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Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuro-imaging

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Abstract

We explored relationships between decline in cognitive processing speed (CPS) and change in frontal lobe MRI/MRS-based indices of cerebral integrity in 38 healthy adults (age 57–90 years). CPS was assessed using a battery of four timed neuropsychological tests: Grooved Pegboard, Coding, Symbol Digit Modalities Test, and Category Fluency (Fruits and Furniture). The neuropsychological tests were factor analyzed to extract two components of CPS: psychomotor (PM) and psychophysical (PP). MRI-based indices of cerebral integrity included three cortical measurements per hemisphere: GM thickness, intergyral and sulcal spans and two subcortical indices: fractional anisotropy (FA), measured using track-based-spatial-statistics (TBSS), and the volume of hyperintense WM (HWM). MRS indices included levels of choline-containing compounds (GPC+PC), phosphocreatine plus creatine (PCr+Cr), and N-acetylaspartate (NAA), measured bilaterally in the frontal WM bundles. A substantial fraction of the variance in the PM-CPS (58%) was attributed to atrophic changes in frontal WM, observed as increases in sulcal span, declines in FA values and reductions in concentrations of NAA and choline-containing compounds. A smaller proportion (20%) of variance in the PP-CPS could be explained by bilateral increases in frontal sulcal span and increases in HWM volumes.

Introduction

We sought to identify neurobiological changes associated with age-related decline in cognitive processing speed (CPS) defined as the speed with which information is mentally processed. Understanding the neurobiology of age-related decline in CPS decline is essential to our understanding of the neurobiology of the cognitive aging, as the decline in CPS is assumed to underlie the age-related decline in many cognitive functions (Hoyer et al., 2004; Salthouse,

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2000; Salthouse and Czaja, 2000). Notably, two major CPS components psychomotor (PM) and psychophysical processing speeds (PP-CPS) showed an important distinction in age-related changes in normal aging (Salthouse, 2000). PM-CPS, a measurement of mental speed involving a large motor component (Salthouse, 2000), declines with age in normal aging (Hoyer et al., 2004; Salthouse, 2000; Salthouse and Czaja, 2000). In contrast, PP-CPS, a measurement of mental speed involving little motor component, shows little change with age in normal aging (Salthouse, 2000; Salthouse and Czaja, 2000). However, both PM and PP-CPS decline during pathological aging, such as during the time course of neurodegenerative disorder and dementias (Hedden and Gabrieli, 2004, 2005).

Two recent reports on the neurobiology of age-related CPS indicated that the decline in PM-CPS is linked to diminished integrity of frontal WM. A study by Bartzokis and colleagues demonstrated that the lifespan trajectories of PM-CPS, measured as maximum finger typing speed, and frontal WM T²-relaxation rate (R²) were significantly correlated ($r=.45$; $p<.001$) (Bartzokis et al., 2008). Bartzokis et al., showed that the decline in the PM-CPS and frontal WM R2 rates started in the 4th decade of life and the rate of this decline accelerated during the late adulthood (6–7th decades of life) (Bartzokis, 2004; Bartzokis et al., 2008). Another study, by Schiavone *et al.*, showed that up to 25% of intersubject variability in PM-CPS in healthy subjects ages 50–90 was explained by fractional anisotropy (FA) of water diffusion measurements (Schiavone et al., 2009). Research from our group and others has shown that these neuroimaging indices were sensitive measurements of myelin integrity, correlated with the cerebral conduction times (Bartzokis et al., 2003; Horsfield and Jones, 2002; Lancaster et al., 2003; Lancaster et al., 2005). Therefore, the age related decline in the PM-CPS appears to be linked with reduction in the propagation speed of action potentials across cortical networks (Ashe and Georgopoulos, 1994; Lutz et al., 2005). The prior discovery of tight coupling between the aging trends in PM-CPS and frontal WM integrity serves as an *a priori* hypothesis in this manuscript.

In the current study, we explore the neuroanatomical association for both PM and PP-CPS and specifically, the neurobiology of the contrast in their age-related trends. We expanded on prior studies by including multiple, well-studied multimodal MRI/MRS indices of cerebral integrity. Our additional goal was to determine which MRI/MRS-based indices of cerebral integrity were most sensitive to decline in CPS during normal aging. This information is urgently needed to provide a clear understanding of the neurobiology of cognitive decline and: (1) clarify factors affecting aging and neurodegenerative processes, (2) assess the impact of genetic predisposition in increasing risk of aging-related neurodegenerative disorder, and (3) aid clinical trials in determining the ability of anti-dementia drugs to mitigate degenerative changes.

To help achieve the above goals, we studied the association between PM and PP-CPS and specific structural and biologically important, biochemical indices of cerebral integrity. Cortical, structural indices of cerebral integrity included the width of sulcal spaces, gray matter (GM) thickness, the width of intergyral span. Subcortical, structural indices included fractional anisotropy (FA) of cerebral WM and the volume of the T2-hyperintense white matter (HWM). Biochemical indices included levels of N-acetylaspartate [NAA], choline-containing compounds [Ch] and phosphocreatine plus creatine [Cr], measured bilaterally in the frontal WM. Short descriptions of individual indices follow:

Sulcal span is a measurement of dilatation of cortical sulci and the compensatory filling of the freed space by CSF. As a measurement of cerebral integrity it is sensitive to atrophic changes in two other cortical indices: *GM thickness* and *intergyral WM span* (Im et al., 2008; Jernigan TL et al., 2001; Kochunov et al., 2005b; Magnotta VA et al., 1999; Symonds LL et al., 1999). *GM thickness* is related to the regional neuronal density in the cortical mantle (Jelsing

et al., 2005; Lerch and Evans, 2005; Selemon et al., 1995). *Intergyrar WM span* describes changes in the volume of gyral WM, that form the bulk of cortical gyri (Im et al., 2008; Kochunov et al., 2005b; Symonds LL et al., 1999). During normal aging, *GM thickness* declines with age and this decline is highly correlated with reductions in FA values in associative cerebral WM tracks (Kochunov et al., 2008c; Kochunov et al., 2007; Magnotta VA et al., 1999; Raz N et al., 1997). The *intergyral WM span* increases non-linearly with age and is found to be significantly correlated with reductions in FA and increases in *T2-hyperintense WM* volume (Kochunov et al., 2008c; Kochunov et al., 2007).

Subcortical indices of cerebral integrity include measurement of the WM bundles that form the core of the cerebrum. *Fractional anisotropy* (FA) of water diffusion describes the directional selectivity of the random diffusion of water molecules (Basser, 1994; Conturo et al., 1996; Pierpaoli and Basser, 1996; Ulug et al., 1995) and is measured using diffusion tensor imaging (DTI). The absolute FA values are sensitive to regional myelination levels, degree of intra-voxel fiber crossing, axonal density and average axonal diameter (Beaulieu, 2002) (Budde et al., 2007). However, age-related changes in regional FA during the course of normal aging were shown to be predominantly due to the change in the local axonal myelination levels (Abe et al., 2002; Gao et al., 2009). Studies in animal models that carefully manipulated cerebral myelination levels have unambiguously shown that FA was highly sensitive marker of regional demyelination (Song et al., 2003; Song et al., 2005). Recent findings by our group (Kochunov et al., 2008b; Kochunov et al., 2007) and others (Abe et al., 2002; Budde et al., 2007; Gunning-Dixon and Raz, 2003) have shown that age-related changes in FA are significantly correlated with changes in other indices of cerebral integrity and executive function. The volume of *T2-hyperintense white matter* (HWM) regions has recently emerged as an important, neuroimaging marker. HWM lesions, regions of high signal intensity in T2-weighted MR studies, are predominantly observed in individuals affected with neurodegenerative disorders that affect cerebral white matter. HWM lesions arise from regions of accumulation of extra-cellular water due to focal degradation of the myelin sheath. The etiology of HWM is nonspecific and could be due to ischemia from small/large vessel pathology, trauma, inflammatory response and other causes (Pantoni and Garcia, 1995). HWM lesions do not appear until late adulthood (5–6th decade of life) and their appearance is associated with the decline in other indices of cerebral integrity (Kochunov et al., 2008c) and executive function (Kochunov et al., 2008b). However, by the 7–8th decades of life HWM lesions are highly prevalent even in the normally aging individual with prevalence rate reported to be as high as 60–100% (de Leeuw et al., 2005; de Leeuw et al., 2001).

Biologically important MRS markers included the concentrations of the following biochemical compounds: N-acetylaspartate [NAA], choline-containing compounds [Ch], and phosphocreatine plus creatine (PCr+Cr) [Cr]. NAA is an important metabolic compound found in the bodies of neuroglial cells and is considered to be a marker of neuronal function (Baslow, 2003) and density (Bjartmar et al., 2002).

Clinical studies report that NAA levels decline following cerebral stroke (Bruhn et al., 1989; Gideon et al., 1992), and in chronic multiple sclerosis (Arnold et al., 1990; Bruhn et al., 1990). Additionally, reductions in NAA concentrations have been associated with many chronic neurodegenerative disorders such as Alzheimer's and alcoholism-induced dementias (Oscar-Berman and Marinkovic, 2003; Schweinsburg et al., 2003). During aging, it has been found that [NAA] either remains stable or decreases (Haga et al., 2007; Riederer et al., 2007). However, a decline in NAA concentrations in the frontal WM regions was found to be associated with a decline in executive function in normal aging individuals (Charlton et al., 2007).

The MRS [Ch] marker consists of a signal primarily from phosphorylcholine and glycerophosphocholine (PC + GPC) compounds. Choline containing compounds are involved in pathways of phospholipid synthesis and degradation. These molecules are major parts of cell membranes. In previous aging studies, [Ch] was shown to remain stable with age until the 7–8th decades of life (Brooks et al., 2001; Haga et al., 2007).

Declines in [Ch] were found to be associated with reduction in membrane-based phospholipids (Miller, 1991) and were observed with age in patients chronically suffering from schizophrenia (Chang et al., 2007) and alcoholism (Mason et al., 2005; Oscar-Berman and Marinkovic, 2003; Schweinsburg et al., 2003). Lastly, the MRS [Cr] marker is a composite measure of the concentration of creatine kinase and phosphocreatine compounds. These compounds play an important role in cellular energy metabolism. It has been suggested that phosphocreatine in combination with creatine kinase serves as an energy buffer keeping ATP levels constant through the creatine kinase reaction (Iles et al., 1982). Creatine has been found to be present in both neuronal and glial cell cultures (Miller, 1991; Urenjak et al., 1992). In normal aging, [Cr] was reported to show no significant changes with age (Haga et al., 2007), however it is known to decrease with age in many chronic cerebral disorders (deGraaf, 2008).

Our preliminary hypothesis was that the MRI/MRS indices of frontal WM integrity would explain a large fraction of intersubject variability in cognitive processing speed. This hypothesis was based on the prior findings of neurobiology of CPS decline in normal aging. We predicted that the indices of cerebral integrity such as DTI-FA, gyral WM span and MRS-markers, would be highly sensitive to age-related decline in CPS. This prediction was based on the assumption that age-related deterioration of cerebral WM would impair neural processing, producing behavior slower on CPS measurements (Bartzokis et al., 2008).

Methods

Subjects

Thirty eight (26 females, 12 males), healthy, right-handed individuals, 57 to 90 years of age (average age = 67.9 ± 9.1 years), were recruited as the part of the International Consortium on Brain Mapping (ICBM) project (Mazziotta JC et al., 1995; Mazziotta JC et al., 2001). Subjects' medical history was reviewed to rule out endocrinal, neurological, and psychiatric illnesses. Neuropsychological testing and brain imaging were performed at the Research Imaging Center, University of Texas Health Science Center at San Antonio. All experiments were conducted with an approval from the Internal Review Board and all subjects signed an informed consent.

Neuropsychological testing

All subjects were assessed with a comprehensive neuropsychological test battery, administered by a neurophysiologic assessment technician. The battery included the following tests of age-related decline in processing speed: Grooved Pegboard, a test of psychomotor speed (Matthews and Klove, 1964); Symbol Digit Modalities Test (SDMT), a test of coding speed (Smith, 1991); Wechsler Coding, another test of coding speed (Wechsler, 1997); and D-KEFS Category Fluency Test (Furniture/Animals Form), a test of semantic, retrieval speed (Delis et al., 2004).

MR imaging and spectroscopy

Comprehensive imaging and metabolic assessments for this study were acquired using a Siemens 3T Trio scanner and an eight-channel phase array head coil. An optimized, imaging/spectroscopy protocol was used to acquire high-resolution diffusion, T1- and T2-weighted images and frontal white matter H^1 spectra of biologically important biochemical compounds.

Diffusion weighted imaging—A single-shot, spin-echo, echo-planar gradient recalled echo sequence was used to acquire diffusion weighted data with the spatial resolution of $1.7 \times 1.7 \times 3.0$ mm. The sequence parameters were TE/TR=87/8000ms, with 86 diffusion weighted directions and two diffusion weighing values of $b = 0$ and 700 s/mm^2 and three $b = 0$ images. The number of diffusion directions, number of $b = 0$ images and the magnitude of the b values were calculated using an optimization technique that accounts for the diffusivity of cerebral WM and T2 relaxation times (Jones et al., 1999). The total sequence acquisition time was 12 min.

T1-weighted imaging—High-resolution (isotropic $800 \mu\text{m}$), T1-weighted images were acquired using a retrospective motion-corrected protocol (Kochunov et al., 2006). Under this protocol, seven full-resolution volumes are acquired using a 3D TurboFLASH sequence with an adiabatic inversion magnetization preparation contrast pulse (scan parameters: TE/TR/TI=3.04/2100/785 ms, flip angle=11 degrees). The sequence yields uniform tissue contrast across the imaging volume. Imaging time was 26 min.

T2-weighted imaging—The T2-weighted data were acquired with a high-resolution (isotropic 1mm), 3D turbo-inversion recovery Fluid Attenuated Inversion Recovery (FLAIR) sequence with the following parameters: TR/TE/TI/Flip angle=5sec, 353 ms, 1.8s, 180 degrees. This sequence uses a non-selective inversion recovery pulse to prevent CSF pulsation artifacts (Bakshi et al., 2000). Imaging time was 15 min.

MR spectroscopy of frontal white matter—A Point Resolved Spectroscopy (PRESS) sequence using the Single Voxel Spectroscopy (SVS) localization method was used with the following parameters: TR = 1500 ms, TE = 135 ms, flip angle = 90 degrees, refocusing angles of 180 degrees and 256 averages. Two spectra (the water-reference and water suppressed) were acquired bilaterally. The SVS volumes were defined fully within the white matter of the forceps minor area of each hemisphere in order to prevent partial volume averaging with CSF and GM. Total scan time was ~12 min.

Data Processing

Structural image processing consisted of preprocessing of T1-weighted FA and HWM images to prepare them for extraction of cortical and subcortical indices of cerebral integrity. Preprocessing of spectroscopic data prepared it for measurements of levels of three important MRS biomarkers: Choline (Ch), Creatine (Cr), and N-acetylaspartate (NAA).

Preprocessing of T1-weighted images—Preprocessing of T1-weighted images consisted of removing non-brain tissues, global spatial normalization and radio frequency (RF) inhomogeneity correction. Non-brain tissues such as skin, muscle and fat were removed using an automated skull stripping procedure provided by the Brain Extraction Tool (Smith, 2002) (see Figure 1A). The extracted brain images were cropped at the level of the cerebellum. Next all brain images were globally spatially normalized to the Talairach coordinate system to remove gross differences in brain location, size and orientation. Automated, nine-parameter (three rotations, three scales, three translations) FSL FLIRT global spatial normalization software (Smith et al., 2004) was used to register all images to a Talairach template (Kochunov et al., 2002). All images were resliced to isotropic $800 \mu\text{m}$ spacing using a 3D, 15-voxel-wide sinc interpolation kernel. Images were radio-frequency (RF) inhomogeneity corrected using the FAST tool with its default parameters (Figure 1B) (Zhang Y et al., 2001). RF corrected images were imported into the BrainVISA database and processed through its sulcal extraction and identification pipelines, as described by Kochunov and colleagues (2005).

Extraction and identification of frontal sulcal surfaces—The BrainVISA image processing pipeline extracts hemispheric spherical meshes from segmented gray and white matter images (Figure 1C, 1D). The medial surface of the cortical in-folds is obtained using a homotopic erosion technique (Mangin et al., 1995). A “crevasse detector” is used to reconstruct sulcal structures as the medial surfaces from two opposing gyral banks that span from the most internal point of the sulcal fold to the convex hull of the cortex (Mangin et al., 1995, 2004) (Figure 1E). Next, the BrainVISA neural network-based sulcal identification was used to identify and label sulcal structures with classification accuracy, which ranged from 95% for primary and secondary fissures to around 70% for the highly variable tertiary sulcal structures (Rivière et al., 2002). Two skilled neuroanatomists reviewed the results of the automated sulcal identification. In an infrequent event (~5–15%) where a sulcus was assigned an incorrect label, the sulcus was manually relabeled while overlaid on the cortical surface (Figure 1F). Frontal cortical regions were composed of five cortical sulci located in the frontal lobe: superior-frontal, intermediate-frontal, inferior-frontal, precentral and central sulci. Sulci selected for this analysis were previously used to study age-related changes morphological, metabolic and cognitive changes during senescence (Kochunov et al., 2005b; Kochunov et al., 2008c; Kochunov et al., 2007)

FA processing: The tract-based spatial statistics (TBSS) software (Smith et al., 2006) was used for multi-subject analysis of fractional anisotropy images, with details of this analysis described elsewhere (Kochunov et al., 2007). In the first step, fractional anisotropy (FA) images were created from raw DTI data using the FSL FDT diffusion analysis toolkit (Smith SM, 2002). This step provided correction for eddy-current induced spatial distortions and involved a voxel-wise fit to the diffusion tensor model. In the next step, FA images for all subjects were nonlinearly aligned to a group-wise, minimal-deformation target (MDT) brain and resampled to an isotropic 1mm resolution. The group’s MDT brain was identified by warping all FA images in the group to each other (Kochunov et al., 2001). Next, individual FA images were averaged to produce a group-average anisotropy image. This image is used to create a group-wise skeleton of white matter tracts. Finally, FA images were projected onto the group-wise skeleton of white matter structures. This step accounted for residual misalignment among individual white matter tracts.

HWM preprocessing: Hyperintense white matter (HWM) volume was measured from T2-weighted FLAIR images as described in (Kochunov et al., 2007). FLAIR images were preprocessed by removal of non-brain tissue, registration to the T1-weighted images/Talairach frame, and RF inhomogeneity correction.

Quantification of MRS markers: We quantified the following three cerebral MRS markers: levels of Choline- and Creatine containing compounds [Ch], [Cr], and level of N-acetylaspartate (NAA). Quantification of MRS markers was performed using software by Acorn NMR Inc. Livermore, CA. The frequency domain data were processed using deconvolution and peak-fitting. The phase was adjusted and a baseline correction using a fifth order polynomial was performed. The concentration levels for each metabolite were quantified by dividing the area under the corresponding peak by the area under unsuppressed *in vivo* water peak in the same volume of interest.

Cortical/subcortical indices of cerebral integrity

Based on the prior research from Bartzokis and colleagues and this group (Kochunov et al., 2007), we identified the following cortical indices of frontal lobe integrity: GM thickness and sulcal and intergyral span measurements from five frontal sulci averaged for each hemisphere. Subcortical indices consisted of: FA values measured for the region of interest that overlapped with the MRS SVS region and for the anterior portion (genu) of the corpus callosum, which

contains commissural fibers connecting pre-frontal cortexes (Figure 2); the concentration levels for the three MRS indices and whole brain HWM volume. Descriptions of methods for structural-MRI based indices of cortical and subcortical indices of cerebral integrity were published elsewhere (Kochunov et al., 2005b; Kochunov et al., 2008c; Kochunov et al., 2007); a short description follows. Tools discussed here are available for download from, <http://ric.uthscsa.edu/personalpages/petr/>.

Sulcal span—Sulcal span was defined as the average span of the sulcal space along the normal projections to the medial sulcal mesh (Figure 2). High resolution medial sulcal meshes for each sulcus were created using the BrainVISA (<http://brainvisa.info>) sulcal extraction pipeline. Geometrically, a medial sulcal mesh traverses the sulcal space in the middle of the sulcal “span” dimension, parallel to the gyral gray matter borders, and spans the entire sulcal “depth” dimension (Figure 2). Sulcal span was calculated as the Euclidean distance between two points on the gyral gray matter mesh on either side of the sulcal surface (Figure 2).

Intergyral span—Intergyral span was calculated by extending the sulcal span tracings until they intersected with the surface corresponding to the gyral gray matter-white matter interface. Gyral span was defined as the Euclidean distance between two points residing on the gyral white matter mesh on either side of the sulcal surface (Figure 2).

Gray matter thickness—Gray matter thickness was calculated by starting a new tracing at the point of intersection between a normal projection to the sulcal mesh and the exterior gray matter mesh. To measure GM thickness, a normal projection to the exterior gray matter mesh was traced until it intersected with the interior gray matter mesh that describes the gray matter-white matter interface (Figure 2). The point of intersection between the normal projection and the interior gray matter mesh corresponds to voxels with partial white matter/gray matter values of ~50%.

Fractional Anisotropy—FA values were measured for two regions of interest (ROI): the frontal ROI (Figure 2(II) yellow boxes) and the ROI at the genu of the corpus callosum (CC) (Figure 2(II) red box). The frontal lobe white matter FA average value was calculated from the bilateral $4 \times 4 \times 4 \text{ cm}^3$ ROI placed symmetrically, at the level and on either side of forceps minor (Figure 2). FA values for the genu of the CC were calculated from a 10 mm wide band of median CC. This band was subdivided along the anterior-posterior direction into three equal subparts: genu, midbody and splenium (Kochunov et al., 2005a). The region of genu was chosen as the histological white matter tracing studies in cadavers indicated that it contains the thinly myelinated, tightly packed association fibers connecting the bilateral superior and intermediate frontal cortices (Aboitiz, 1992; Aboitiz et al., 1992; Highley et al., 1999).

HWM volume—Regions of HWM were manually traced (painted) from the FLAIR images by two experienced neuroanatomists with high ($r^2 = .85$) inter-rater reliability using an in-house 3D tracing software (<http://ric.uthscsa.edu/mango>) (Figure 2). HWM volume was calculated by summing the volumes of individual regions.

Data analysis

Factor analysis of neuropsychological tests—Scores from the four neuropsychological tests sensitive to CPS (Grooved Pegboard, Coding, Symbol Digit Modalities Test, and Category Fluency) were subjected to a factor analysis. Factor analysis was performed to reduce the number of dependent variables and to produce non-collinear estimates of processing speed. Factor analysis used principal components analysis (PCA) to extract linear composites of correlated variables with eigenvalues > 1 . PCA yielded eigenvalues describing the amount of variance among variables explained by a factor. A varimax rotation

was then used to remove co-linearity e.g. to orthogonalize individual eigenvectors. Results of the factor analysis yielded factor loadings (correlations between a variable and a factor) and factor scores (a subject's standardized score on each factor).

Association between CPS and frontal indices of cerebral integrity—Linear and age-corrected partial correlation analysis was used to examine relations among CPS factors and MRI/MRS indices of cerebral integrity. Indices of cerebral integrity that showed a significant age-corrected correlation with CPS factors were selected for the further analysis. This selection criterion allowed us to identify association between structural indices and cognition independent of age (Kochunov et al., 2008b). Cortical and subcortical indices that showed a significant age-related correlation with CPS factors were distilled to produce non-collinear components using another factor analysis. This step reduced the number of dependent variables to achieve a ratio of dependent variables to subjects of ~1:10 (Osborne and Costello, 2004). Finally, a two-stage regression was performed to probe the multivariate effects of structural indices of cerebral integrity and intersubject variability in CPS. Factor scores distilled from MRI/MRS indices were entered at the first stage, and subject's age was entered at the second stage to estimate the unexplained residual variability. The regression analysis yielded the degree of variance described at each entry step and whether the change was significant. It also produced standardized coefficients (β) that estimate linear associations between CPS variables (the criterion) and structural and biochemical indices of cerebral integrity (the predictors).

Results

Cognitive processing speed

Three of the four neuropsychological tests of CPS showed a significant correlation with age for which speed decreased with increasing age (Table 1). The highest correlation with age was observed for the Pegboard test, whereas the results of the Category Fluency tests did not show a significant correlation with age (Table 1). Two factors were extracted from the results of the neuropsychological tests, together capturing over 80% of the intersubject variability (Tables 2). Factor 1 was related to Pegboard, SDMT and Coding. Factor 2 was related to category fluency and Coding (Table 2). We labeled the first factor “psychomotor CPS” (PM-CPS), as it was sensitive to neuropsychological tests with large motor component: pegboard, Coding, and SDMT (Tables 2). This factor demonstrated a significant correlation with age ($r=.72$; $p<1e-5$) (Figure 3).

We labeled the second CPS factor “psychophysical CPS” (PP-CPS) as it was sensitive to Category fluency and Coding, and showed less sensitivity to the motor component. Factor 2 was not significantly correlated with age ($r=.02$; $p\sim.9$) (Figure 3).

Frontal indices of cerebral integrity

All frontal MRI/MRS measurements of cerebral integrity were significantly correlated ($p<.05$) with age (Table 3). Furthermore, all correlations indicated that cerebral integrity decreased with increasing age, e.g. GM thickness showed a significant decline with age. Among the cortical indices, the highest correlation with age ($r=.66$, $p<1e-6$) was observed for the sulcal span of the left frontal lobe, while the lowest correlations with age ($r=-.42/.42$; $p<.01$) were observed for the left GM thickness and right intergyral span. Among subcortical indices, the numerically highest correlation with age was seen for the frontal FA values ($r=-.65$; $p=1e-6$) while the lowest correlation with age was observed for the frontal white matter levels of the choline-containing compounds [Ch] ($r=-.43$ $p<.01$)

CPS factors and indices of cerebral integrity

Linear and age-corrected partial correlation analyses were used to probe associations between PM- and PP-CPS factors and MRI/MRS indices of cerebral integrity. Linear correlations between PM-CPS and cortical indices of cerebral integrity were significant for eleven out of twelve indices (Table 4). The signs of correlation coefficients indicated that reduction in CPS, e.g. numbers of items coded correctly on SDMT corresponded with decreases in cerebral integrity e.g. decreasing GM thickness. Among cortical indices, the highest correlation was observed for the sulcal span and PM-CPS ($r = -.73$; $p < 1e-6$). The correlation between PM-CPS and left GM approached statistical significance ($r = .31$; $p = .06$) (Table 4). Among the subcortical indices, [Ch] showed the highest correlation with PM-CPS ($r = .62$; $p < 1e-6$), while the lowest correlation was seen for HWM volume ($r = -.40$; $p = .01$) (Table 4). Age-corrected partial correlation analysis showed that the PM-CPS factor was significantly ($p < .05$) correlated with one cortical index of (right frontal sulcal span), and three subcortical indices ([Ch], [NAA]; and FA values in the Genu of CC) (Table 5).

Linear correlation analysis which described relationships between the PP-CPS factor and frontal indices of cerebral integrity reported no significant correlations. However, following correction for age, the PP-CPS factor was significantly correlated with two cortical indices (right and left frontal sulcal span) and one subcortical measurement: HWM volume (Table 5).

Regression analysis

Association of PM- and PP-CPS factors, indices of cerebral integrity and age were further studied using a two-stage regression analysis. MRI/MRS indices that showed significant age-corrected association with the PM/PP-CPS were subjected to factor analysis to produce two orthogonal factors. These factor were entered at the first stage of the regression (Tables 6,7) where they explained ~58% of the variability of the PM-CPS factor (Table 8).

Factor 1, which was sensitive to the right sulcal span measurements and FA of genu (Table 8), produced the most significant change in r ($\Delta r = .59$, $p < 1e-5$) and explained the largest portion of variability (~35%). Factor 2, which was sensitive to the frontal WM concentrations of NAA and Ch (Table 6) explained additional 21% of intersubject variability. Subject's age entered the second stage of the analysis explained an additional 13% of the variance (Table 8). Both steps of the regression produced statistically significant changes in r ($p \leq .05$) and statistically significant regression coefficients (β) (Table 8).

Similarly, orthogonalized factor scores extracted from three MRI indices of cerebral integrity (Table 7) explained about ~20% of the variability of the PP-CPS factor (Table 9). Two factors, one sensitive to the bilateral sulcal span measurements and the other sensitive to HWM volume, each explained about 10% of the variance. Inclusion of subject's age did not explain any additional variability (Table 9).

Discussion

This study was designed to explore the neurobiological bases of age related decline in processing speed. We found that a large portion of intersubject variance in cerebral processing speed (CPS) could be explained by intersubject differences in both structural and metabolic indices of frontal cerebral integrity. This study replicates previously reported neurobiological associations for CPS decline and extends findings in two important ways. First, we showed that a multimodal MRI/MRS approach greatly expands the ability to study neurobiology of decline in CPS during normal aging. Using this approach we confirmed the *a priori* hypothesis that age-related decline in psychomotor (PM) CPS is linked to decline in integrity of frontal WM. The multi-modal measurements explained large (58%) fraction of the intersubject

variability in PM-CPS, compared to ~20% explained by other methods that used a single measurement. Additionally, we found that the decline psychophysical (PP) CPS was partially explained by the atrophy of cerebral WM, although, the neurobiological factors involved were different from these for PM-CPS.

Changes in CPS and decline in cerebral integrity

The factor analysis distilled results of the neuropsychological assessments into PM and PP-CPS categories. The age-related trends of the CPS factors fully confirmed prior findings and the PM- and PP-CPS factors showed contrasting age-related trends. The finding of strong age-related decline of the PM-CPS factor was expected. It is well known that PM-CPS has the strongest decline with age during normal aging (Hedden and Gabrieli, 2004; Salthouse, 2000). Another expected outcome was that the PP-CPS factor was not significantly correlated with age, also consistent with previous reports (Hedden and Gabrieli, 2004, 2005).

Importantly, we explored the cerebral indices that accounted for the decline in PM-CPS. Specifically, frontal WM integrity explained a large fraction (58%) of intersubject variance in PM-CPS factor. Factor analysis distilled neuroanatomical measurements into two orthogonal categories. The first category was sensitive to cortical (right sulcal span) and subcortical (FA values in the genu) white matter integrity and explained 35% of the variance in the PM-CPS. This finding corroborates our previous research where changes in sulcal span and FA in genu were correlated with a decline in the executive function (Kochunov et al., 2008a). The second category, sensitive to the frontal lobe WM concentrations of NAA, explained additional 23% of PM-CPS variability. These findings suggest that an age-related decline in PM-CPS is associated with age-related decline of frontal WM integrity, based on declining FA, and age-related reduction in glial cell density, based on declining WM NAA concentrations.

Another hypothesis that was supported was that WM indices cerebral integrity explained a substantial portion (21%) of intersubject variability in the PP-CPS factor. Bilateral measurements of sulcal span and the volume of hyperintense WM lesions, each explained approximately 10% of the intersubject variance. These findings suggest that the decline in PP-CPS, while not prominent in normal aging, is related to an overall atrophy of cerebral WM, measured as dilation of the sulcal spaces and increases in the cerebral HWM volume.

Contrast in PM and PP-CPS aging trends for normal and pathological aging

The differences in neuroanatomical associations for PM- and PP-CPS point at distinct neurobiological processes associated with normal and pathological aging. Decline in PM-CPS is expected in normal healthy individuals with age (Salthouse, 2000). This decline is hypothesized to be caused by the age-related increases in refractory conduction times, especially in thinly myelinated associative WM fibers (Bartzokis, 2004; Bartzokis et al., 2008; Sinha et al., 2006). The results of this study offered additional support for this hypothesis. Intersubject variability in the PM-CPS factor was mainly explained by indices of cerebral integrity quantifying reduction of cortical WM volumes, decline in integrity of the thinly myelinated associative tracts, and decreases in glial cell density of the frontal WM.

Prior research indicated that PP-CPS does not significantly decline with age in normal aging (Salthouse, 2000). However, the decline in PP-CPS is prominent in pathological aging, such as during the time course of neurodegenerative dementias (Hedden and Gabrieli, 2004, 2005). Our findings were supportive of prior reports and linked the decline in PP-CPS with neuroanatomical changes suggestive to deviation from normal, healthy aging. Unlike the PM-CPS factor, PP-CPS was not significantly associated with neuroanatomical indices of age-related demyelination, such as DTI FA. Instead, the intersubject variability in PP-CPS factor was explained by the cerebral volume of the HWM and dilation of sulcal spaces. These findings

suggest that the decline PP-CPS was associated with cerebral atrophy: gliosis and atrophy of cerebral WM and shrinkage of the frontal cortex with replacement of freed space by CSF. These findings are consistent with neurobiological associations reported in clinical literature where increases in the HWM volume and expansion of sulcal spaces were shown predictive of cognitive decline, independent of age (Bastos Leite et al., 2004; Gunning-Dixon and Raz, 2000, 2003; Raz et al., 1998).

Limitations

The main limitation of this study was the relatively small number of subjects. The explorative nature of study led to use of exploratory statistical techniques such as factor analysis, to distill individual CPS components and trends in indices of cerebral integrity. However, factor analysis typically requires a high ratio of subjects to variables, with one rule of thumb being 10 subjects for one variable (Osborne and Costello, 2004). Ideally, this study would have been done by factor analyzing all available neuropsychological and MRI/MRS indices. However, the small number of subjects limited our choice of CPS-sensitive tests and constrained our analysis only to the frontal measurements of cerebral integrity. Even so, the approach yielded fruitful results.

Another limitation of this work is the fact that our study involved a cross-sectional approach, not serial or longitudinal designs. Any interpretation of the age-related trends in cross-sectional studies as “cause and effect” should be made with caution. Prior research has shown that cross-sectional measurements cannot fully represent the trajectory of age-related change (Kraemer et al., 2000; Royall et al., 2005) obtained from serial examination of longitudinally studied cohorts.

We discovered that only a small (20%) fraction of intersubject variability in PP-CPS factor was explained by neuroanatomical measures. A possible limitation of this work is the choice of the neuropsychological tests used to assess PP-CPS. PP-CPS factor in our study was formed from timed tests of category fluency (D-KEFS Category Fluency Test) and Coding. Classically, PP-CPS is assessed as the minimum inspection time necessary to accurately process a complex visual or auditory stimulus (Salthouse, 2000). However, previous research provided evidence that results of the category fluency tests can indeed be used as sensitive measurements of the perceptual speed (Salthouse, 2005; Salthouse et al., 2003).

Two additional limitations should be noted. First, concerns ambiguity in the direction of effects. One possibility is that cerebral health abnormalities impair neural processing, which leads to cognitive slowing. Another possibility is that cognitive slowing reflects overall cognitive declines, which lead to cerebral health abnormalities. The correlational and cross-sectional design of our study cannot exclude either possibility. The possibilities could be tested using longitudinal designs, which could examine whether cognitive changes precede brain changes (or vice versa), or experimental designs, which could manipulate cognitive or brain activity and observe its effects. Second, concerns the neuropsychological (NP) tests used to measure PS. The goal of our study was to examine the role of PS in cerebral health using common NP tests. The NP tests were multidimensional, measuring a variety of PS processes (e.g., perceptual, cognitive, motor), but were not designed to isolate any one process. Our results provide initial (and we believe valuable) information about the role of two PS components (viz., PS-PM and PS-PP) in cerebral health. Further research systematically manipulating PS processes related to these components is needed to clarify the role of each PS process in cerebral health.

Conclusions

The objective of this study was to identify which MRI/MRS-based indices of cerebral integrity were sensitive to CPS-decline in healthy aging individuals. We analyzed an association

between neuropsychological assessment of psychomotor and psychophysical cognitive processing speed and a set of diverse structural and biochemical MRI/MRS indices of cerebral integrity. Declines in both PM-CPS and PP-CPS components corresponded to changes in cerebral integrity sensitive to decline in frontal white matter health. Up to 58% of variability in PM-CPS was explained by changes in WM integrity sensitive to myelination levels of associative fiber tracts and known to decline in the course of the normal aging. About 21% of variability in the PP-CPS was also explained by declines in cerebral integrity found to indicative of neuropathological changes. This work was a continuation of our research to study the advantages of multimodal MR methodology to track neurobiological changes occurring in normal aging. Since healthy aging spans many decades, there is a great potential for therapeutic intervention to slow down the progress of neurobiological changes associated with mental slowing. Our results should guide future studies in the selection of neuroimaging indices for studies in aging populations

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Figure 1.

T1-weighted image processing pipeline for extraction of indices of cortical integrity consists of skull stripping (A); spatial normalization, radio-frequency homogeneity correction, and tissue segmentation (B); extraction of gray and white matter surfaces (C,D); extraction of sulcal folds (E); and automated labeling of sulci (F).

Figure 2.

(**I**) Cortical T1-w image processing pipeline (Figure 1) produced sulcal surface (green) and pial GM (gray) and inner WM (red) surfaces. For each sulcus three average measurements of cortical cerebral integrity are computed: average intergyral (A), sulcal (B) spans and average GM thickness (C). Intergyral span (A) is defined as the 3-D distance between opposing points on the WM mesh along the normal projection to the sulcal surface. Sulcal span (B) is defined as a 3D distance between opposing points on the GM mesh along the normal projections to the sulcal surface. Gyrar GM thickness (C) is defined as a distance between pial GM and inner WM meshes at the direction normal to the pial GM surface. (**II**) Diffusion-tensor fractional anisotropy images were processed using track-based-spatial-statistics method. Average FA values were calculated for bilateral frontal (yellow box) regions and for the genu of corpus callosum (red box). (**III**) FLAIR images were processed by manually tracing the regions of hyperintense white matter (red volume). (**IV**) H1-MR single voxel spectroscopy data, water suppressed (red) and reference (blue) spectra, were obtained from bilateral $2 \times 2 \times 2$ cm regions (yellow boxes), shown on subject's average MR imaging, in the frontal white matter bundles (forceps minor area)

Figure 3.
Age-related trends for psychomotor (PM) and psychophysical (PP) cognitive processing speed factors

Table 1

Neuropsychological assessment tests of processing speed.

NP Instrument	Average±stdev	r with age (p)	Description of the measurement
Pegboard	84.5±17.6	.69**	Time to complete the pegboard (sec) with randomly positioned slots. Subjects must rotate the pegs to fit into the slots. Subjects place pegs in holes first with one hand, then with the other. A longer completion time is indicative of slowing.
SDMT	40.9±9.2	-.55**	The number of correctly coded verbal symbols during a 90 sec interval. Subjects code symbols into digits based on the reference key. A lower score indicated fewer items correctly coded and was indicative of slowing.
Coding	44.5±10.1	-.48	The number of correctly coded non-verbal symbols during a 90 sec interval. Subjects code symbols into digits based on the reference key. A lower score indicated fewer items correctly coded and was indicative of slowing.
Category Fluency	12.8±3.3	-0.05	The number of correct words, from two alternating domains: furniture and animal names, named in 60 seconds. A lower score indicated fewer words and was indicative of slowing.

Bold font indicates a statistically significant correlation (p<0.05).

** Correlation is significant at p<.0001

Table 2

Orthogonalized results of the factor analysis of neuropsychological (NP) tests sensitive to processing speed.
(what is the measure here correlation coefficients?)

NP Instrument	Factor 1 (47%)	Factor 2 (34%)
Peg Board	-.85	.17
SDMT	.81	.44
Coding	.73	.53
Category Fluency	.05	.91

Table 3

Correlation coefficient with age for cortical and subcortical measurements of frontal lobe cerebral integrity.

Cortical indices	GM right	GM left	Sulcal span right	Sulcal span left	Intergyr. span right	Intergyr. span left
	-.47**	-.42*	.66**	.69**	.42*	.44**
Subcortical indices	CrI	ChI	INAAI	FA Frontal	FA Genu	HWM volume
	-.54**	-.43*	-.45*	-.65**	-.44*	.52**

Bold font indicates a statistically significant correlation (p<0.05).

** Correlation is significant at p<.0001

Linear correlations between factor scores extracted from NP measurements of processing speed and cortical and subcortical indices of cerebral integrity.

Table 4

Cortical indices	GM right	GM left	Sulcal span right	Sulcal span left	Intergyr span right	Intergyr span left
PM CPS Factor	.41	0.31	-.73 **	-.67 **	-.43	-.35
PP CPS Factor	-.22	-0.24	.03	.02	-.15	-.07
Subcortical indices	[Cr]	[Ch]	[NAA]	FA Frontal	FA Genu	HWM volume
PM CPS Factor	.54 **	.62 **	.57 **	.59 **	.54 **	-.40
PP CPS Factor	-0.1	.24	.20	.21	.01	.31

Bold font indicates a statistically significant correlation (p<0.05).

** Correlation is significant at p<.0001

Age-corrected partial correlations between factor scores extracted from NP measurements of processing speed and cortical and subcortical indices of cerebral integrity.

Table 5

Cortical indices	GM right	GM left	Sulcal span right	Sulcal span left	Intergvral span right	Intergvral span left
PM CPS Factor	.05	.02	-.47	-.31	-.21	-.04
PP CPS Factor	-.04	-.02	-.33	-.38	-.18	-.10
Subcortical indices		[Chl]	[NAA]	FA Frontal	FA Genu	HWM volume
PM CPS Factor	.26	.50**	.40	.22	.35	-.02
PP CPS Factor	-.08	.27	.24	.30	.02	.37

Bold font indicates a statistically significant correlation (p<0.05).

** Correlation is significant at p<.0001

Table 6

Factor analysis was performed on the anatomical and metabolic measures that showed significant age-corrected correlation with PM-CPS factor

	Orthogonal Components	
	Factor 1 (42%)	Factor 2 (37%)
sulcal span right	-.887	-.201
FA genu	.745	.374
[Ch]	.528	.662
[NAA]	.217	.926

Table 7

Factor analysis was performed on the anatomical and metabolic measures that showed significant age-corrected correlation with PP-CPS factor

	Orthogonal Component	
	Factor 1 (61%)	Factor 2 (38%)
sulcal span right	.942	.264
sulcal span left	.921	.324
HWM volume	.298	.954

Table 8

Two-stage regression result for the PM-CPS factor.

Model	r	Adjusted r	Significance of Δr	Standardized Beta	Significance of beta
Factor 1	.59	.55	<1e-5	0.59	1<1e-5
Factor 2	.76	.73	0.001	0.47	.001
Age	.84	.80	~.01	-0.46	.003

Table 9

Two-stage regression result for the PP-CPS factor.

Model	r	Adjusted r	Significance of Δr	Standardized Beta	Significance of beta
Factor 1	.33	.29	.33	-0.32	.03
Factor 2	.46	.40	.31	0.31	.05
Age	.46	.40	.01	-0.02	.6