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Slowing down: age-related neurobiological predictors of processing speed

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Processing speed, or the rate at which tasks can be performed, is a robust predictor of age-related cognitive decline and an indicator of independence among older adults. This review examines evidence for neurobiological predictors of age-related changes in processing speed, which is guided in part by our source based morphometry findings that unique patterns of frontal and cerebellar gray matter predict age-related variation in processing speed. These results, together with the extant literature on morphological predictors of age-related changes in processing speed, suggest that specific neural systems undergo declines and as a result slow processing speed. Future studies of processing speed – dependent neural systems will be important for identifying the etiologies for processing speed change and the development of interventions that mitigate gradual age-related declines in cognitive functioning and enhance healthy cognitive aging.

Keywords: aging, processing speed, cerebellum, prefrontal, source based morphometry

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The white-knuckle experience of being a passenger in a car driven by an older adult with slow **processing speed** is a salient example of the significant impact that age-related slowing of motor function and decision making has on daily life. **Age-related change** in processing speed is a primary predictor of the cognitive declines that older adults experience (Salthouse and Ferrer-Caja, 2003) and is a strong predictor of people who need help with daily activities (Wahl et al., 2010). Understanding the neurobiological changes that contribute to age-related changes in processing speed is critical for developing interventions that limit age-related cognitive declines; a need that is underscored by the anticipated doubling in population by 2050 of adults over 60 years in developed countries (United Nations, Department of Economic and Social Affairs, Population Division, 2007).

Our interest in processing speed at the MUSC Hearing Research Program includes the impact of processing speed on auditory function declines that older adults experience. Slowed processing speed predicts auditory sensitivity to temporal changes in sounds (Harris et al., 2010), as well as lip reading (Feld and Sommers, 2009); a skill that benefits listeners in noisy conditions (MacLeod and Summerfield, 1987). These findings suggest that declines in processing speed influence information processing from low level sensory to higher cortical functions that are important for speech understanding. In short, declines in systems that support processing speed could significantly impact the ability of older adults to follow conversation, the efficacy of interventions for age-related hearing loss, and the efficacy of interventions in general.

Processing speed is typically assessed with timed tests of speeded behavior that involve multiple perceptual and cognitive functions, including stimulus perception, working memory, decision making and motor planning, motor performance, and sometimes adjusting motor performance after evaluating performance. Given that so many neural systems are required to perform a processing

speed task, it is not surprising that so much of our behavioral performance can be related to measures of processing speed. One processing speed test used in our research is a variant of the Trail Making Test called the Connections Test (Salthouse et al., 2000). The Connections Test was designed to limit motor demands and disambiguate perceptual and motor speed from working memory and inhibitory function. The Connections test involves the sequential search, target identification (numbers or letters), motor planning and response, performance monitoring, and identification of the next item in the sequence (alphabetic or numerical order). These functions can be dissociated from response inhibition and working memory by contrasting performance (Connections Simple) with a test in which subjects alternate between attending to numbers and letters (Connections Complex), thereby requiring a subject to keep the order in mind across stimulus dimensions and to inhibit inappropriate responses to the same stimulus dimension across two trials. The important point is that processing speed tests involve multiple functions requiring the coordination of multiple neural systems that are at risk for age-related declines.

The engagement of multiple neural systems for performing speeded tasks means that age-related decline across a variety of neural systems could have additive effects on processing speed. This also raises questions about how best to identify the unique factors that contribute to individual variation in processing speed performance. We have used a structural covariance approach for analyzing brain morphology data, described below, with the goal of identifying putative neural systems that most contribute to processing speed declines. This review (1) summarizes the extant literature that links processing speed to neuroanatomical variation, with an emphasis on (2) our independent component analysis (ICA) or **source based morphometry** findings for evidence of two specific patterns of frontal and cerebellar structural covariance, and (3) proposes functional neural systems that may underlie the processing speed declines that older adults experience.

Processing speed
A behavioral construct that reflects the rate at which tasks can be performed. Processing speed is typically assessed with timed tasks in which the person must perform a task as quickly as possible. Historically, reaction time experiments could be considered as the earliest measures of processing speed.

Age-related changes
Neurobehavioral changes that occur with age are best characterized by longitudinal studies. In this review, change is used to describe results in the context of cross-sectional findings. It is likely that neural aging compounds or exaggerates the impact of individual variation in cognitive functions.

Source based morphometry
A structural imaging analysis that involves comparing groups or correlating a particular measure with an estimate of volume from across a spatial pattern of voxels that have a common pattern of covariance. This technique reduces the number of comparisons that are typically performed in voxel-based morphometry analyses, while allowing one to identify unique effects and control for noise that may be reflected in a given pattern of covariance. This approach may be particularly valuable when a global latent variable like age influences voxel-based measures across the brain.

NEUROBIOLOGICAL PREDICTORS OF PROCESSING SPEED

Readers of this review should consider that many age-related processing speed findings reported in the literature are cross-sectional in nature, including the primary findings reviewed here. This is important because there are developmental (Laasonen et al., 2002; Deary et al., 2010) and sampling factors that could affect the outcome of cross-sectional studies on processing speed. In addition, the neural systems that are critical for understanding individual variation in cognition may differ across the lifespan (Zimmerman et al., 2006). There may be qualitative neurobiological changes that distinguish older adults from the oldest adults. Our approach has been to include adults across the lifespan because cognitive aging appears to begin when people reach 20–30 years of age (Salthouse, 2009). For this reason, we consider many of the findings summarized in this review to reflect effects of chronological age. Importantly, however, longitudinal findings of processing speed change have supported the robust cross-sectional findings of processing speed declines on cognitive function (Finkel et al., 2009). We anticipate that neural systems exhibiting cross-sectional processing speed changes will also exhibit robust within subject changes with processing speed.

A BRIEF HISTORY AND GLOBAL CORTICAL DECLINES

One early neurobiological explanation for age-related changes in processing speed focused on cortical declines in neuropil (Morris and McManus, 1991). Age-related differences in total gray matter volume have been related to differences in processing speed (Chee et al., 2009), which theoretically could result in degraded or noisy representations that would slow the recognition of stimuli and decision making. For example, primary auditory cortex neurons in the aged rat exhibit elevated excitation that has been related to a loss of GABAergic function (Caspary et al., 2008). These changes likely stem from reduced inhibitory interneuron input onto dendritic arbors that are diminished in the aged rat (Vaughan, 1977) and in older adult human auditory association cortex (Jacobs and Scheibel, 1993). Similar changes could occur across perceptual, planning, and motor systems that support speeded task performance. Thus, age-related changes in cognition are likely to be driven by changes in the connectivity of neural systems (Dickstein et al., 2007).

Another prominent explanation for processing speed declines is that a loss of myelination could slow conduction rates and therefore slow processing speed (Morris and McManus, 1991; Fjell and Walhovd, 2010). Age-related differences in whole brain white matter fractional anisotropy have been associated with processing speed (Coffey et al., 2001; Charlton et al., 2006; Vernooij et al., 2008; Schiavone et al., 2009), although this variation likely reflect a loss of myelinated axons. There is a myelin-specific explanation that could account for age-related changes in processing speed. The number of oligodendrocytes does not decline with age in the rhesus monkey and

have been observed to re-myelinate axons whose oligodendrocytes have died (Peters, 2009). The consequence, however, is (1) a shortening in the lengths of the new myelin sheaths, (2) additional nodes of Ranvier that could alter conductance speed, and (3) the potential for altered neural firing patterns that could further diminish the quality of neural signals affected by axonal and neuropil loss (Peters, 2009).

The early hypotheses for processing speed decline focused on global changes in gray and white matter, due in part to the available evidence. Over the last 20 years there has been mounting evidence for regional specificity in the severity of age-related change in gray matter volume. While nearly the entire brain exhibits reduced volume with age (Brickman et al., 2008; Chee et al., 2009; Fjell et al., 2009), anterior insula, inferior frontal, superior frontal, medial frontal, and cerebellar regions exhibit some of the most pronounced changes with age when measured with automated (Good et al., 2001; Resnick et al., 2003; Salat et al., 2004; Tisserand et al., 2004; Lemaitre et al., 2005; Chee et al., 2009) and manual measures (Raz et al., 1997, 2005, 2010; Jernigan et al., 2001; Tisserand et al., 2002; DeCarli et al., 2005; Raz and Rodrigue, 2006). Given the substantial changes in frontal white matter that also occur with age (Bendlin et al., 2010; Giorgio et al., 2010; Westlye et al., 2010), these results suggest that frontal cortex is undergoing de-afferentation and subsequent decline with increasing age. We return to this premise below with respect to vascular explanations for changes in processing speed. One important point is that these findings could explain why frontal cortex exhibits fewer functional connections with other cortical and sub-cortical regions in older compared to younger adults (Meunier et al., 2009), with reduced control of sensory and perceptual processing. Similarly, the cerebellar hemispheres could be considered as having domain general roles in the support of cognitive function, where the substantial aging effects on morphology (Raz et al., 2010) could affect perceptual and cognitive task performance. Perhaps because of their widespread influence on behavior, frontal and cerebellar regions are consistently related to a variety of speeded or timed cognitive tasks. This review focuses on frontal and cerebellar associations with processing speed.

FRONTAL CORTEX AND PROCESSING SPEED

Frontal cortex has been a primary target for the study of age-related processing speed changes because of the relatively pronounced aging effects on frontal cortex morphology and interest in prominent hypotheses for cognitive aging such as the Frontal Aging Hypothesis (West, 1996) and the Inhibition Deficit Hypothesis (Hasher and Zacks, 1988; Hasher et al., 1999). Volumetric, voxel-based, and sulcal morphometry examinations of frontal gray matter have demonstrated associations with performance across a wide variety of cognitive tasks. Importantly, the frontal gray matter findings appear to be dependent on the susceptibility of frontal white matter to age-related decline.

Regions of frontal gray matter that exhibit cross-sectional change with age and predict processing speed are presented in **Figure 1** from a sample of 42 adults that ranged in age from 19 to 79 years (Eckert et al., 2010). Younger adults with elevated medial frontal and lateral frontal gray matter volume demonstrated faster processing speed compared to older adults with lower gray matter volume in these regions. This pattern of frontal results is consistent with volumetric and voxel-based gray matter associations with processing speed that were observed in a sample of 248 subjects ranging in age from 55 to 86 years (Chee et al., 2009). Similarly, the volume of prefrontal cortex has been observed to predict a drawing speed (Kennedy and Raz, 2005), an estimate of perceptual comparison speed (Schretlen et al., 2000), and a measure of fluid intelligence in older adults (Raz et al., 2008; Kennedy et al., 2009). Frontal sulcal span, an indirect measure of gray matter declines in frontal cortex, has also been associated with processing speed (Kochunov et al., 2010).

Individual variation in prefrontal gray matter volume among older adults is strongly related to frontal white matter volume (Raz et al., 2003). Perhaps then it is not surprising that multiple measures of frontal white matter morphology or integrity have been associated with processing speed, including transverse relaxation rate (Bartzokis et al., 2010), midline genu area of the corpus callosum (Jokinen et al., 2007), and fractional anisotropy and/or mean diffusivity (Deary et al., 2006; Grieve et al., 2007; Bucur et al., 2008; Kennedy and Raz, 2009a; Schiavone et al., 2009; Bendlin et al., 2010; Kochunov et al., 2010; Penke et al., 2010). An example of the robust association between fractional anisotropy in frontal lobe white matter and processing speed is presented in **Figure 2**. Individual variation in frontal lobe fractional anisotropy has been related to processing speed in healthy young adults (Turken et al., 2008), suggesting the interesting possibility that aging exaggerates normal structure – function associations (Harris et al., 2009).

A large body of literature implicates white matter pathology in the cognitive slowing of older

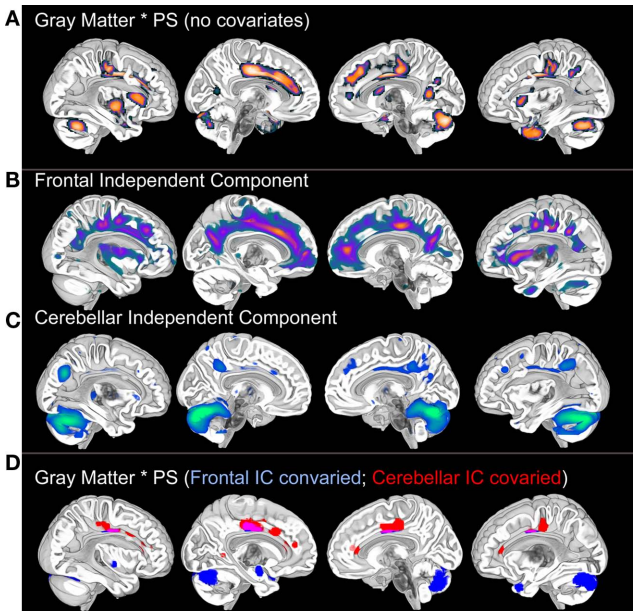

FIGURE 1 | Voxel-based gray matter variation (modulated) predicts Connections Simple processing speed performance (A). These results are not significant at the $p < 0.001$ (uncorrected) level after controlling for age, thereby demonstrating the dependence of the results on age. Posterior cingulate, cuneus, cerebellar, and medial temporal regions exhibited weak associations with processing speed ($p < 0.05$, uncorrected) after controlling for age, suggesting that age may exaggerate normal variation in brain morphology and processing speed. SBM (please see **Figure 3** for an SBM summary) demonstrates unique patterns of frontal and cerebellar gray matter variance **(B,C)** that each accounted for different distributions of the processing speed results [**(D)**: $p < 0.001$ after controlling for variance representing either the frontal or the cerebellar independent components]. Importantly, by controlling for either gray matter component we can see that there are at least two sources that contribute to the association between gray matter and processing speed in this sample. In a separate analysis, these component specific effects were not significant using a $p < 0.001$ threshold when age was covaried. There were weak $p < 0.05$ associations with processing speed in cingulate and cerebellar regions after controlling for either component and age, again suggesting the influence of additive developmental factors (Deary et al., 2010). Results displayed on the MNI template. PS, processing speed; SBM, source based morphometry.

adults (Gunning-Dixon and Raz, 2000; Kennedy and Raz, 2009b; Vernooij et al., 2009; Kochunov et al., 2010; Vidal et al., 2010; please see Gunning-Dixon et al., 2009 for additional review). White matter hyperintensities, a common age-related finding in periventricular regions (Almkvist et al., 1992; Soderlund et al., 2003; Cook et al., 2004), have a gradual impact on cognition over time (Silbert et al., 2009) and appear to affect regional gray matter morphology even before overt cognitive changes are observable (Ota et al., 2010). They are generally considered to be a sign of cerebral small vessel disease and the severity of the hyperintensities has been related to hypertension (Brickman et al., 2010), blood pressure (Kochunov et al., 2010; Kuo et al., 2010), coronary artery calcification (Vidal et al., 2010), and endothelial dependent vasodilation (Hoth et al., 2007).

White matter pathology has been observed independently of effects related to systolic blood pressure and cholesterol (Chowdhury et al., in press) suggesting that multiple mechanisms can produce white matter damage. Age-related changes in pericytes, cells that contribute to the blood brain barrier, may provide an explanation for both hypoxia related damage and neurotoxic damage stemming from microvessel leakage. Pericyte deficient mice exhibit progressive loss of cerebral perfusion and a loss of dendritic spines that has been attributed to the leakage of damaging proteins through the blood brain barrier and subsequent neuronal loss (Bell et al., 2010). Both conditions would produce an inflammatory response and could explain why variation in interleukin-6 has been associated with changes in macaque frontal white matter (Willette et al., 2010). Regardless of the mechanism, damage to periventricular white matter appears to disrupt pathways projecting to and from frontal lobe regions that support performance on processing speed tasks.

CEREBRO-CEREBELLAR AND PROCESSING SPEED DECLINES

Cerebellar morphology also undergoes robust age-related structural change but has not received the same experimental attention as frontal cortex

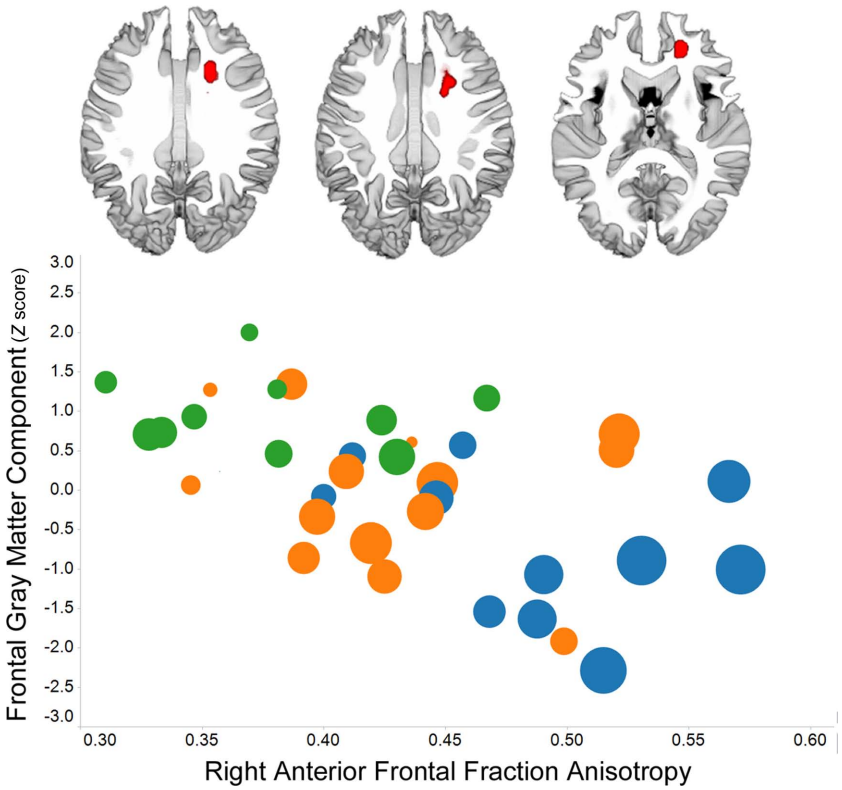

FIGURE 2 | Voxel-based analysis of fractional anisotropy data demonstrates a right frontal association with Connections Simple processing speed ($p < 0.01$, family-wise discovery rate corrected) in 36 of the 42 subjects whose data were included in the Figure 1 analyses. The graph shows the association between frontal fractional anisotropy and the frontal gray matter component from **Figure 1**, the presence of white matter hyperintensities among people with low fractional anisotropy and low frontal gray matter (circle color: no hyperintensities – blue; some hyperintensities – orange; pronounced hyperintensities – green), and that PS is related to each of these variables (larger circle size reflects faster processing speed). (The TSPOON approach designed to control for smoothing kernel effects, Lee et al., 2009, was used to process the 2 mm × 2 mm in plane resolution images that were collected on a Philips 3T with 32 directions using an 8-channel phased array head coil. The B0 and FA data were co-registered to each subject's T1 image and then normalized into study-specific space using the DARTEL parameters obtained for the T1 images.)

with respect to age-related changes in processing speed. This is due, in part, to image processing choices that exclude the cerebellum and because the prominent theories of cognitive aging (the Frontal Aging Hypothesis and the Inhibition Deficit Hypothesis) focus on frontal cortex. While there may be a publication bias related to negative findings, relations between cerebellar morphology and processing speed have been observed and provide support for a fronto-cerebellar aging hypothesis (Hogan, 2004).

Hogan (2004) proposed that changes in feedback and feedforward cerebro-cerebellar interaction result in greater within subject variation in task performance, reduced behavioral automaticity, and increased demands on cognitive control, as well as reduced working memory capacity. This hypothesis is based on normative and patient evidence linking the cerebellum to cognitive and perceptual functions (e.g., Eckert et al., 2003; Chen and Desmond, 2005; Desmond et al., 2005; Steinlin, 2007) and its distinct patterns of structural and functional connectivity with motor, sensory, and attention-related cortical regions (e.g., Kelly and Strick, 2003; Habas et al., 2009; Krienen and Buckner, 2009; Schmahmann, 2010). In particular, limits on the cerebellum's role in modifying motor function in response to sensory and perceptual feedback (Ivry, 1997) could affect performance on perceptual and motor processing speed tasks.

Cross-sectional age-related changes in cerebellar morphology have been associated with processing speed (MacLullich et al., 2004; Paul et al., 2009; Eckert et al., 2010) and a measure of general intelligence among older adults (Hogan et al., 2011). In particular, we observed that processing speed was predicted by regional

cerebellar gray matter volume (**Figure 1**). This voxel-based effect was present throughout the vermis and cerebellar hemispheres (superior to the horizontal fissure). The vermis finding is spatially consistent with a finding that the midline surface area of vermis (declive, folium, tuber region) predicted age-related Digit-Symbol Substitution Test performance, which was significant even after controlling for an estimate of intracranial volume (MacLullich et al., 2004). In addition, a volumetric measure of the same vermis region and total cerebellar gray matter volume were significantly related to age-related changes in Trail Making Test (alternating condition) performance (Paul et al., 2009). In the Paul et al. (2009) study, however, the vermis measure did not significantly predict Trail Making Task performance after accounting for a measure of prefrontal volume (Brodmann areas 9 and 46). The specificity of these frontal and cerebellar findings is addressed below.

As suggested by Hogan (2004), the processing speed and cerebellar findings could be explained by problems with sensory – motor integration. For example, a history of falling and slow processing speed has been associated with delayed horizontal saccades during the initiation of a footlift for a stepping task (Greany and Di Fabio, 2008). In addition, left cerebellar volume has been related to gait speed in older adults (Rosano et al., 2007; although see Rosano et al., 2008) and right cerebellar hemisphere volume has been associated with balance difficulty among older adults (Rosano et al., 2007). A sensory–motor integration explanation could also explain why cerebellar volumes have been associated with perceptual motor skill as measured by total time on target for a pursuit rotor task (Raz et al., 2000), although not for a timed mirror tracing task (Kennedy and Raz, 2005). Age-related differences in cerebellar volume has also been significantly correlated with associative learning as measured by eye-blink conditioning (Woodruff-Pak et al., 2000, 2001). Together, these findings suggest that the behavioral effects of cerebellar aging are variable across subjects, perhaps because of individual variability in developmental factors (Deary et al., 2010), and may have widespread effects on a variety of cerebellar functions.

Based on the perceptual motor skill associations with cerebellar morphology, we asked whether performance on the Connections processing speed test could be influenced by increasing performance across the two trials of each sub-test [numbers only, letters only, numbers – letters (starting with numbers), letters – numbers (starting with numbers)]. There was no evidence indicating that people with elevated cerebellar gray matter exhibited the greatest improvement in performance across the trials. In fact, there was weak evidence for the opposite effect. People with low cerebellar gray matter volume were more likely to improve across the first to second trials of the alternating letters – numbers condition compared to people with elevated cerebellar gray matter volume ($p < 0.05$ uncorrected; no significant relations were seen for the other Connections conditions). This finding suggests that the processing speed and cerebellar relation was not due to a specific learning effect, however it is possible that we could not detect evidence of procedural learning because of (1) the balanced order in which the sub-tests are administered or (2) ceiling effects on the first trial of the Connections sub-tests in people with the greatest cerebellar gray matter volume. Importantly, however, these results are consistent with evidence that variation in cerebellar morphology is related to the initial stages of skill acquisition (Raz, 2000).

Returning to the Hogan (2004) cerebellar hypothesis for cognitive aging, we also wondered whether variation in performance across the Connections tests could be related to age and cerebellar morphology. A measure of each subject's variance in processing speed was obtained from the SD of subject *Z* scores from the Connections sub-tests, where the *Z* score was based on the mean performance of the sample for each subtest. Rather than greater variability among the oldest subjects, an inverted U function was observed where by middle-aged subjects exhibited the most variable Connections performance (age × Connections variance; quadratic $r = 0.41$, $p < 0.05$; linear $r = -0.05$, ns). There were not clear linear or non-linear relations with cerebellar morphology and the Connections variance measure, but it is intriguing to consider that elevated variance in performance among middle-aged subjects may be an early behavioral marker for neurobiological declines that slow processing speed and cognition.

Finally, there are questions about the etiological factors that drive age-related cerebellar changes and that would contribute to slowed processing speed. We observed that cerebellar associations with processing speed occurred independently of periventricular white matter hyperintensities, suggesting that cerebral small vessel disease was not a primary factor for changes in cerebellar morphology in our sample. Similarly, white matter hyperintensities did not account for the association between cerebellar volume and gait speed observed in the Rosano et al. (2007) study. The results of other studies, however, have indicated that primary declines in prefrontal cortex

contribute to cerebellar changes in morphology (Bugalho et al., 2007) that predict processing speed (Paul et al., 2009).

There is the strong likelihood that cerebellar and frontal regions vary in susceptibility to different age-related risk factors. The high metabolic demands of cerebellar Purkinje cells, which demonstrate a substantial loss in number with age (Hall et al., 1975; Andersen et al., 2003), may increase the risk for cell death due to oxidative stress. Indeed, oxidative stress is one factor contributing to cerebellar aging in mice (Lee et al., 2000). The results of human imaging studies indicate that leptin may serve to protect against oxidative stress based on evidence that plasma concentration of leptin was associated with elevated cerebellar and hippocampal gray matter in middle-aged and older adults (Narita et al., 2009) and evidence that leptin treatment increases cerebellar gray matter in leptin deficient patients (Matochik et al., 2005). These findings, together with developmental findings in C57 mice showing that leptin promotes cerebellar Purkinje cell survival and neurite outgrowth (Oldreive et al., 2008), suggest the interesting possibility that leptin limits the impact of oxidative stress on cerebellar Purkinje cells whose high metabolic rate places them at risk for age-related declines as it does for *in vitro* hippocampal Purkinje cells (Guo et al., 2008). This leptin explanation for cerebellar health is just one example for what is likely a multifactorial aging process in the cerebellum.

IDENTIFYING UNIQUE PATTERNS OF CEREBRAL AGING

The review above suggests that age-related changes across multiple systems could affect processing speed. The frontal findings, in particular, could explain why changes in auditory gap detection (Harris et al., 2010) and tactile temporal order thresholds (Craig et al., 2010) have been related to visual–motor measures of processing speed. It is difficult to determine, however, from the results presented in **Figure 1A** whether widespread anatomical effects stem from a common mechanism or whether unique neural systems are affected. This is a particularly significant problem for cross-sectional chronological aging studies where disentangling neurobiological patterns of aging can be difficult. Our approach to addressing this challenge has been to use ICA or source based morphometry to identify unique patterns of structural covariance in the data that uniquely predict age-related differences in processing speed and that might provide insight into the affected neural systems.

Independent component analysis of functional imaging data is helping to identify consistent patterns of neural activity across experiments that are thought to reflect distinct neural systems for focused and scanning attention, motor function, or auditory and visual processing (Beckmann et al., 2005; Eckert et al., 2008a). Indeed, this type of analysis may help to identify atypical coherence in neural systems that underlie changes in processing speed. For example, the ability to switch between functional networks that are thought to represent focused attention to a task (dorsal attention network; Sridharan et al., 2007) and self-referential thinking (default mode network; Andrews-Hanna et al., 2010) has been related to within subject variability in children's task performance (Kelly et al., 2008), appears to be impaired in older adults (Grady et al., 2006), and may also relate to variable processing speed performance in middle-aged adults.

Independent component analysis of structural MRI data has been described as source based morphometry because unique patterns of variation are thought to have common underlying influences or sources (Xu et al., 2009; **Figure 3**). Specific regions of gray matter may covary across subjects because of variation in fiber pathways connecting distant areas, the amount of neuropil, vascular support, or image artifact. For example, this technique identified periventricular white matter regions where white matter hyperintensities were observed (Figure 6 in Eckert et al., 2010). In addition, the component included regions where there was less gray matter in frontal cortex (IC7, **Figure 3**). This result suggested that a common source, presumably cerebral small vessel disease, was affecting gray and white matter segmentation in people with reduced frontal gray matter and lower fractional anisotropy in frontal white matter.

The source based morphometry analysis also identified six other independent spatial patterns of gray matter covariance (**Figure 3**). We identified multiple patterns of gray matter variation that were related to age but only some were related to processing speed. One component coincided spatially with the default mode network (IC1), which was nearly perfectly correlated with total brain volume ($r = 0.90$, $p < 0.001$), related to age ($r = -0.34$, $p < 0.05$), but not uniquely predictive of processing speed. The frontal component (IC7) related to vessel disease and a cerebellar component (IC4) were each associated with age and uniquely predicted processing speed (**Figures 1 and 3**). Importantly, unique **frontal-cerebellar predictors of processing speed** were identified with this analysis.

Frontal–cerebellar predictors of processing speed
This review focuses on changes in the morphology of frontal and cerebellar regions that may constitute unique systems predictive of processing speed and that may be targets for mediating the slowing of cognitive function that occurs with aging.

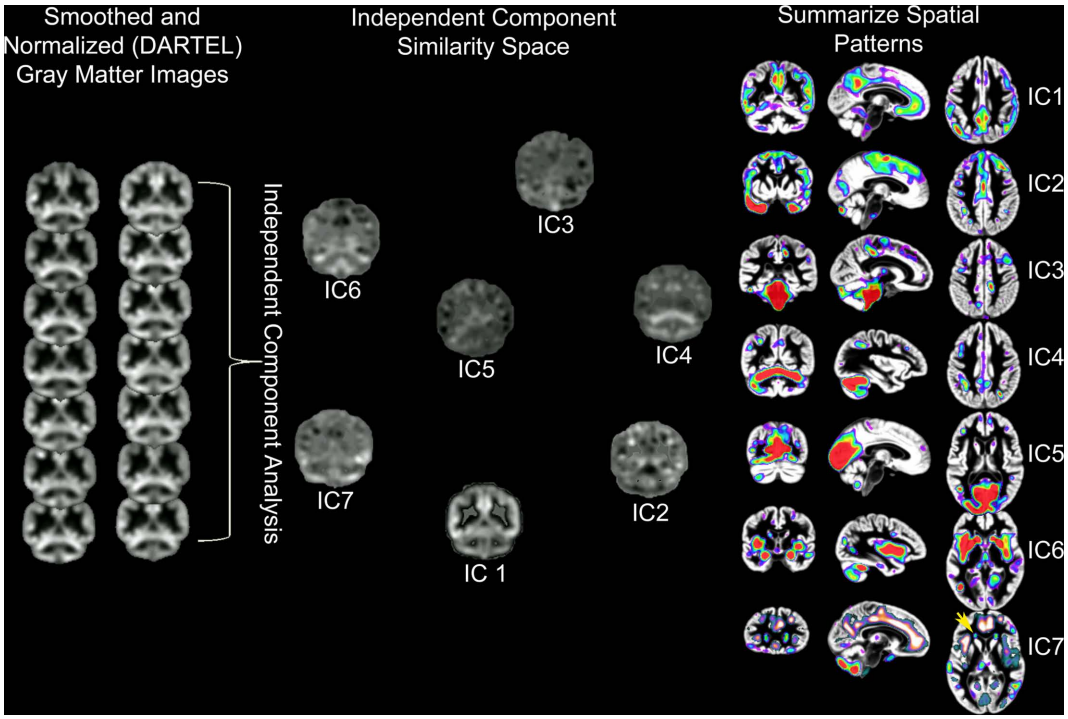

FIGURE 3 | Source based morphometry or ICA of gray matter probability images across 42 subjects. Each subject's T1-weighted image is segmented to generate a gray matter probability image that is normalized to a common coordinate space and smoothed. ICA is performed across the sample of gray matter images. The degree to which each independent component (IC) or unique pattern of variance can be compared to the other ICs with a variety of metrics, including an estimate of similarity space. The brain regions that contribute most to each component can be identified by displaying each component with scaled intensity values (*Z* score = 1–3 above). Each IC also has an inverse component or regions that are negatively correlated with regions in the IC. An example is presented for IC7 where white matter hyperintensity related segmentation error (yellow arrow) is identified by ICA and is inversely correlated with decreased frontal gray matter (e.g., anterior cingulate, anterior insula, and superior frontal sulcus regions represented by hot signal intensities above). ICs 4 and 7 are discussed below and were uniquely related to processing speed. This is important because these results suggest there are independent age-based sources that affect gray matter variation in cerebellar (IC4) and frontal (IC7) regions that are associated with processing speed.

A nice feature of the source based morphometry approach is that each component can be covaried in a whole brain analysis to identify regions uniquely associated a variable of interest. This type of analysis is presented in **Figure 1** and demonstrates: (1) that the frontal and cerebellar regions were uniquely predictive of processing speed; (2) the spatial extent of these effects; and (3) that some brain regions were significantly correlated with processing speed after controlling for either component. The latter is a particularly exciting demonstration of the potential for source based morphometry as an analytical tool because some of these regions, the cingulate for example, had voxels that were influenced by both the source of the frontal component and the source of the cerebellar component. In other words, this is like height being influenced by iodine deficiency and parental height, but in this case the gray matter volume of a specific brain region appears to be influenced by multiple additive aging risk factors. **Figure 4** provides a summary of these results, presented in the context of the multifactorial nature cognitive aging.

TOWARD A SYSTEMS UNDERSTANDING OF AGE-RELATED CHANGES IN PROCESSING SPEED

The structural components that we identified with source based morphometry included patterns of variation that have been observed in functional imaging studies using ICA (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Habas et al., 2009). These results suggested that source based morphometry could be used to identify structural variation that corresponds to functionally defined neural systems. Although source based morphometry results will be dependent on variation within a sample, further support for the potential of the source based morphometry approach to identify neural systems was the observation that individual variation in a cerebellar component was related to individual variation in a white matter

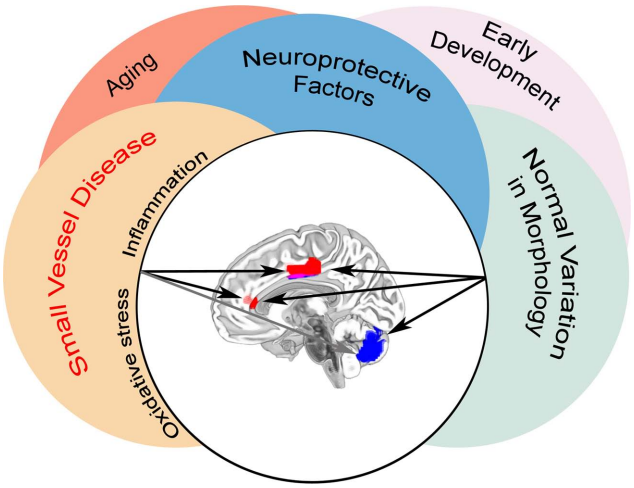

FIGURE 4 | Summary of potential factors affecting frontal and cerebellar morphology and processing speed. On the left side of the figure, aging affects brain morphology through the damaging effects of oxidative stress and inflammation (small vessel disease is in red because of consistent evidence linking cerebral small vessel disease to structural declines and slowed processing speed). These detrimental effects are likely buffered by neuroprotective factors such as (1) leptin and growth factor levels that limit the impact of oxidative stress, (2) norepinephrine or blueberry limits on inflammatory responses in animal models (Heneka et al., 2010; Willis et al., 2010), (3) neurotrophic factors (Kim et al., in press; Raz et al., 2009), and (4) positive lifestyle behaviors such as aerobic exercise (Rosano et al., 2010; Voss et al., 2010). The gray arrow indicates that oxidative stress and inflammation likely affects cerebellar morphology, in comparison to the black arrows for which there is empirical evidence of significant associations. The right side of the figure is designed to emphasize that early development has a significant influence on the degree to which older adults will demonstrate atypical morphology and impaired processing speed (Deary et al., 2006, 2010), but could also influence the expression of neuroprotective factors and the development of lifestyle patterns of behavior and modulate risk for age-related neural declines. While this summary figure is general in nature, it is designed to emphasize the multifactorial and interactive effects of aging neural systems on processing speed.

component that included the middle cerebellar peduncles, cerebral peduncles, and posterior limb of the internal capsule (Figure 5 in Eckert et al., 2010). The possibility that source based morphometry captures variance reflecting neural systems may therefore provide some insight into the neural systems that influence processing speed.

Our results and the existing literature suggest that a dorsal attention (Sweeney et al., 2001) or prefrontal-mediated system for maintaining focused attention, inhibitory control, and working memory is significantly affected by microvascular damage. This interpretation is consistent with evidence that prefrontal gray matter volume has been related to perseveration on the Wisconsin Card Sorting Task (Raz et al., 2003, 2008). It is important, however, to note that our processing speed results were most pronounced for the Connections Simple test compared to the Connections Complex task that required inhibiting a previous response.

Older adults may become particularly dependent on prefrontal cortex to maintain normal performance when age-related declines in sensory systems make relatively easy tasks more challenging because of degraded stimulus representations (Eckert et al., 2008b). Indeed, elevated frontal activity is a common finding in functional imaging studies of aging (Cabeza et al., 2002; Grady et al., 2005) and appears to reflect compensatory engagement of frontal cortex in some studies (Townsend et al., 2006). Performance across a variety of tasks may slow or exhibit impairment with subsequent declines in a dorsal attention system, particularly for tasks that require sustained attention or the inhibition of distracting information. For this reason, changes in a dorsal attention system could account for slowed processing speed across sensory domains.

Interestingly, the dorsal attention system appears to include regions of the cerebellar hemispheres (Krienen and Buckner, 2009). The frontal and cerebellar gray matter components observed in Eckert et al. (2010) did exhibit some spatial overlap even though they each predicted additive variance in those overlapping regions. It is possible that primary aging effects are occurring across the dorsal attention system, but are differentially concentrated across people. This could explain why cerebellar measures might be uniquely predictive of processing speed in some

studies and not others. The same neural system may be affected, but there may be regional specificity in the degree to which it is affected.

Changes in a dorsal attention or executive attention system could also explain why older adults exhibit difficulty inhibiting attention, as measured by eye-movements, to distracting or irrelevant visual targets (Kramer et al., 1999). This would have the downstream effect of slowing performance because of difficulty making a saccade to a new target, a function that is critical for many processing speed tasks. It is also possible that direct effects on an eye-movement system could influence processing speed, which is suggested by our findings that processing speed covaries with gray matter variation in the frontal eye-fields, cingulate, dorsolateral prefrontal cortex, and vermis (Fujikado and Noda, 1987; Hayakawa et al., 2002; Ploner et al., 2005). Older adults have been observed to exhibit impaired horizontal saccades (Carter et al., 1983; Sharpe and Zackon, 1987), but not in every study (Pratt et al., 2006). Understanding the degree to which frontal and cerebellar declines relate to horizontal saccade performance may provide insight into the statistical linkage between neuroanatomical variation in these regions and processing speed.

Cerebellar morphology associations with processing speed most likely reflect a change in the ability of the cerebellum to integrate sensory and motor information to help guide smooth and quick movements. Impaired integration of visual and proprioceptive information because of granule cell loss and/or impaired output of this information because of Purkinje cell loss could slow behavior and increase movement errors. This prediction is supported by evidence that older adults have difficulty stopping arm movements smoothly and make more corrective movements during reaching than younger adults (Brown, 1996). It is unclear, however, whether specific cerebellar zones and related function are affected because of the widespread cerebellar vermis and hemisphere effects observed in MRI studies (**Figure 1**).

In summary, the existing literature and our SBM findings strongly implicate a dorsal attention system in the processing speed declines of older adults. Impaired function of a domain general system would account for slowed task performance across such a wide variety of behavioral tasks. Questions remain how best to enhance healthy aging of this system, although exercise appears to have positive benefits (Colcombe et al., 2003; Rosano et al., 2010). In addition, the degree to which cerebellar declines reflect impairments in specific cerebellar systems and/or reflect changes in a dorsal attention system is unclear. Addressing these questions and identifying the mechanisms for declines in neural systems that support processing speed has the potential to enhance healthy cognitive aging.

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