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Neuroanatomical Correlates of Fluid Intelligence in Healthy Adults and Persons with Vascular Risk Factors

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The main objective of this study was to examine the effects of regional brain changes on cognitive decline and the modifying influence of vascular risk (VR) factors. We present latent difference score analyses of associations among 5-year changes in 12 regional brain volumes and age-sensitive cognitive functions in 87 adults (32 with identifiable VR factors). We found reliable individual differences in volume change for 11 of the 12 brain regions but not in the cognitive measures that showed average longitudinal decline. Thus, associations between rates of change in fluid intelligence and brain volumes could not be assessed. We observed, however, that lower levels of fluid intelligence were associated with smaller prefrontal and hippocampal volumes. Lower fluid intelligence scores were also linked to greater longitudinal shrinkage of the entorhinal cortex (EC). After accounting for the effects of age, sex, and VR factors, the orbitofrontal cortex and the prefrontal white matter (PFw) volumes as well as the 5-year change in the EC volume predicted fluid intelligence level. VR was independently associated with smaller prefrontal volumes and lower fluid intelligence. Thus, prefrontal and medial–temporal systems may play different roles in age-related differences and changes in cognitive performance.

Keywords: entorhinal cortex, fluid intelligence, hippocampus, longitudinal latent growth models, prefrontal cortex, white matter

Introduction

Aging, even when uncomplicated by significant disease, is associated with differential changes in brain structure (see Raz and Rodrigue 2006 for a review) and cognitive performance (see Horn 1982; McArdle et al. 2002). However, the relationship between age-related differences in neuroanatomy and cognition is not well understood. Despite multiple attempts to clarify the specific links between neural and cognitive properties across a wide range of ages, the results are marred by inconsistencies (see Raz 2000; Coffey et al. 2001; Raz and Rodrigue 2006 for reviews). Some studies revealed significant associations between regional brain properties, such as volumes, cortical thickness, or white matter integrity, and performance on the tasks that putatively depend on those regions (Golomb et al. 1994; Raz et al. 1998, 1999, 2000; Schretlen et al. 2000; Tisserand et al. 2000; Gunning-Dixon and Raz 2003; Rosen et al. 2003; Kennedy and Raz 2005; Mungas et al. 2005; Fjell et al. 2006; Gianaros et al. 2006; Jessen et al. 2006; Moffat et al. 2007). Gray matter density in a widespread network of cortical regions positively correlates with IQ (Haier et al. 2004; Colom et al. 2006), and various IQ indices correlate modestly but consistently with the total brain size (Rushton and Ankney 1996). However, a quantitative summary of correlational studies of memory and hippocampal volume yielded an essentially null result (Van Petten 2004), and in some samples, negative correlations between local brain volumes and executive functions were observed (Salat et al. 2004; Van Petten et al. 2004; Duarte et al. 2006).

The reasons for these discrepancies are unclear, but variability in sample composition probably is one. Selection of participants for the studies of brain–behavior relationships is usually nonrandom. One of the important dimensions on which the samples of convenience may differ is the proportion of participants with preclinical morbidity, such as vascular disease. Overt vascular disease at various levels of severity becomes increasingly common after the fifth decade of life, and age-related alteration in vascular functions such as control of the arterial blood pressure have been linked to cognitive changes frequently observed in persons of advanced age (Waldstein et al. 1991; Elias et al. 1993; Anstey and Christensen 2000). Of all types of vascular disease, hypertension is the most prevalent one: it affects more than 60% of all adults older than 60 years of age (Hajjar and Kotchen 2003) and thus could be considered an attribute of common though not "successful" aging.

Hypertension exerts negative influence on cognitive skills that are considered particularly age sensitive (Horn 1982), such as memory and executive functions (Waldstein et al. 1991; Elias et al. 1993). That influence is notable even when hypertension is treated and brought to relatively mild levels (Head et al. 2002; Raz, Rodrigue, Acker, 2003). Population-based cross-sectional studies established cardiovascular disease and vascular risk (VR) factors, such as hypertension, as significant mediators of age-related differences in brain integrity and cognitive performance (Saxton et al. 2000; Gorelick 2005; Gianaros et al. 2006). Therefore, it is possible that admixtures of participants who suffer from preclinical vascular disease may be at least partially responsible for the observed pattern of age-related changes and for the discrepancies among the studies. Another possible source of between-study variability is the confounding of age-related and other individual differences in cross-sectional studies of multiple brain regions, some of which may show elevated individual variation (Tisserand et al. 2004; Raz et al. 2005). The problem of differential variability compounds the problem of commonality of variance between age and other predictors that is inherent to cross-sectional models (see Hertzog 1996; Lindenberger and Pötter 1998; Hofer and Sliwinski 2001).

A longitudinal design, although not free of its own problems, can address most of the outlined concerns. Several recent studies showed that longitudinal change in specific regions rather than individual differences in regional volume predicts performance on memory and executive function tasks at follow-up (Rodrigue and Raz 2004; Mungas et al. 2005; Cohen et al.

2006). However, those studies were limited to measurement of only a few brain regions and a few selected cognitive domains.

The goal of this study was to address the limitations of the extant literature and to examine the relations between differential brain shrinkage in multiple regions and senescent changes in multiple cognitive domains. We attempted to separate the effects of healthy (successful) aging from those of common pathological conditions such as increased VR and vascular disease. To that end, we examined the associations between brain and cognition in a sample of adults of both sexes who spanned a broad age range and varied in their vascular health. To restrict the number of possible models and associated statistical tests, we applied advanced longitudinal data analysis methods to first identify cognitive abilities that showed statistically reliable mean change during the 5-year follow-up period. We then assessed associations between the volume of each different brain region, on the one hand, and aging-sensitive cognitive performance, on the other. Finally, we evaluated the influence of demographic and health factors such as calendar age, sex, and broadly defined VR on the effects of brain volume and brain volume change on cognitive performance.

In examining brain–cognition relations, we took advantage of the multivariate longitudinal design. First, to assess the volume of all 12 investigated brain regions, we relied on the bihemispheric measurements. Using left and right measures of the same construct (brain volume) provides a statistically superior estimate than analyzing either hemispheric measurement alone. Second, the longitudinal feature allows separating temporally stable individual differences in brain structure and cognition from individual differences in change. The latent difference score model (LDM; McArdle and Nesselroade 1994) provides optimal (i.e., unbiased and reliable) statistical estimates of brain volume, based on commonality of hemispheric measurements. LDM formally separates information about the baseline and change in constructs, as is only possible in a longitudinal design. LDM also provides a formal test for the existence of individual differences in change, answering an important question of whether individuals show reliable differences in the pace of brain volume change and cognitive decline (or improvement). In contrast, analyses such as [multiple] regression or repeated-measures analysis of variance do not benefit by any of these advantages. In particular, they 1] typically include variables with less desirable statistical properties (e.g., reliability), 2] do not separate formally baseline from change, so that the 2 are typically confounded, and 3] assume that there is variation in longitudinal change, rather than testing it. Hence, LDM is an optimal approach to testing the associations between regional brain volumes and cognitive performance and has already been successfully applied to the investigation of brain changes (Raz et al. 2005).

We limited brain measures in this study to regional volumes because white matter abnormalities, although indicative of white matter integrity changes, are too rare in younger adults; hence, including those measures would reduce the sample size by almost 50% and greatly reduce generalizability of results. The links between white matter integrity and longitudinal change in cognitive performance in middle-aged and older adults are examined elsewhere (Raz et al. 2007).

Materials and Methods

Participants

The sample employed in this study was an extension of the one used in our recent study of brain change (Raz et al. 2005), and the readers are referred to that source for a detailed description of recruitment and retention characteristics. The sample consisted of healthy, well-educated adults from a major metropolitan area in the United States of America. Of 323 participants who initially took part in the study, 140 persons (43% of the total eligible pool; 62% of the responders) agreed to participate in the study 5 years later. Those who declined cited busy schedule, length of commute, poor health, objection to magnetic resonance imaging (MRI), and lack of interest. The participants signed a consent form approved both by the University Committee for Protection of Human Subjects in Research and by the Hospital's Patients Participation Committee. All participants were screened with a mail-in health questionnaire completed by the participants and augmented by telephone and personal interviews.

Of those who agreed to participate, 127 participants (91%; 39% of the total) have completed the follow-up study. The screening criteria used to determine eligibility at the beginning of the original study (first measurement) were applied to the 5-year follow-up sample. Persons who reported history of neurological or psychiatric conditions, head trauma with loss of consciousness for more than 5 min, thyroid disease, treatment for drug and alcohol problems, or a habit of taking 3 or more alcoholic drinks per day were excluded from the study. Participants with 2 types of cardiovascular problems reported at baseline—hypertension controlled by medication (14 cases) and mitral valve prolapse (MVP, 3 cases)—were retained in the sample. Hypertension is a widely acknowledged risk factor for brain and cognitive declines (Waldstein et al. 1991), whereas MVP has been identified as a risk factor for cardiovascular-related mortality (Avierinos et al. 2002) and cerebrovascular accidents (Cohen et al. 1997). Hypertensive participants took standard hypertensive treatment: beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and potassium-sparing diuretics. None of the participants used antiseizure medication, anxiolytics, or antidepressants.

Participants who acquired vascular conditions during the 5 years of follow-up were retained in the study and, together with those who had VR factors at baseline, were treated as a separate group. All subjects were screened for dementia at baseline and follow-up using a modified Blessed information-memory-concentration test (Blessed et al. 1968) with a cutoff of 25 points (80% correct), and at follow-up using mini-mental state examination (Folstein et al. 1975) with a cutoff of 26 (87% correct). Participants were also screened for depression with the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff 1977) using a cutoff of 15. All participants were consistent right-handers, as indicated by a score above 75% on the Edinburgh handedness questionnaire (Oldfield 1971). An experienced neuroradiologist (J.D.A.) examined the scans for space occupying lesions.

Of the 127 subjects tested at follow-up, MRI data on 26 subjects (20%) were either completely lost (4 cases) or not suitable for a longitudinal analysis (22 cases with a different field of view that confounded time of measurements with coarser resolution). Additional 14 subjects had a substantial amount of missing cognitive data. Thus, the final sample consisted of 87 participants (32 men), which constituted 27% of the eligible cohort. Among them, 55 remained healthy throughout the study and met the outlined screening criteria, whereas 32 carried a variety of VR factors or had vascular disease diagnosed during the follow-up period. At 5-year follow-up, the vascular disease/VR group consisted of 27 participants with hypertension, 3 with MVP, 2 with type II diabetes, 2 with heart disease that required angioplasty (one) and cardiac bypass (one), one who suffered a heart attack, one with a diagnosed cerebellar bleed, and 2 with a diagnosis of minor strokes. Some participants had more than one of the listed conditions.

The groups did not differ in education or general cognitive status at either measurement occasion; both were examined at the same delay. The VR group contained fewer men, perhaps due to the population patterns of vascular morbidity and mortality (Li et al. 2006). In comparison to healthy participants, the VR group was somewhat older and had higher systolic and diastolic blood pressure, although at the levels that would be considered borderline hypertensive at worst. For descriptive statistics and group comparisons, see Table 1.

MRI Protocol

All imaging was performed on 1.5-T Signa scanners (General Electric [GE] Co., Milwaukee, Wisconsin) installed in the same hospital.

Table 1
Sample descriptors for healthy and vascular risk (VR) participants

Descriptor\group	Healthy	VR	*P*
N	55	32	
Age at baseline (years)	51.11 (20–77)	59.75 (38–77)	0.03
Delay between baseline and follow-up	5.23 (5–6)	5.31 (5.0–6.0)	0.19
Education (years)	16.12 (12–21)	15.93 (12–21)	0.76
Percent of male participants	43	25	0.08
Blessed score at baseline	29.03 (25–31)	28.51 (25–31)	0.15
Blessed score at follow-up	28.91 (25–31)	28.59 (25–31)	0.29
Mini-mental state examination score	28.82 (26–30)	28.91 (27–30)	0.72
Blood pressure, systolic (mm Hg)	121.84 (98–155)	134.44 (112–178)	<0.00001
Blood pressure, diastolic (mm Hg)	76.78 (64–97)	82.61 (69–104)	<0.003

Note: Numbers in the second and third column represent means, unless otherwise indicated, with the range in parentheses; *P* values refer to independent sample *t*-tests.

However, whereas only one magnet was used for the baseline scanning, 2 additional magnets were employed for retesting 4 of the subjects at follow-up. One subject was rescanned on an identical GE Signa magnet located in an adjacent room, and 3 subjects were rescanned on a mobile 1.5-T GE magnet located at the entrance to the imaging center. The scanners were routinely calibrated using the same standard GE phantom.

Volumes were measured on 2 sets of images acquired at baseline and 5-year follow-up with a T_1-weighted 3-D spoiled gradient recalled sequence of 124 contiguous axial slices, echo time = 5 ms, repetition time = 24 ms, square field of view = 22 cm, acquisition matrix 256 × 192, slice thickness = 1.3 mm, and flip angle = 30°.

MR Image Processing

Image processing and regional volume measures are described in detail elsewhere (Raz, Rodrigue, Kennedy, Dahle, et al. 2003; Raz, Rodrigue, Kennedy, Head, et al. 2003; Raz, Gunning-Dixon, et al. 2004). The images acquired on both occasions were coded, and the order of their tracing was randomized within each subject by a person other than the operators who traced the region of interest (ROIs). The operators were blind to the time of acquisition of the specific images, VR status, and the demographic characteristics of the participants, as well as to the magnet on which the scan was acquired. To ensure the blindness of the operators, the baseline measurements previously published in cross-sectional studies (Raz et al. 1997, 1998, 2001; Raz, Gunning-Dixon, et al. 2004; Raz, Rodrigue, et al. 2004) were not used and all structures were measured anew as described in our previous publication (Raz et al. 2005). Reliability of ROI measures, assessed using a conservative intra-class correlation formula that presumes random selection of raters (Shrout and Fleiss 1979), were all in excess of 0.90 (Raz, Gunning-Dixon, et al. 2004).

In this study, we used the volumes of the intracranial vault (ICV), lateral prefrontal cortex (LPFC), orbital frontal cortex (OFC), the prefrontal white matter (PFw), inferior parietal white matter (IPw), inferior temporal cortex (IT), fusiform cortex (FG), visual (pericalcarine) cortex (VC), the hippocampus (HC), the entorhinal cortex (EC), the caudate nucleus (Cd), and the cerebellar hemispheres (Cb), as computed in our previous report (Raz et al. 2005). Inferior parietal (IPL) volumes were not used because they showed no variance in change (Raz et al. 2005).

Cognitive Measures

Fluid Intelligence

We administered 2 tests of fluid reasoning known for their sensitivity to age, Cattell Culture Fair Intelligence Test (CFIT, 2A and 3A combined) (Cattell RB and Cattell AKS 1973) and Letter Sets Test (parts 1 and 2) from the Educational Testing Service Factor-Referenced Test Kit (Ekstrom et al. 1976). The CFIT is essentially a test of nonverbal reasoning composed of 4 subtests per form. The test is commonly used as a marker of fluid intelligence in studies of lifespan development aging and consists of nonverbal reasoning problems covering a wide range of difficulty [Raz et al. 1998; Rabbitt and Lowe 2000; Schretlen et al. 2000]. Each subtest consists of 10–14 items tapping different nonverbal abstract reasoning domains, including detection of similarities in designs, completing matrices according to specific rules, and solving nonverbal syllogisms. In all problems, the participant has to derive the rule required to solve the problem. The first subtest requires completion of a linearly aligned series of stimuli according to the rule to be derived by the participants. The second subtest calls for analyzing the stimulus, discovering the differences, and selecting the "odd man out." The third is similar to the first in calling for rule-based set completion, only in the framework of 2 × 2 and 3 × 3 matrices. The fourth subtest requires solution of nonverbal syllogisms by determining spatial relations between the components of the stimuli and applying the rule to the target. The test is timed, with 2.5–4 min allowed for completion of each subtest [a total of 12 min]. The index of performance is the number of total correct items across the 8 subtests. Form B was given for both CFIT tests on the second testing occasion. Standardized IQ scores were also assigned for each form of CFIT on the basis of the standardization sample tables provided by the test publisher [Cattell RB and Cattell AKS 1973]. Using the raw and the standard scores from the standardization sample tables [Cattell RB and Cattell AKS 1973], we computed the form A to form B conversion factor. Form B turned out to be about 15% more difficult than form A and thus, decline in raw scores could have reflected that difficulty differential. We, therefore, used the computed conversion factor and the fact that the total raw score is an unweighted sum of the subtest scores to adjust the form B [follow-up] subtest scores. Such global adjustment could have offset some of the true declines. However, we believe that it was better to err in the conservative direction than to face a possibility of reporting spurious "losses." The Letter Sets Test served as an additional index of fluid reasoning. This test is composed of 2 forms containing 15 items each. Five sets of 4 letter series are presented in each item, and the participants' task is to find the rule that relates 4 of the 5 sets to each other and to mark the one that does not fit this rule. Participants work for 7 min on each form [for a total of 14 min]. The score on this test is the total number of correct items minus 0.25 point for each incorrect item. An identical test was administered at follow-up.

Working Memory

The participants performed 2 verbal working memory (WM) tasks: computation span (CSPAN) and listening span (LSPAN) forms B (Salthouse et al. 1990) and a nonverbal WM task: size judgment span (SJS) (Cherry and Park 1993). Both CSPAN and LSPAN tasks measure the ability for simultaneous storage and processing of verbal information and are very similar in structure, administration, and scoring. In CSPAN, the participant is asked to solve simple arithmetic problems while simultaneously remembering the last digit in each problem. In LSPAN, the participants listen to simple sentences. After each sentence, they are asked to answer a question about its content and to report its final word. Although there are 3 ways of scoring the span tests, the absolute span, which is calculated by summing the number of correct items across blocks of trials on which the participant answered all of the items correctly, was chosen because it produces a reasonably wide range of scores and is not particularly prone to capitalization on chance. During the second testing occasion 5 years later, alternate test forms were given [form A]. Forms A and B of the LSPAN and CSPAN tests were not of equal difficulty. No standardized scores [as for Cattell CFIT] are available for those tests. Thus, normative data were collected in our lab on 354 participants (177 per form, matched on age, sex, and education). These data yielded correction factors for translation between forms A and B: 1.09 for LSPAN and 0.71 for CSPAN [Raz N, unpublished data]. These correction factors were applied to the scores, in this study, in order to correct for differential difficulty of the forms. On SJS, participants were read aloud lists of objects and animals and were asked to repeat each list with the items arranged in the ascending order of their size. The score on this test was the cumulative number of correct trials. The same SJS form was administered at follow-up.

Vocabulary

Verbal comprehension was measured by vocabulary tests (V-2 and V-3) from the ETS Kit of factor-referenced cognitive tests (Ekstrom et al. 1976). The tests assess knowledge of word meaning in a 5-alternative multiple-choice format V-2 consists of 18 items and has a rated difficulty

of 7th to 12th grade. V-3 consists of 24 items ranging from very easy to very difficult and has an extended range of difficulty corresponding to 7th to 16th grade levels. For each word, the participant is to choose the word that has the same meaning (i.e., a synonym). The index of performance is the total number of correct items minus 0.25 point for each incorrect item [penalty for guessing]. Both timed and untimed scores were recorded. Part 1 of V-2 and V-3 was used at baseline, and Part 2 of V-2 and V-3 was administered at follow-up.

Statistical Analyses

Data Conditioning and Analytic Approach

Before the main analyses, the data were examined for possible sources of systematic error. The effects of the scanner (Magnet 1, Magnet 2, and the Mobile Unit) on the ICV measured at follow-up were examined using 2 separate linear models. In these models, ICV was the dependent variable, and, in addition to magnet, age and sex were also included. The results of these analyses demonstrated that the change in the magnet that occurred between baseline and follow-up has not affected ICV. Thus, variations in scanner resulted in no systematic bias. The mean ICV remained relatively stable across the 5-year delay, with a mean 5-year change of only 0.62%. That small difference, however, was statistically significant (t_{85} = 2.02, P < 0.05) and justified the adjustment of the regional volumes by the ICV. Another reason for such adjustment was that the ICV differed between the sexes with men having larger crania (t_{85} = 6.51 and 6.73 for baseline and follow-up, both with P < 0.0001). It was not, however, correlated with age: r = –0.06 and –0.07 for baseline and follow-up, respectively, both nonsignificant (NS). The adjustment to ICV was performed on each ROI volume in each hemisphere via a formula based on the analysis of covariance approach: adjusted volume = raw volume – b × (ICV – mean ICV), where b is the slope of regression of an ROI volume on ICV. The adjusted volumes were used as dependent variables in the analyses presented below.

Latent Difference Modeling

To test whether there were changes in cognitive abilities and in brain ROI volumes both at the sample and at the individual level, we applied latent difference modeling (McArdle and Nesselroade 1994). By latent variable, we mean a variable that cannot be measured, but whose properties can be inferred by what is common to a set of selected measured variables (e.g., a region's brain volume assessed by what is common to the 2 hemisphere's measurements). Indeed, measured variables are especially vulnerable to the consequences of imperfect reliability of measurement (Cronbach and Furby 1970; cf., Rogosa and Willett 1985; Baltes et al. 1988), whereas latent variables are better behaved in this regard. This approach is very common in studies of cognitive performance but has only recently been applied in structural brain studies (Raz et al. 2005). The LDM provides the best estimate of each construct (e.g., regional volume) at baseline and at follow-up and calculates the mean and the variance of reliability-adjusted difference scores as the best estimates of change. As a consequence, LDM allows to formally test whether regional brain changes differ across individuals, and, if so, to estimate the strength of associations between these changes, although at the same time also considering the baseline measures. We applied to the current data the same LDM approach as described in our previous publication (Raz et al. 2005). Specifically, for each ROI, we used the volumes of the 2 hemispheres to define the ROI volumes, at baseline and at follow-up. Separate LDMs were constructed for each ROI to estimate the sample mean change and the individuals' differences in change in the specific regions. Specifically, each LDM estimated 5 parameters: 1] mean volume at baseline, T1; 2] variance in volume at T1; 3] mean volume change from T1 to follow-up, T2; 4] variance in volume change from T1 to T2; and 5] the covariance between volume at T1 and change in volume between T1 and T2. Likewise, cognitive abilities were defined by sets of identical indicators at T1 and T2. To obtain empirical estimation of the LDM parameters, equality constraints were imposed on the following parameters, unless stated otherwise: 1] residual means of the left hemisphere across time to accommodate possible time-invariant hemisphere differences in volume; 2] unique variances of the left hemisphere across time; 3] unique variances of the right hemisphere across time; 4] factor loadings of the right hemisphere across time; 5] autocorrelated residuals of the two hemispheres. To define the metric of latent factors, the factor loading of the left hemispheres were set to unity at both occasions. With 4 observed variables and 10 free parameters, this measurement model is overidentified with degrees of freedom [df] = 4, which means that it can be estimated empirically and eventually rejected if not representative of the data structure (e.g., Kline 1998). Tenability of this model is consistent with the assumption of strict metric invariance (Meredith 1964), i.e., that the relation between observed and latent variables does not change over time so that differences at the latent level can be interpreted with confidence. As in our previous work (Raz et al. 2005), we proceeded in 2 steps: first, we fitted LDMs for each of the 12 ROIs. The results concerning change were that in only one ROI individuals did not evidence differential change in volume. In other words, for all but one region inferior parietal lobule, shrinkage rate varied significantly across individuals. In the second step, we applied a multivariate LDM that simultaneously analyzed the 11 regions showing differential shrinkage to explore covariance in change across ROIs. Only this multivariate model allows testing the associations among the rates of change across the ROIs.

The analyses of brain–cognition relations reported here build on this work and proceeded in 3 incremental steps. First, we identified cognitive measures that showed reliable mean change as well as variance in change and were psychometrically suitable for LDM. Second, we applied multivariate LDMs to the data that included cognitive ability scores satisfying the first step and all ROI volumes measured in our previous work (Raz et al. 2005). This allowed identifying statistically reliable relations between the ROI volumes and cognitive ability. Third, we computed separate follow-up LDMs for each ROI that showed reliable relations to cognition in the second step. This third step allowed us to examine the extent to which these relations were attenuated or moderated by sex, chronological age, and VR status. To better ascertain the influence of the covariates, we added the potential moderating variables hierarchically, in the order of their theoretical importance: first only age, then sex, and finally VR.

Results

A Pattern of Cognitive Changes

First, we examined the pattern of change in cognitive performance to establish which tasks evidenced significant decline during the 5-year follow-up period. Those comparisons (Table 2) reveal significant diversity in the longitudinal course of cognitive abilities. Performance on vocabulary test, an index of crystallized ability, remained stable over time. In addition, several indices of fluid intelligence (letter series, Cattell IQ- form 2, and 2 of the subtests of Cattell IQ form 3) and one index of WM (SJS) did not show reliable mean declines. The 4 measures that did—the subtests 1 and 3 of the Cattell IQ form 3, listening span, and CSPAN—were selected as candidate indicators for LDM. The logic of such selection was that brain volume shrinkage was not expected to correlate with individual differences in the cognitive change that are centered around zero, and thereby, on average, are not indicative of aging-related losses in cognitive functioning. Exploratory factor analysis revealed 2 factors that accounted for more than 80% of the variance and corresponded to 2 distinct constructs, a fluid ability factor (measured by the 2 Cattell subtests), and a WM factor (measured by LSPAN and CSPAN). Although separate LDMs were specified for each construct, a model containing the WM factors failed to converge. Inspection of raw data suggested a lack of sensitivity in both measures at the low end of the scale (e.g., floor effects). Thus, despite reliable mean decline, the 2 WM measures were unsuitable for the establishment of a WM construct in the context of LDM. We, therefore, limit further analyses to the fluid intelligence measures.

Table 2
Cognitive performance indices at baseline (T1) and follow-up (T2)

Test	Baseline	Follow-up	Paired *t*	Correlation with age: Baseline	Correlation with age: Follow-up
Fluid intelligence					
Letter series	9.40	9.53	0.52	−0.19	−0.42***
Cattell IQ form 2	99.79	99.97	0.14	−0.42***	−0.53***
Cattell IQ form 3	107.08	97.57	−6.59***	−0.42***	−0.55***
Raw subtest 1	7.22	5.66	−9.61***	−0.41***	−0.48***
Raw subtest 2	6.60	6.54	−0.28	−0.21*	−0.32**
Raw subtest 3	5.33	4.67	−3.62***	−0.32**	−0.32**
Raw subtest 4	5.34	5.41	0.37	−0.27*	−0.52***
WM					
LSPAN	22.17	17.08	−4.71***	−0.36***	−0.45***
CSPAN	15.78	13.41	−2.39*	−0.27*	−0.28*
SJS	9.14	9.01	−0.73	−0.40***	−0.47***
Crystallized intelligence					
Vocabulary	27.26	27.16	−0.19	0.23*	0.13

Note: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3
Regional brain volumes and fluid ability (G_f): LDM analyses summary

ROI	Level T1 *r*	Level T1 *z*	Level T2 *r*	Level T2 *z*	Change *r*	Change *z*
LPFC	0.28*	2.12	0.35*	2.63	0.23	1.45
OFC	0.36*	2.72	0.36*	2.70	−0.02	−0.13
PFw	0.32*	2.45	0.37*	2.84	0.20	1.54
VC	0.23	1.29	0.23	1.76	−0.05	−0.33
Cd	0.16	1.09	0.16	1.27	−0.05	−0.31
HC	0.25	1.94	0.36*	2.71	0.34*	2.07
EC	−0.03	−0.23	0.13	1.01	0.47*	2.84
Cb	0.11	0.92	0.11	0.92	−0.02	−0.13
IPw	0.06	0.50	0.12	0.94	0.27	1.37
FG	0.23	1.77	0.22	1.68	0.03	0.21
IT	−0.02	−0.16	0.05	0.43	0.20	1.37

Note: In the measurement model for G_f, the estimated correlation of baseline (T1) and follow-up (T2) values was $r = 0.98$. The variance in change was not reliable (variance = 0.107; standard error = 0.382; $z = 0.281$) and was hence set to zero in the multivariate models. The first 2 columns refer to correlations between brain volumes at T1 and G_f at T1. The 2 middle columns refer to correlations between brain volumes at T2 and G_f at T2. The last 2 columns refer to correlations between changes in brain volume from T1 to T2 and G_f. Here results are identical for fluid ability at T1 or T2, as individual differences in fluid ability were perfectly correlated across occasions. Cd, caudate nucleus; IPw, inferior parietal white matter; IT, inferior temporal cortex; VC, visual (pericalcarine) cortex.
*$P < 0.05$.

Fluid Intelligence, Brain Volumes, and Regional Brain Shrinkage

The LDM fitted to the fluid ability variables was satisfactory (χ^2 = 3.97 for df = 1, P = 0.046; comparative fitness index (CFI) = 0.972; standardized root-mean-square residual (SRMR) = 0.077; root-mean-square error of approximation (RMSEA) = 0.186, 90%; confidence interval [CI] = 0.390–0.019) and revealed that mean decline was highly reliable, t = –9.39, $P < 0.001$. The initial LDM for fluid ability did not converge when full metric invariance was imposed. Convergence was attained after relaxing the constraints: on unique variances of the Cattell form 3 subtests 1 and 3 across time and factor loadings of the Cattell form 3 subtest 3 across time. This model no longer meets a stringent requirement of metric invariance [exact equality of loadings] between T1 and T2. However, it still presumes configural invariance, i.e., that the same tests define the same latent factors over time (cf., Meredith 1964). However, no individual differences in change were observed for fluid abilities, t = 0.28, NS. In other words, all individuals showed decline over 5 years in cognitive abilities, but this decline was not differential. Despite reliable group mean change, individual differences in fluid ability were perfectly stable over the 5-year interval; the corresponding correlation between fluid intelligence assessment at baseline and follow-up did not differ from r = 1.0. The lack of reliable individual differences in cognitive change precluded the exploration of relations between regional brain shrinkage and change in cognitive performance. Therefore, the following analyses were restricted to associations between fluid intelligence measured at baseline and follow-up and regional brain volumes measured at the same occasions as well as volume changes observed in over the 5-year period. In those analyses, we added fluid ability to the multivariate LDM of the 11 ROIs that evidenced significant individual differences in brain volume change in our previous study (Raz et al. 2005). In that model, the variance of change in fluid ability and all relevant covariance terms were set to zero (for further statistical justification, see Ghisletta and Lindenberger 2004). The fit for this model was marginal (χ^2 = 1335.43 for df = 861, $P <$ 0.01; CFI = 0.921; SRMR = 0.047; RMSEA = 0.081, 90% CI = 0.088–0.071). The brain–cognition relations estimated by this model are summarized in Table 3.

The table displays the correlations between fluid ability (G_f) and brain volumes at baseline (T1; columns 2 and 3) and follow-up (T2; columns 4 and 5), as well as the association between fluid ability at follow-up and 5-year brain volume changes (columns 6 and 7). The displayed z values are associated with the respective correlations. Because fluid ability at baseline and at follow-up were perfectly correlated, the estimates of correlations between brain volume changes and fluid ability scores at both occasions are identical. The results indicate that larger prefrontal volumes (gray and white matter) were associated with higher fluid intelligence at both occasions. A similar association between the hippocampal volume and fluid intelligence was significant only at follow-up, although at baseline a trend in the same direction was evident. Notably, greater change (shrinkage) of both the HC and the EC was associated with lower fluid ability.

Influence of Demographic and Health Factors on Associations between Brain and Cognition

The analyses of the effects of demographic (age and sex) and health-related modifiers (VR) on the observed relationship between brain and cognition were conducted only on the ROIs that showed reliable relations to cognitive performance in the second analytical step, that is, LPFC, OFC, PFw, HC, and EC. These models are a bivariate variation of LDM and include fluid intelligence factor (G_f) and in turn, each target ROI. Five extended LDMs were tested to examine if and how each ROI volume, age, sex, and VR assessed at baseline and a 5-year change in ROI volume affect cognitive performance at follow-up. Unlike in the previously presented models, in the bivariate LDMs, each ROI was distinctly examined in relation to G_f. The associations between brain volume and cognitive performance were not specified by directionless correlations, as in the previous analyses, but by regression weights. In particular, brain volume at T1 and the change in brain volume between T1 and T2 were specified to influence cognitive performance at T2. A third specification would have been possible, where cognitive performance at T1 and differential change in cognitive performance between T1 and T2 [had 3 been evidenced in the previous analyses] would influence brain volume at T2. The 3 specifications [i.e., strictly correlational, brain volume influencing cognitive performance, and cognitive performance affecting

brain volume] are statistically equivalent, and our choice among them was guided by substantive rationale. In particular, we assumed that for physiological reasons it is more plausible to assume that structural brain changes affect cognitive performance rather than the opposite (for a particular test supportive of this assumption, see McArdle et al. 2004); the covariates measured at baseline (age, sex, and VR) were presumed to influence the regional volumes at the same time, the change in regional volumes between baseline and follow-up, and G_f at follow-up. The effects of the baseline regional volume and its 5-year change on cognitive performance at follow-up are hence statistically controlled for the influence of the covariates. To understand better the role of the various covariates, we proceeded in a hierarchical fashion. First, the effects of brain volume on cognitive performance were controlled for chronological age. We then incrementally added the statistical control for sex and finally also introduced VR into the model.

The analyses indicated that a greater calendar age was reliably associated with lower fluid intelligence and with smaller volumes in all regions except the EC. Similarly, the rate of shrinkage in PFw and EC accelerated with age. There were no sex differences in any of the indices, neural or cognitive.

Across all 3 versions of this final model, the shrinkage in EC volume predicted 11% of the variance in cognitive performance at follow-up. Notably, that influence was independent of the effect of chronological age. Finally, in the model with all covariates, only the volume of the OFC and the PFw retained their positive association with fluid intelligence at follow-up, accounting, respectively, for 5% and 4% of the variance. VR was unrelated to any of the regional volumes at baseline. When fluid intelligence was predicted from age, OFC volume factor, and VR group membership in a general linear model, all 3 predictors showed significant independent contribution. The main effects were as follows—age: $F_{1,83} = 27.21$, $P < 0.001$; OFC volume: $F_{1,83} = 24.97$, $P < 0.001$; VR: $F_{1,83} = 10.50$, $P < .002$. No significant interactions were noted (all $F < 1$).

Discussion

The goals of this study were to assess the effects of regional brain shrinkage on age-related changes in specific cognitive domains and to examine to what extent the pattern usually associated with aging is shaped by VR factors. These goals were partially met. The results indicate that the pace of age-related decline in a specific brain region, EC, is indeed associated with cognitive ability: persons with lower fluid intelligence exhibited faster shrinkage. Notably, the volume of that region was unrelated to age or cognitive performance at baseline or follow-up, and without a longitudinal follow-up, the links between EC and age-related differences in cognition would have been missed. At baseline, we indeed observed a significant positive association between the volumes of the prefrontal regions (OFC and PFw) and fluid abilities, thus replicating some of the reported findings (Schretlen et al. 2000; MacLullich et al. 2002; Gong et al. 2005; Staff et al. 2006). Our findings also converge with reports that nondemented older adults of average cognitive status have smaller prefrontal cortices than their more cognitively successful counterparts (Chey et al. 2006).

Thus, we observed an interesting dissociation: in spite of significant shrinkage in the prefrontal regions, there was no link between the rate of shrinkage and change in cognitive performance. That was true even regarding the PFw in which age-related acceleration of volume decline was noted. Similar age-related acceleration of shrinkage without cognitive differences being linked to the pace of change was observed in the HC as well. In contrast, the actual volume of the prefrontal structures correlated with cognitive performance. Such correlations are more difficult to interpret than longitudinal effects. Prefrontal volume differences may be predicated not only on aging but also on the developmental history that although remaining unknown determines the size and shape of brain structures. Indeed, prefrontal volume appears to peak at the onset of puberty and negative age-related differences are noticeable already in adolescence (see Lenroot and Giedd 2006 for a review), with adult development continuing that trend (Raz and Rodrigue 2006). In contrast, EC shows no age-related differences in young and middle age adults and exhibits declines only in old age (Raz and Rodrigue 2006 for a review). Thus, entorhinal volume variability may be attributable to causes that have little to do with normal adult maturation and aging. Because entorhinal pathology is the earliest sign of Alzheimer's disease (AD; Braak H and Braak E 1991), it is possible that individuals who showed entorhinal shrinkage represent the prodromal cases of AD. However, establishing that would take further follow-up data unavailable for this sample. On the balance, therefore, it appears that our results support the notion of a dissociation between prefrontal and medial temporal systems. According to that view, prefrontal declines may be a characteristic of normal aging in contrast to medial temporal changes that are harbingers of pathology (Hedden and Gabrieli 2004).

That approach, however, fails to take into account the influence of vascular pathology that may shape the aging brain. In this sample, participants who were free of VR and vascular disease at baseline and remained healthy throughout the 5-year follow-up faired significantly better than their peers in the group, both in preservation of prefrontal volume (gray and white) and in cognitive performance. Moreover, the effects of age, VR, and orbitofrontal volume on fluid intelligence were independent and no interaction among them was noted. Thus, although VR, as previously shown, contributes mainly to reduction in the volume of regions most vulnerable to aging, its effects do not overlap with those of other factors subsumed under calendar age. Identifying those additional sources of variance in prefrontal and other cerebral structures is an important task for the future.

To place the findings in the general context of aging, we need to take into account that the sample employed in this study was decidedly unrepresentative. Most of the participants who were selected at baseline for their good health returned for the follow-up visit by-and-large unchanged, with only the minority of them undergoing decline in their vascular health. Thus, not only the initial sample was not representative of a typical population but also attrition and self-selection made it even less representative at follow-up. Such sample transformations are not unusual. Moreover, they are typical of longitudinal studies in which less cognitively able, more depressed, and less healthy participants tend to drop out (Lindenberger et al. 2002). The goal of this study was to examine the best case scenario of aging and to gauge the influence of the factors usually associated with normal aging on the observed pattern of preservation and decline. Thus, the negative findings (lack of decline) do not necessarily disagree with declines that could have been observed in larger, more representative samples. What we do

learn, however, is that even under the best circumstances, some age-related brain deterioration is observed, and deterioration in some areas such as the EC is associated with poor cognitive performance.

Other factors could have affected the observed pattern of results. One of such important factors omitted in this study could be information about the genetic background of its participants. Significant differences in the volume of age-sensitive regions, such as the HC and the PFC, and in cognitive skills that rely on those regions have been linked to specific genetic polymorphisms (Egan et al. 2001; Malhotra et al. 2002; Tsai et al. 2003; Bruder et al. 2005; de Frias et al. 2005; Bueller et al. 2006; Nemota et al. 2006; Zinkstok et al. 2006; but see Ho et al. 2005, for negative findings). Moreover, lack of cognitive change in some cognitive domains examined in our sample could have been an expression of a higher percentage of participants with more favorable genotype.

We were unable to fulfill one of the main objectives of the study, that is, the evaluation of the effects of brain shrinkage on cognitive decline. The reason for that was the lack of reliable individual variability in the pace of cognitive change. This finding is consistent with reports of remarkable stability in individual differences in intelligence (Hertzog and Schaie 1986, 1988; Rabbitt et al. 2003), and it renders moot the investigation of the factors contributing to age-related differences in cognitive decline. In light of significant individual variations in the pace of regional brain shrinkage, such uniformity of cognitive change is remarkable. It is unclear whether differential reliability could contribute to that state of affairs, but it is possible that it reflects a more fundamental phenomenon. Specifically, it is possible that regardless of brain changes, people continue to find resources that allow them to maintain their relative standing in cognitive performance, at least until more severe physiological or pathological changes occur. This interpretation is consistent with a notion of cognitive prowess as a hedge against age-related deterioration, a view known as the cognitive reserve hypothesis (see Stern 2002; Whalley et al. 2004; Valenzuela and Sachdev 2006 for reviews).

It is possible that, at least in part, the lack of individual differences in fluid decline was inferred due to a statistical "blind spot" in the analysis. Sometimes, an apparent lack of variance in change of a variable may hide significant changes at one of the extremes of the variable's range (e.g., nonlinearity; cf., McArdle et al. 2004). Unfortunately, that possibility could not be assessed in a 2-wave longitudinal study of this limited sample size and will have to be examined in a multiwave study that would allow estimating the change trajectories. A related limitation of this study is that our sample might have included insufficient number of "old–old" individuals to demonstrate late-life accelerations of decline. In some samples that included individuals with significant health deterioration during the follow-up period, memory changes were observed only at the seventh decade of life, with global brain changes preceding them by 3 decades (McArdle et al. 2004).

Brain structural integrity in this study was assessed by manual volumetry methods that are highly reliable and avoid registration problems associated with automated procedures (e.g., Krishnan et al. 2006). However, those methods allow examination of only a limited number of selected brain regions. Region selection in this study was driven by theoretical considerations as well as ability to measure them with reliability exceeding intraclass correlations of 0.90 (see Raz, Gunning-Dixon, et al. 2004 for details). Therefore, some of the recently identified regions of interest vis-a-vis aging and age-related disease were not measured. One such region is the posterior cingulate gyrus that has been demonstrated as a region of increased vulnerability to metabolic dysfunction in early AD as well as the region of highest expression of an amyloid-sensitive compound in nondemented adults (Buckner 2004). In a recent study, that region also was the only one in which age-related differences in cortical thickness were associated with extremes of fluid abilities in healthy elderly (Fjell et al. 2006). Thus, inclusion of posterior cingulate gyrus in future studies may add to the explanation of age-related differences in cognitive performance.

In sum, we observed reliable decline in regional brain volumes that was especially pronounced in the tertiary association cortices and the HC and reliable decline in fluid intelligence tests and WM. The 5-year declines in the EC, a medial temporal structure implicated in the earliest stages of AD, were associated with lower fluid intelligence, independently of age, sex, or VR. Notably, we observed no links between the entorhinal volume and cognition at baseline or follow-up. On the other hand, greater prefrontal volumes (orbital cortex and white matter) were linked to higher fluid intelligence, whereas the reliable shrinkage in those regions was not associated with cognitive performance. Furthermore, frontal but not entorhinal volumes were reduced in persons with VR. Thus, we observed a frontal–mediotemporal dissociation that suggests a possibility of at least 2 mechanisms of brain aging: one related to genetic and developmental processes and augmented by vascular disease risk and the other driven by factors associated with Alzheimer-type pathology. Further longitudinal studies with multiple waves of measurements are needed to put that speculation to a test.

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