston, 2000). The modulated GM and WM partitions were then smoothed with a 12-mm FWHM isotropic Gaussian kernel to account for slight misalignments of homologous anatomical structures and to ensure statistical validity under parametric assumptions.

We used a statistical conjunction approach (Price & Friston, 1997) to test where both samples had the same or different correlations between RT and GM or WM tissue. There were four basic conjunction analyses (each was repeated separately for each RT task and for GM or WM): (1) areas with a positive correlation between RT and GM in both the middle-aged and the senior groups; (2) areas with a negative correlation in both groups; (3) areas with a negative correlation in the middle-aged group but a positive correlation in the seniors; (4) areas with a positive correlation in the middle-aged, but a negative correlation in the seniors. The first two analyses showed where the groups were the same with respect to any RT and brain structure relationships, and the second two showed where the groups differed. Note that positive correlations show that longer (i.e., slower) RT is associated with more volume. Negative correlations show that shorter (i.e., faster) RT is associated with more volume.

The SPM2 design matrix used with the conjunction analyses to determine GM or WM volume correlations with the simple RT task included sex and total intracranial volume (TIV; the sum of total GM, WM, and CSF volumes) as nuisance covariates. The same design matrix was used for RT in the memory task, except that number of errors was included as an additional nuisance variable as was RT in the simple task (RT in both tasks was correlated; $r = .58$, $p < .01$). Data are presented as significant at $p < .05$, corrected for multiple comparisons (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992; Worsley et al., 1996). All significant voxel cluster sizes greater than 1 are shown. Coordinates of clusters (centroids) are converted from original Montreal Neurological Institute (MNI) coordinates to those of the Talairach brain atlas (Talairach & Tournoux, 1988). Anatomical locations of the significant areas are based on the best estimate from the Talairach atlas. The portion of maximum variance accounted for by each correlation (at the centroid) was calculated as $r^2 = t^2/(df+t^2)$, using df = 12 and 10, respectively, for simple RT and memory RT analyses (from the SPM design matrix).

RESULTS

In the simple stimulus–response task, the average median RT was 283 msec (*SD* = 38) for the middle-aged group and 307 msec (*SD* = 63) for the seniors. Two subjects made 1 error each, and 16 subjects made no errors.

In the memory task, the average median RT for the middle-aged subjects was 770 msec ($SD = 150$); the mean number of errors was 8.0 ($SD = 5.4$). For the seniors, the average median RT was 801 msec ($SD = 84$); the mean number of errors was 8.0 ($SD = 2.0$). Although the seniors tended to be slower in both tasks, RTs did not significantly differ between the two groups.

In the simple stimulus–response task, there were no significant correlations ($p < .05$, corrected for multiple comparisons) between RT and GM in any of the four conjunctions. For WM, there was a single significant finding in the conjunction reflecting a negative correlation in both groups. This was in the right fusiform gyrus, BA 37 (53 voxels, $x = 37, y = -49, z = -12$, T = 4.60).

In the continuous recognition memory task, two of the conjunction combinations showed significant GM correlations with RT ($p < .05$, corrected). In the first conjunction, both the middle-aged and the senior groups showed positive correlations between RT and GM in the right and left globus pallidus, in the left thalamus, and in the left parahippocampus. The locations are detailed in Table 1 and shown in Figure 1A. These are areas where faster RT is associated with *less* GM volume. In the second conjunction, there were several areas where the middle-aged group showed a negative correlation between GM and RT, but in which there was a positive correlation in the seniors. These areas are detailed in Table 2 and shown in Figure 1B. They include BAs 46, 9, 10, and 6 in the left frontal lobe and BAs 8 and 9 in the right medial frontal gyrus; BAs 19 and 37 in the right occipital lobe, BA 13 in the right insula, and BA 41 in the right temporal gyrus. These are areas where faster RTs are associated with *more* GM in the middle-aged group, but with *less* GM in the seniors.

There were no significant correlations in the conjunction where both groups had negative correlations between RT and GM or in the conjunction where middle-aged subjects showed positive correlations and seniors showed negative ones. There were no significant WM/RT correlations in any of the four conjunction combinations for the memory task.

DISCUSSION

To our knowledge, this is the first report using VBM to determine whether regional brain structure variation is related to individual differences in RT. Faster RT on a memory task was correlated with *less* GM in three brain areas—the globus pallidus, the thalamus, and the parahippocampus—in both the middle-aged and the senior groups. Similarly, for the seniors, faster RT was associated with *less* GM in several Brodmann areas, especially in BAs 46, 9, and other parts of the frontal lobe, whereas *less* GM in the same areas was associated with slower RT in the middle-aged group. The globus pallidus, thalamus, parahippocampus, and BAs 46/9 have all been reported to be associated with memory (Braver et al., 2001; Cabeza et al., 2004; Gambaryan & Sarkisyan, 1983; Van der Werf et al., 2003), particularly working memory (Cabeza & Nyberg, 2000). The inverse relationships in these areas between GM and RT found in this study are consistent with earlier ROI morphometric studies showing inverse correlations between regional brain volume and performance on memory tasks (Salat et al., 2002; Van Petten et al., 2004), although one earlier study found that faster RT was related to a larger thalamus in young and middle-aged adults (Van der Werf et al., 2001).

Currently, it is not known why less tissue is related to faster RT; however, this observation is consistent with a growing body of evidence that regionally efficient brain function and structure may be associated with better cognitive performance (Cabeza et al., 2004; Daselaar et al., 2004; Haier et al., 1995; Haier et al., 1992; Haier et al., 1988; Landau et al., 2004; Salat et al., 2002; Van Petten et al., 2004) and even possible compensatory mechanisms (Cabeza, Anderson, Locantore, & McIntosh, 2002; Haier, Alkire, et al., 2003). Irrespective of direction, we note that the brain regions identified by VBM to be associated with continuous recognition memory in these samples, including the globus pallidus, thalamus, and BAs 9/10, overlap substantially with the dorsolateral prefrontal circuit (Cummings, 1993) and its afferent connections (BAs 46 and 7). This fronto-subcortical circuit is implicated in mediation of memory storage and retrieval strategies (Tekin & Cummings, 2002). Thus, VBM may help to elucidate interactions between age and brain circuits largely inaccessible to ROI approaches.

Since there is so little data on RT and brain structure, the apparent interactions among age, GM, and RT should be viewed as interesting, but tentative, empirical observations. Additional hypothesis testing will be necessary, especially in larger samples where VBM becomes more stable (Davatzikos, 2004; Friston & Ashburner, 2004) and anatomical localization becomes more exact. For ex-

Table 1
Areas Where GM and RT to the Memory Task are Positively Correlated ($p < .05$, Corrected) in Both Middle-Aged and Senior Groups

Nearest GM Area	Cluster Size	x	y	z	T	r^2
Right medial globus pallidus	65	20	−12	−1	5.07	.72
Left parahippocampal gyrus, BA 27	584	−6	−34	0	4.93	.71
Left thalamus		−6	−26	−2	4.82	.70
Left lateral globus pallidus	3	−18	−13	0	4.41	.66

Note—GM, gray matter; RT, response time; BA, Brodmann area; *x*-, *y*-, *z*-coordinates are from the Talairach atlas.

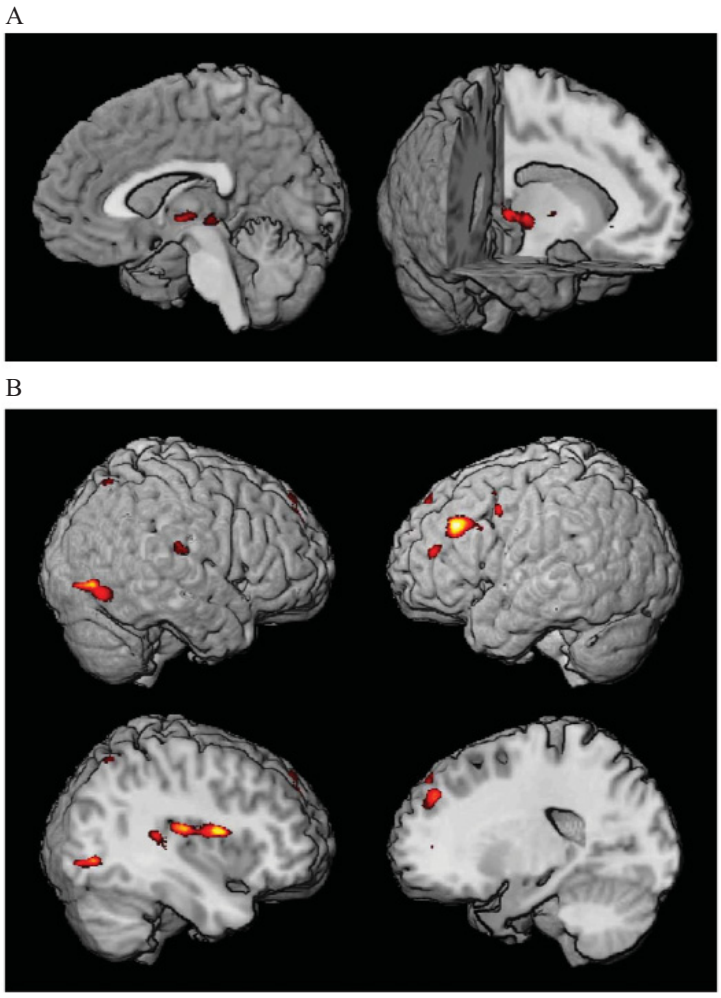

Figure 1. (A) The conjunction of where gray matter and response time (RT) in the continuous recognition memory task are correlated. These are positive correlations common to both samples showing that faster RTs are related to *less* GM in the left thalamus and to *less* gray matter in the left parahippocampus (sagittal view in left panel) and in the right globus pallidus (cut-away in right panel). The *x*-, *y*-, *z*-coordinates of these areas (centroids) are shown in Table 1 ($p < .05$, corrected for multiple comparisons). (B) Four sagittal views of the conjunction of where RT in the continuous recognition memory task and gray matter is negatively correlated in the middle-aged sample but positively correlated in the seniors. In these areas, faster RT is related to *less* gray matter in the senior group but to *more* gray matter in the middle-aged group. The coordinates and names of these areas (centroids) are shown in Table 2 ($p < .05$, corrected). The results in panels A and B are displayed on a study-specific 3-D template ($p < .10$, corrected); images are oriented so that the right side of each image is the right hemisphere.

ample, in a larger sample, our finding in the thalamus might be better described as in the pulvinar and the finding might extend into the red nucleus. Increased statistical power may also identify additional areas and circuits where brain volume is related to RT.

It should also be noted that our senior group tended to have slower RTs than those for the middle-aged group, as expected, but that these differences were not significant. Our senior group performed each task quite well; the variability of RT was less in the seniors than in the middle-aged group. It has been noted (Tisserand & Jolles, 2003) that elderly subjects may show volume decreases linked to poor cognitive performance only in the presence of neuropathology. More representative samples, matched for performance between age categories, may show different results, as may other cognitive tasks designed to differentiate various aspects of memory functions. In addition to matching subject groups on age and sex, it may also be advisable to match subject groups on general intellectual ability, since individual differences in intelligence are correlated with regional brain activation during passive information processing (Haier, White, &

Table 2
Areas Where GM and RT to the Memory Task are Positively Correlated ($p < .05$, Corrected) in the Senior Group and Inversely Correlated in the Middle-Aged Group

Nearest GM Area	Cluster Size	*x*	*y*	*z*	T	r^2
Right inferior occipital gyrus, BA 19	750	37	−70	1	7.67	.85
Right inferior occipital gyrus, BA 19		42	−76	−1	6.27	.80
Right middle occipital gyrus, BA 37		48	−66	−5	5.42	.75
Left middle frontal gyrus, BA 46	849	−50	31	28	7.35	.84
Right medial frontal gyrus, BA 9	1,077	3	48	30	6.72	.82
Right medial frontal gyrus, BA 8		2	51	39	4.93	.71
Left medial frontal gyrus, BA 6		−6	44	32	4.36	.66
Right insula, BA 13	597	37	6	12	6.09	.79
Right insula, BA 13		38	−5	14	4.29	.65
Right insula, BA 13	518	38	−17	16	5.22	.73
Right insula, BA 13		46	−19	18	5.10	.72
Left middle frontal gyrus, BA 10	87	−28	45	11	5.15	.73
Left middle frontal gyrus, BA 9	55	−42	8	37	4.96	.71
Right transverse temporal gyrus, BA 41	87	38	−33	12	4.96	.71
Right superior parietal lobule, BA 7	12	39	−59	56	4.63	.68

Note—GM, gray matter; RT, response time; BA, Brodmann area; *x*-, *y*-, *z*-coordinates are from the Talairach atlas.

Alkire, 2003) and with regional GM and WM variation (Haier, Jung, Yeo, Head, & Alkire, 2004, 2005).

Although GM and WM are highly hereditable in some areas more than others (Posthuma et al., 2002; Thompson et al., 2001), there is also some evidence that GM volume increases with practice (Draganski et al., 2004). Whether regional brain volumes influence RT or whether RT experience influences brain volumes, individual differences in total or regional brain volumes appear to be potentially confounding variables to be taken into account in cognitive brain imaging experiments, along with age, sex, and handedness. For example, trained athletes, musicians, or avid computer game players may yield experimental results under some circumstances that do not generalize well to the wider population if structural brain variation is not taken into account. Any effects of structural brain variation are often ignored when whole brain size and shape are normalized in imaging studies that rely on fitting all brains into a standard space for statistical analyses.

Our findings indicate that regional variation in GM volume is related to individual differences in speed of processing in a continuous recognition memory task. This suggests that regional brain volumes should be studied as potential sources of variance to help ascertain functional and structural brain effects independently of one another in functional cognitive imaging experiments. This differentiation is an important step in establishing the relationships among brain structure, function, and cognition.

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(Manuscript received September 15, 2004;
revision accepted for publication February 24, 2005.)