### Title

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# Associations among executive function Abilities, free Water, and white matter microstructure in early old age

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ABSTRACT

*Background:* Studies have investigated white matter microstructure in relation to late-life cognitive impairments, with fractional anisotropy (FA) and mean diffusivity (MD) measures thought to capture demyelination and axonal degradation. However, new post-processing methods allow isolation of free water (FW), which captures extracellular fluid contributions such as atrophy and neuroinflammation, from tissue components. FW also appears to be highly relevant to late-life cognitive impairment. Here, we evaluated whether executive functions are associated with FW, and FA and MD corrected for FW ($FA_{FWcorr}$ and $MD_{FWcorr}$).

*Method:* We examined 489 non-demented men in the Vietnam Era Twin Study of Aging (VETSA) at mean age 68. Two latent factors capturing 'common executive function' and 'working-memory specific' processes were estimated based on 6 tasks. Analyses focused on 11 cortical white matter tracts across three metrics: FW, $FA_{FWcorr}$, and $MD_{FWcorr}$.

*Results:* Better 'common executive function' was associated with lower FW across 9 of the 11 tracts. There were no significant associations with intracellular metrics after false discovery rate correction. Effects also appeared driven by individuals with MCI (13.7% of the sample). Working memory-specific tasks showed some associations with $FA_{FWcorr}$, including the triangularis portion of the inferior frontal gyrus. There was no evidence that cognitive reserve (i.e., general cognitive ability assessed in early adulthood) moderated these associations between executive function and FW or FA.

*Discussion:* Executive function abilities in early old age are associated primarily with extracellular fluid (FW) as opposed to white matter ($FA_{FWcorr}$ or $MD_{FWcorr}$). Moderation analyses suggested cognitive reserve does not play a strong role in these associations, at least in this sample of non-demented men.

## 1. Introduction

Executive functions (EFs) are cognitive control abilities that regulate thought and action (Friedman and Miyake, 2017; Miyake and Friedman, 2012). EFs are some of the first cognitive abilities to decline in aging, with cortical thinning occurring in their associated brain regions (Bakkour, Morris, Wolk, & Dickerson, 2013; Buckner, 2004; Fjell et al., 2009; Huizinga, Dolan, & van der Molen, 2006). EF deficits are also prominent in the early stages of Alzheimer's disease and mild cognitive impairment (MCI; Baudic et al., 2006; Junquera et al., 2020; Kirova, Bays, &

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Lagalwar, 2015; Ramanan et al., 2017), making their study critically important with respect to cognitive aging. However, the multi-faceted nature of EFs has hampered our understanding of their associations with brain structure. The goal of this study was to shed light onto the neural substrates of EF in early old age (mean age 68) by examining associations with white matter microstructure while also accounting for free water (FW), extracellular fluid that can be isolated from tissue comments in measures of fractional anisotropy (FA) and mean diffusivity (MD) using post-processing techniques (Pasternak et al., 2009). Moreover, to advance our understanding of the possible role of cognitive reserve in these associations, we evaluated whether these associations are moderated by general cognitive ability measured in young adulthood (mean age 20).

## 2. Framework of executive function

EFs capture a heterogeneous set of processes, with measures typically including tests of prepotent response inhibition, working memory updating, and/or task-set shifting (Miyake and Friedman, 2012; Miyake et al., 2000). These EF processes are moderately to highly correlated with one another, especially at the latent construct level (Friedman et al., 2008; Gustavson et al., 2018b; Miyake et al., 2000; Vaughan & Giovanello, 2010). A highly influential model – the unity/diversity model – has highlighted this common variance across multiple EF subdomains, and models it as a "Common EF" latent factor (Friedman et al., 2008; Gustavson et al., 2018b; Miyake and Friedman, 2012). The general variance reflected in Common EF represents the goal management abilities needed to initiate a task and pursue goal-directed actions in the face of other distractions (Friedman and Miyake, 2017; Miyake and Friedman, 2012), and this model has demonstrated good fit in a range of samples across the lifespan (Engelhardt et al., 2015; Freis et al., 2021; Friedman et al., 2016; Gustavson et al., 2018a).

Depending on the availability of data, other factors are fit to capture variance specific to one EF subdomain and not the others (e.g., working memory-specific variance). Working memory-specific variance is of particular interest because it has been proposed to reflect gating in the basal ganglia (Friedman and Miyake, 2017), but is also strongly genetically correlated with intelligence (Friedman et al., 2008; Gustavson et al., 2022a), suggesting its neural correlates could be distributed across the brain. In the Vietnam Era Twin Study of Aging (VETSA) sample analyzed here, our model of EF includes Common EF and Working Memory-Specific factors, both of which demonstrate strong stability across middle age (Gustavson et al., 2018a). Longitudinal decline in the Common EF factor across the first three waves of VETSA (mean ages 56 to 68) is also associated with higher Alzheimer's disease genetic risk scores (Gustavson et al., 2022b) and greater self-reported subjective cognitive decline across the same window (Gustavson et al., 2021). These findings underscore the importance of studying the neural correlates of EF during the transition from late middle age to early old age.

## 3. Measurement of white matter microstructure

The most common metrics for assessing white matter microstructure in studies of cognitive aging are FA and MD. FA quantifies directional diffusion within a given voxel (with higher FA corresponding to stronger directionality) and is thought to represent density and coherence of white matter regions. MD represents the average diffusivity of water molecules within a voxel regardless of direction and may reflect reduction in neuropil or increases in cerebrospinal fluid (Alexander, Lee, Lazar, & Field, 2007; Clark et al., 2011; Selemon & Goldman-Rakic, 1999). Typically, better cognitive function is associated with higher FA and lower MD (Bennett and Madden, 2014; Charlton et al., 2006; Mabbott et al., 2006). Age-related trends indicate that FA increases through early adulthood before decreasing throughout the rest of the lifespan (Westlye et al., 2010) with MD displaying the opposite pattern (decreasing through early adulthood before increasing later in life). Thus, reduced FA in older populations is thought to be associated with axonal degradation and demyelination (Beaulieu, 2002) and with cognitive decline in normal aging and AD (Bozzali et al., 2012; Cremers et al., 2016; Kennedy and Raz, 2009; Mielke et al., 2012). By contrast, increased MD in normal aging and AD may reflect reduction in neuropil or increases in cerebrospinal fluid (Alexander et al., 2007; Clark et al., 2011; Selemon & Goldman-Rakic, 1999).

Importantly, new post-processing techniques now allow for isolation of extracellular fluid (FW) from tissue components of white matter microstructure (Pasternak et al., 2009). Such measures yield FA and MD measures that are corrected for FW and therefore focused on intracellular diffusion (hereafter, $FA_{FWcorr}$ and $MD_{FWcorr}$). Beyond this, FW may be useful as it is associated with objective cognitive assessments and cognitive change (Archer et al., 2020), self-perceived cognitive decline (Archer et al., 2021), and is elevated in MCI and AD (Maier-Hein et al., 2015) even after correcting for white matter hyperintensities (Dumont et al., 2019). Moreover, such cognitive measures do not appear associated with $FA_{FWcorr}$ and $MD_{FWcorr}$ measures (Archer et al., 2020), thus raising the possibility that earlier findings for FA and MD may have been driven by FW. FW measures are thought to represent a combination of FW in extracellular space and FW contamination from cerebrospinal fluid in adjacent voxels. Increased FW may also indicate neuroinflammation, atrophy, or the breakdown of myelin cell membranes (Dumont et al., 2019; Gullett et al., 2020; Pasternak, Shenton, & Westin, 2012). Therefore, their continued study in relation to cognition across midlife and early old age will help shed light on neurocognitive changes and risk for AD.

## 4. Executive function and white matter microstructure

In one of the few studies of younger adults to examine white matter microstructure using a Common EF factor, individual differences in Common EF were associated with greater FA in the right superior longitudinal fasciculus (SLF) and left anterior thalamic radiation (Smolker, Friedman, Hewitt, & Banich, 2018). Working memory updating-specific ability was not associated with white matter microstructure measures and shifting-specific ability was associated with MD throughout the brain. However, as noted above, it is unclear whether findings from FA and MD measures in this earlier work may be driven by FW.

Studies of older adult samples that have examined associations between EFs and FW had relatively high proportions individuals with MCI or dementia, and focused on EF composite scores that shed light on common but not specific aspects of EF (Archer et al., 2020; Ji et al., 2017; Maillard et al., 2019). For example, in a study of 319 older adults (M = 72–73 years; 49 % MCI), EF was associated with lower FW in multiple cortical white matter tracts including the fornix, inferior longitudinal fasciculus, tapetum, uncinate fasciculus, & cingulum bundle, but not associated with $FA_{FWcorr}$ in these same tracts (Archer et al., 2020). Another study (M = 78 years; >50 % MCI or dementia) demonstrated that baseline levels of global FW were associated with cross-sectional and longitudinal changes in EF and episodic memory, but that $FA_{FWcorr}$ and $MD_{FWcorr}$ were not associated with EF or memory (Maillard et al., 2019). Finally, in AD patients, FW was associated with EFs across nearly all white matter regions, as well as lower FA in the bilateral frontal, parietal, and occipital fibers (Ji et al., 2017).

These findings highlight the importance of directly modelling FW in studies of EF as Common EF may be primarily associated with extracellular fluid (i.e., FW) rather than intracellular white matter microstructure (i.e., FA and MD), with associations with FA being observed only in patients with dementia. Measures of extracellular diffusion may be more sensitive to subtle differences in structural integrity compared to intracellular measures, therefore FW represents a particularly relevant measure to assess brain health in early old age. Additionally, because studies have focused on composite measures, they have not examined whether these associations with FW are observed for Common EF versus other specific EF components (e.g., working memory-specific).

Moreover, existing studies have focused on samples with high proportions of subjects with MCI and/or AD, and it will be important to examine whether these associations still exist when focusing on a sample more representative of the population (i.e., MCI rates closer to 10–15 %), or when focusing solely on cognitively normal adults.

Finally, when examining the neural underpinnings of EFs, we considered the role of young adult cognitive reserve, which we defined as an individual's total cognitive resources during early adulthood (Kremen et al., 2022). Theories of cognitive reserve suggest that some individuals do not exhibit the cognitive or functional deficits expected based on their brain pathology (Barulli and Stern, 2013; Stern, 2012, 2013; Whalley, Deary, Appleton, & Starr, 2004), which might manifest as reduced associations between EF and white matter (and FW) in individuals with high reserve. We focus on young adulthood as a time when aging effects will have had essentially no impact on cognitive capacity. While some studies suggest that cognitive decline in EFs are sensitive to cognitive reserve (McKenzie et al., 2020; O'Shea et al., 2015; Roldan-Tapia, Garcia, Canovas, & Leon, 2012), little research has examined whether cognitive reserve moderates associations between EFs and brain (Krch et al., 2019). In a prior study of individuals in the same sample as the present study, the association between hippocampal volume and episodic memory was higher among individuals with lower levels of cognitive reserve; those with higher reserve were more resilient against the potentially deleterious effects of hippocampal atrophy (Vuoksimaa et al., 2013). However, whether cognitive reserve moderates associations between Common EF and white matter microstructure has not been examined. If EFs are sensitive to cognitive reserve, then EF abilities should be more strongly associated with neuroimaging measures in individuals with low reserve. Such findings would indicate that individuals with high reserve are more able to retain the same level of EF ability in the face of neurodegeneration compared to individuals with low reserve.

## 5. The current study

In the current study, we used data from the third wave of the Vietnam Era Twin Study of Aging (VETSA) sample (mean age 68) to examine associations between EF and white matter microstructure using 3 metrics: FW, $FA_{FWcorr}$, and $MD_{FWcorr}$. We predicted that EFs would be uniquely associated with FW within multiple cortical white matter tracts, consistent with earlier work (Archer et al., 2020). Less is known about the associations between working memory-specific abilities and white matter, so these analyses are considered exploratory. Finally, we examined whether associations between EFs and white matter would be moderated by cognitive reserve based on general cognitive ability assessed when subjects were about age 20 (over 45 years prior to the assessments of EFs and white matter described here) (Kremen et al., 2022).

## 6. Methods

### 6.1. Subjects

Data analyses focus on 489 male twins who participated in the third wave of the longitudinal VETSA project. VETSA participants were recruited randomly from a previous study of members of the Vietnam Era Twin Registry (Tsuang, Bar, Harley, & Lyons, 2001). All individuals served in the United States military at some time between 1965 and 1975, but nearly 80 % reported no combat exposure. Sample characteristics are displayed in Table 1, alongside descriptive statistics for executive function tests and our index of cognitive reserve. Participants are generally representative of American men in their age cohort with respect to health, education, and lifestyle characteristics (Kremen et al., 2011; Kremen et al., 2006; Schoenborn & Heyman, 2009).

All wave 3 MRI data were collected at the University of California, San Diego (UCSD). All participants gave their written informed consent before participation, and the study protocol was approved by the Institutional Review Boards at all participating institutions.

**Table 1**
Demographic characteristics and descriptive statistics for executive function tasks.

| | N | Mean | SD | Range | Skewness | Kurtosis |
|---|---|---|---|---|---|---|
| *Demographic Characteristics* | | | | | | |
| Age | 489 | 67.53 | 2.62 | 61.37, 71.72 | −0.44 | −1.34 |
| Years of Education | 489 | 14.01 | 2.07 | 8, 20 | 0.45 | −0.23 |
| Diabetes (% yes) | 489 | 0.22 | | | | |
| Hypertension (% yes) | 489 | 0.56 | | | | |
| Race/Ethnicity (% White Non-Hispanic) | 489 | 0.88 | | | | |
| *Executive Function Tests* | | | | | | |
| Stroop - Color-Word Score* | 483 | 30.23 | 8.79 | 2.17, 59.17 | 0.03 | 0.28 |
| Color Score | 483 | 60.22 | 10.66 | 17.44, 88.44 | −0.29 | 0.60 |
| Word Score | 487 | 85.40 | 14.20 | 36.37, 126.37 | −0.01 | 0.19 |
| Trail Making Test - Switching* (log RT) | 485 | 4.58 | 0.38 | 3.73, 5.48 | 0.54 | −0.12 |
| Number Sequencing (log RT) | 485 | 3.54 | 0.35 | 2.65, 4.97 | 0.65 | 0.69 |
| Letter Sequencing (log RT) | 485 | 3.56 | 0.35 | 2.77, 5.01 | 0.63 | 0.36 |
| Category Switch - Switching Trial Score* | 488 | 11.87 | 2.60 | 0.17, 20.17 | −0.10 | 1.26 |
| Category Fluency Score | 488 | 36.25 | 7.50 | 15.92, 62.92 | 0.25 | 0.26 |
| Letter Number Sequencing | 488 | 8.83 | 2.30 | 1.74, 15.74 | −0.11 | 0.14 |
| Reading Span | 482 | 33.03 | 4.90 | 18.53, 44.53 | −0.10 | −0.27 |
| Digit Span | 488 | 16.27 | 3.50 | 6.89, 26.79 | 0.30 | −0.40 |
| *Cognitive Reserve* | | | | | | |
| AFQT (Age 20) | 481 | 0.34 | 0.67 | −1.18, 2.32 | 0.07 | −0.33 |

*Note:* Some executive function measures (indicated with a *) were first corrected for baseline conditions prior to analyses (e.g., for the Stroop task, the Color-Word Score was regressed on the Color Score and Word Score and the residuals were exported as the primary dependent measure). All executive function measures are adjusted for practice effects, leveraging data from returnees and new subjects at waves 2 and 3 to adjust for the fact that some subjects have been exposed to the task multiple times. AFQT = Armed Forces Qualifications Test percentile score (transformed based on military norms).

### 6.2. Measures

#### 6.2.1. Executive function

EF abilities were measured with 6 tasks spanning prepotent response inhibition, task-set switching, and working memory span domains. Inhibition was assessed with the Stroop task (Golden and Freshwater, 2002; Stroop, 1935). Shifting was assessed using the (a) Trail Making Test switching trial and (b) the category-switching subtest for verbal fluency from the Delis-Kaplan Executive Function System (D-KEFS) (D-KEFS; Delis, Kaplan, & Kramer, 2001). All measures of inhibition and switching were adjusted for appropriate baseline conditions. Working memory span was assessed with the letter number sequencing and digit span subtests of the Wechsler Memory Scale-III (Wechsler, 1997) and the reading span test (Daneman and Carpenter, 1980). Prior to analyses, all

cognitive scores in the full VETSA wave 3 study were adjusted for practice effects, leveraging data from attrition replacement participants who completed the task battery for the first time at wave 2 or wave 3 to estimate the increase in performance expected in returnees who completed the tests two or more times (Elman et al., 2018).

Our model of EF was initially validated in waves 1 and 2 of VETSA (Gustavson et al., 2018a; Gustavson et al., 2018b) and includes 2 latent factors: a "Common EF" latent factor (based on performance across all 6 tests) and a "Working Memory-Specific" factor (based on additional variance in the 3 working memory span tests not already captured by the latent factor). Prior waves also administered an additional test (the AX-Continuous Performance Test), but this was not included in the wave 3 assessment due to time constraints. Preliminary analyses indicated the latent factor model of EF continued to fit the data well in this subsample of individuals who completed the MRI assessment at wave 3 of VETSA, so we did not fit any additional confirmatory models of EF. Additionally, our confirmatory model of EF is supported by a recent study that fit a latent growth model of Common EF and Working Memory-Specific factors across all 3 waves of VETSA in the full sample (Gustavson et al., 2022b).

#### 6.2.2. General cognitive ability (age 20)

General cognitive ability—our index of cognitive reserve—was assessed in young adulthood when VETSA participants were first inducted into the military (mean age 20 years) with the 100-item multiple-choice Armed Forces Qualifications Test (AFQT; Bayroff and Anderson, 1963). The AFQT demonstrates a strong correlation ($r = 0.84$) with measures of intelligence such as the Wechsler Adult Intelligence Scale (Lyons et al., 2009) and consists of 4 subscales assessing vocabulary, arithmetic ability, tool/mechanical knowledge and reasoning, and visual-spatial ability. AFQT scores also correlate moderately with the self-reported number of years of education ($r = 0.31$), but here we capitalized on having a far more precise index than years of education, i.e., a direct measure of overall cognitive ability from young adulthood (Kremen et al., 2022). AFQT percentile scores were converted into z-scores. Thus, the mean of 0.34 (see Table 1) is approximately equivalent to an IQ of 105.

### 6.3. Image acquisition

Images were acquired with two GE 3 T Discovery 750 × scanners (GE Healthcare, Waukesha, WI, USA) with eight-channel phased array head coils. The imaging protocol included a sagittal 3D fast spoiled gradient echo (FSPGR) $T_1$-weighted (T1w) volume optimized for maximum gray/white contrast (TE = 3.164 msec, TR = 8.084 msec, TI = 600 msec, flip angle = 8°, matrix = 256x192, in-plane resolution = 1x1 mm, slice thickness = 1.2 mm, slices = 172). Diffusion data were acquired with a multi-shell diffusion-weighted scan (54-directions, b values = [0 (x3), 666 (x6), 1333 (x15), 2666 (x15), 4000 (x15)] s/mm$^2$, integrated with a pair of b = 0 images with opposite phase-encode polarity, TR = 6600 msec, TE = 81.1 msec, matrix = 96x96, in-plane resolution = 2.5x2.5 mm, slice thickness = 2.5 mm, 54 slices).

### 6.4. Image processing

Data were preprocessed using the PreQual pipeline to correct for distortions/motions and eddy currents (Cai et al., 2021; Schilling et al., 2019). The multi-shell data was then subset to a single shell (b = 1333) and inputted into DTIFIT to calculate FA and MD for each participant. The single shell data was also input into MATLAB code to calculate FW, $FA_{FWcorr}$, and $MD_{FWcorr}$ (Jenkinson et al., 2012; Pasternak et al., 2009). In short, this code leverages a variational network framework to split the diffusion image into a bi-tensor model – one which is the FW contamination, and the other is the tissue compartment. New, FW-corrected metrics ($FA_{FWcorr}$, $MD_{FWcorr}$) can then be quantified. Importantly, the FW metric itself can also be leveraged in analysis. A standard space representation for the FW, $FA_{FWcorr}$, and $MD_{FWcorr}$ maps was created by non-linearly registering the DTIFIT-derived raw FA image and applying this transform to the FW-corrected maps (Avants, Epstein, Grossman, & Gee, 2008).

Following standardization, mean FW, $FA_{FWcorr}$, and $MD_{FWcorr}$ values were quantified within several well-established white matter tractography templates for each imaging session (Archer et al., 2019; Archer et al., 2020; Brown et al., 2017). These templates included the cingulum bundle, fornix, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus as well as homologous transcallosal connections of the inferior frontal gyrus (IFG) pars opercularis, IFG pars orbitalis, IFG pars triangularis, inferior temporal gyrus, medial frontal gyrus, and middle frontal gyrus (see Fig. 1 for a visual representation of all 11 tracts). We focused on this set of 11 cortical white matter tracts which have previously been linked to executive function and subjective cognitive decline in recent studies (Archer et al., 2021; Archer et al., 2020). Additionally, we included a final set of measures capturing FW, $FA_{FWcorr}$, and $MD_{FWcorr}$ across all white matter tracts in the brain (including both cortical and subcortical tracts) to capture global FW and white matter microstructure as our recent work has highlighted strong genetic influences shared across all white matter tracts (Gustavson et al., 2019).

### 6.5. Data analysis

Phenotypic correlational and regression analyses were conducted in Mplus version 8.3 (Muthén and Muthén, 1998–2017), which accounts for missing observations using full-information maximum likelihood. Significance of individual parameter estimates were established with standard error-based 95 % confidence intervals and confirmed with $\chi^2$ difference tests by fixing that parameter to zero. Standard errors and chi-squares were adjusted for clustering within families (twin pairs), and the $\chi^2$ difference tests were appropriately scaled based on scaling factors provided in the Mplus output (Satorra & Bentler, 2001).

To examine associations between EFs and white matter microstructure, we fit a series of regression models in which the latent EF factors were regressed on the candidate white matter measures (one model per white matter measure). The following covariates were included in all analyses: age ($M = 67.53$, $SD = 2.63$, Range = 61.37 to 71.71), diabetes status (22.3 % yes), hypertension status (55.6 % yes), a variable capturing whether individuals were Hispanic and/or nonwhite (11.7 % yes), and two variables capturing scanner differences (one of the two scanners' software was upgraded during the study, so orthogonal contrasts were created to account for potential differences across the three scanner/software groups). Diabetes and hypertension status were based on whether the participant (1) reported being diagnosed by a doctor, (2) reported that they were currently taking medication for diabetes or high blood pressure, and/or (3) reported whether they had high blood pressure on the day of testing (hypertension only).

After identifying which FW and white matter measures were associated with EF factors, we fit additional regression models (one for each measure) in which age 20 general cognitive ability (AFQT) was added to the model. Both EF factors were regressed on AFQT scores, and an interaction term was added (AFQT * diffusion measure) for whichever EF factor was associated with that measure in prior analyses.

#### 6.5.1. Additional statistical considerations

The comprehensive battery of cognitive tasks in VETSA enables diagnosis of mild cognitive impairment (MCI) using the Jak-Bondi approach (Bondi et al., 2014; Jak et al., 2009; Kremen et al., 2014). Due to the relatively young age of this community-dwelling sample, MCI prevalence in this subsample of wave 3 participants who completed MRI measures was 13.7 % (2.2 % missing diagnoses). With 84 % cognitively unimpaired, the primary analyses focused on all participants (see Supplemental Method for detailed description of MCI diagnoses). However, we also report analyses after removing all participants with MCI (or

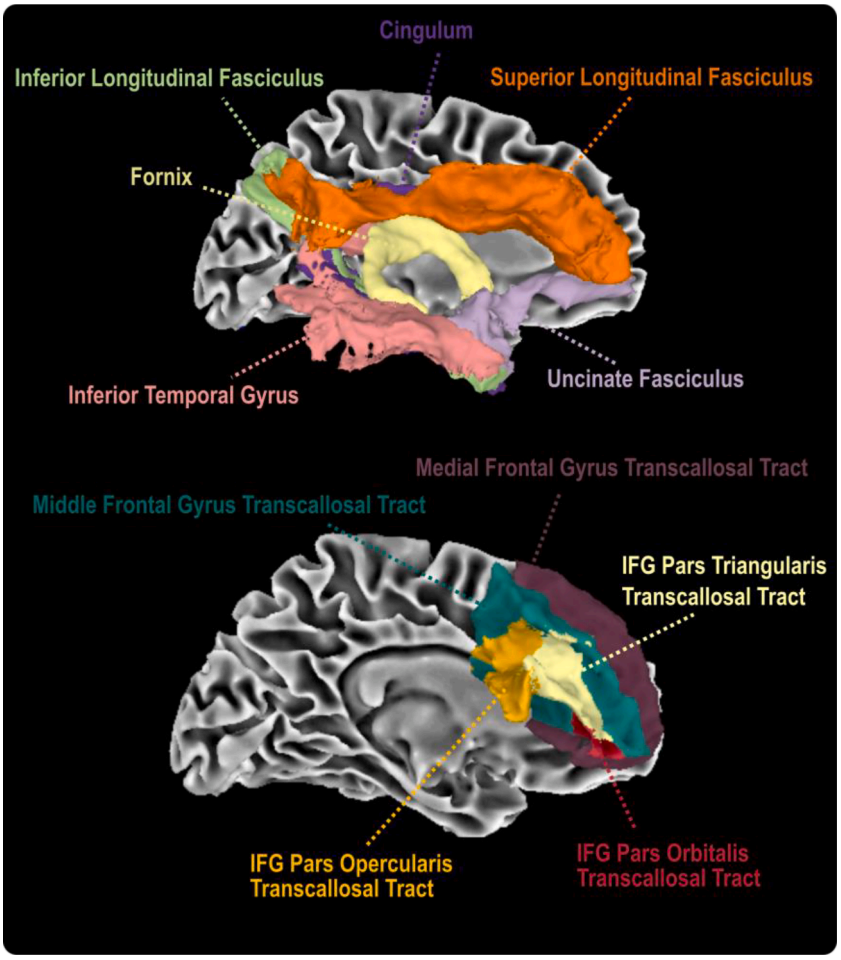


**Fig. 1.** Tractography templates used in the study. All tract templates were previously developed and are freely . available at https://github.com/VUMC-VMAC/Tractography_Templates

missing MCI diagnosis) from analyses (new N = 411). The latter analyses inform whether individuals with lower cognitive ability were primarily driving associations with white matter microstructure. No participants were diagnosed with dementia.

## 7. Results

We first fit a correlational model of the 2 latent EF factors, age 20 general cognitive ability (AFQT), and covariates. Correlations among these measures are displayed in supplemental Table S1 and factor loadings on the EF factors from this model are displayed in Fig. 2. This basic model fit the data well, $\chi^2(30) = 36.84$, $p = .182$, RMSEA = 0.022, CFI = 0.991. The supplement also displays comparisons between FW and white matter measures across cognitively normal and MCI groups (Table S2).

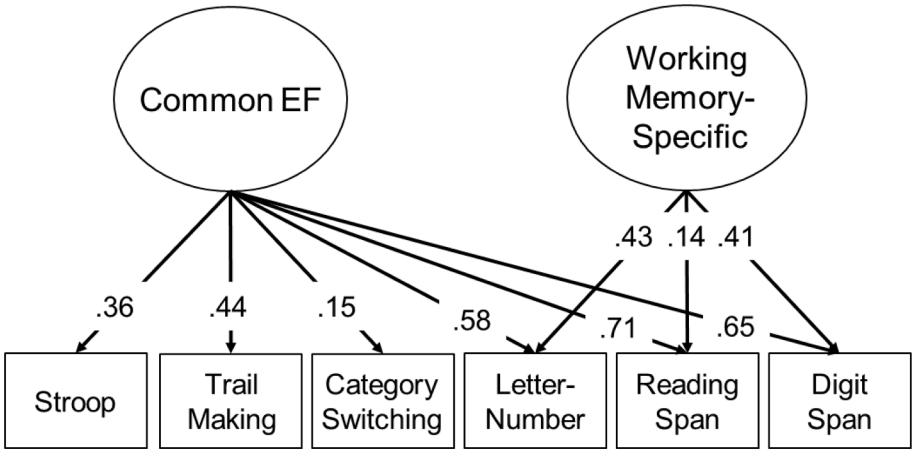


**Fig. 2.** Latent variable model of executive function (EF) from the current study. Ovals represent latent variables and rectangles represent measured variables. This model also includes all covariates (i.e., it is the same as that described in Table S1). All paths are signficant (p <.05).

### 7.1. Associations between executive function and white matter microstructure

Associations between the EF factors and the FW and white matter microstructure measures are displayed in Table 2. The corresponding associations between all covariates and the FW and white matter microstructure measures from these models are displayed in Table 3. Analyses were conducted separately for each tract and for each metric (FW, $FA_{FWcorr}$, and $MD_{FWcorr}$), but associations between any given metric and the Common EF and Working Memory-Specific factors were estimated within the same model. FDR corrections in Table 2 were based on all *p*-values from that column only (e.g., across all associations between the Common EF factor and FW metrics, with separate FDR corrections for $FA_{FWcorr}$ and $MD_{FWcorr}$; 3 additional sets of FDR corrections were examined for associations between Working Memory-Specific and FW, $FA_{FWcorr}$, and $MD_{FWcorr}$). An example of these analyses is displayed in Fig. 3 (for FW across all tracts).

The Common EF factor was associated with FW across 9 of the 11 white matter tracts (and the 'all tracts' measure). In all cases, more FW corresponded to lower Common EF ability (range in $\beta$ = -0.15 to -0.26). Common EF was not associated with $FA_{FWcorr}$ or $MD_{FWcorr}$ in any of the tracts. The Working Memory-Specific factor was associated with greater $FA_{FWcorr}$ in the IFG Triangularis ($\beta = 0.21$), but not with any other FW or white matter microstructure metrics after FDR correction.

Analyses after excluding individuals with MCI are displayed in Table 4. For Common EF and FW, the negative associations were nonsignificant after FDR correction, though significant associations were observed for 2 of the 11 white matter tracts based on uncorrected *p*-values (cingulum and unicinate fasciculus). Associations with the remaining tracts were attenuated by approximately half (range $\beta$ = -0.09 to -0.15). For the Working Memory-Specific factor, the association with FA in the IFG Triangularis remained significant even after FDR correction ($\beta = 0.25$). Additionally, significant associations were observed for FA in the inferior longitudinal fasciculus and the superior longitudinal fasciculus ($\beta = 0.26$ and 0.28, respectively).

### 7.2. Interactions between cognitive reserve and white matter microstructure

Next, in the full sample (i.e., including individuals with MCI and those missing MCI diagnoses), we repeated the same set of analyses after adding age 20 general cognitive ability and its interaction with the relevant white matter measure to the regression model. We only conducted moderation analyses for the white matter measures significantly associated with EF factors in the primary analyses (i.e., Common EF and FW in 9 tracts and the 'all tracts' measure, Working Memory-Specific and $FA_{FWcorr}$ in the IFG Triangularis tract only). Results are displayed in Table 5. Although AFQT scores were strongly predictive of Common EF ($\beta$s = 0.41 to 0.64), they did not moderate any of the associations between the EF factors and FW described above (all uncorrected *p*s > 0.243, FDR-corrected *p*s > 0.782). Finally, we conducted sensitivity analyses using a dichotomous score for cognitive reserve (i.e., grouping subjects as above or below the mean), which also revealed no evidence that cognitive reserve moderated associations between EF factors and FW or FA (see supplemental Table S3).

## 8. Discussion

The goal of the study was to better understand the associations between EF abilities and white matter microstructure in older adults. Results indicated that EF abilities (specifically a Common EF factor comprising performance across 6 tasks) were associated with FW across almost all cortical tracts examined here, but not with $FA_{FWcorr}$ or $MD_{FWcorr}$. Greater Common EF ability was associated with less FW. These findings mirror the associations with age, which was associated with free water across all cortical tracts, but only associated with

**Table 2**
Associations between executive function and white matter microstructure (N = 489).

| Independent Variable | Free Water | | | $FA_{FWcorr}$ | | | $MD_{FWcorr}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* | *p* | *p* (FDR) | β | p | *p* (FDR) | *β* | *p* | *p* (FDR) |
| *Common EF* | | | | | | | | | |
| All Tracts | **−0.23** | **< 0.001** | **< 0.001** | 0.15 | 0.252 | 0.432 | 0.04 | 0.355 | 0.429 |
| Cingulum | **−0.26** | **< 0.001** | **< 0.001** | 0.06 | 0.446 | 0.670 | 0.06 | 0.486 | 0.530 |
| Fornix | **−0.17** | **0.013** | **0.020** | 0.09 | 0.231 | 0.432 | 0.14 | 0.093 | 0.429 |
| IFG Opercularis | **−0.24** | **0.005** | **0.012** | 0.17 | 0.097 | 0.388 | 0.11 | 0.329 | 0.429 |
| IFG Orbitalis | **−0.22** | **0.016** | **0.021** | 0.04 | 0.594 | 0.713 | 0.09 | 0.193 | 0.429 |
| IFG Triangularis | **−0.24** | **0.019** | **0.023** | 0.15 | 0.025 | 0.153 | 0.11 | 0.317 | 0.429 |
| Inferior Longitudinal Fasciculus | **−0.15** | **0.002** | **0.007** | 0.01 | 0.872 | 0.872 | −0.07 | 0.348 | 0.429 |
| Inferior Temporal Gyrus | −0.15 | 0.078 | 0.078 | 0.03 | 0.724 | 0.790 | −0.05 | 0.311 | 0.429 |
| Medial Frontal Gyrus | −0.17 | 0.049 | 0.054 | 0.11 | 0.249 | 0.432 | −0.07 | 0.350 | 0.429 |
| Middle Frontal Gyrus | **−0.25** | **0.007** | **0.014** | 0.14 | 0.138 | 0.414 | 0.10 | 0.327 | 0.429 |
| Superior Longitudinal Fasciculus | **−0.22** | **0.001** | **0.005** | 0.17 | 0.516 | 0.688 | −0.02 | 0.768 | 0.768 |
| Uncinate Fasciculus | **−0.18** | **0.008** | **0.014** | 0.13 | 0.021 | 0.153 | 0.93 | 0.357 | 0.429 |
| *Working Memory-Specific* | | | | | | | | | |
| All Tracts | −0.01 | 0.893 | 0.973 | 0.07 | 0.619 | 0.852 | 0.00 | 0.956 | 0.997 |
| Cingulum | 0.05 | 0.569 | 0.973 | 0.05 | 0.680 | 0.852 | 0.08 | 0.230 | 0.997 |
| Fornix | 0.03 | 0.694 | 0.973 | 0.02 | 0.820 | 0.895 | 0.03 | 0.707 | 0.997 |
| IFG Opercularis | −0.06 | 0.570 | 0.973 | 0.00 | 0.996 | 0.996 | 0.04 | 0.772 | 0.997 |
| IFG Orbitalis | 0.05 | 0.694 | 0.973 | 0.17 | 0.148 | 0.852 | −0.06 | 0.439 | 0.997 |
| IFG Triangularis | −0.02 | 0.907 | 0.973 | **0.21** | **< 0.001** | **< 0.001** | 0.00 | 0.985 | 0.997 |
| Inferior Longitudinal Fasciculus | 0.02 | 0.827 | 0.973 | 0.14 | 0.646 | 0.852 | 0.04 | 0.675 | 0.997 |
| Inferior Temporal Gyrus | −0.05 | 0.631 | 0.973 | 0.06 | 0.492 | 0.852 | 0.04 | 0.704 | 0.997 |
| Medial Frontal Gyrus | 0.02 | 0.829 | 0.973 | 0.07 | 0.527 | 0.852 | 0.05 | 0.587 | 0.997 |
| Middle Frontal Gyrus | 0.00 | 0.973 | 0.973 | 0.04 | 0.705 | 0.852 | 0.00 | 0.997 | 0.997 |
| Superior Longitudinal Fasciculus | −0.04 | 0.661 | 0.973 | 0.14 | 0.241 | 0.852 | 0.02 | 0.782 | 0.997 |
| Uncinate Fasciculus | 0.04 | 0.645 | 0.973 | −0.03 | 0.710 | 0.852 | −0.14 | 0.117 | 0.997 |

*Note:* Each value represents a separate model where Common EF and Working Memory-Specific latent factors were regressed on that white matter microstructure measure, controlling for covariates (age, diabetes & hypertension status, and scanner). Uncorrected *p* values (middle columns) and false-discovery-rate-corrected (FDR-corrected) *p* values (right columns) are also displayed. FDR correction was conducted separately within each set of white matter measures (i.e., within FW measures, within $FA_{FWcorr}$, and within $MD_{FWcorr}$) and separately for Common EF and Working Memory-Specific factors. Bold indicates values that are statistically significant after FDR correction ($p < .05$). IFG = Inferior Frontal Gyrus.

**Table 3**
Associations between covariates and free water and white matter microstructure measures.

| | Age | Diabetes | Hyper-tension | Scanner Contrast 1 | Scanner Contrast 2 |
|---|---|---|---|---|---|
| *Free Water (FW)* | | | | | |
| All Tracts | **0.25** | 0.01 | **0.15** | **0.15** | 0.03 |
| Cingulum | **0.17** | 0.06 | **0.14** | 0.10 | 0.06 |
| Fornix | **0.26** | −0.04 | 0.06 | 0.06 | −0.03 |
| IFG Opercularis | **0.24** | 0.03 | **0.17** | 0.06 | 0.00 |
| IFG Orbitalis | **0.22** | 0.00 | **0.14** | 0.00 | −0.01 |
| IFG Triangularis | **0.23** | 0.01 | **0.18** | 0.11 | 0.06 |
| Inferior Longitudinal Fasciculus | **0.15** | −0.01 | **0.12** | **0.14** | 0.04 |
| Inferior Temporal Gyrus | **0.16** | 0.06 | **0.14** | **0.12** | 0.05 |
| Medial Frontal Gyrus | **0.23** | 0.00 | **0.14** | **0.13** | 0.00 |
| Middle Frontal Gyrus | **0.23** | 0.02 | **0.16** | **0.12** | 0.05 |
| Superior Longitudinal Fasciculus | **0.22** | 0.00 | **0.17** | **0.14** | 0.05 |
| Uncinate Fasciculus | **0.23** | 0.01 | **0.15** | **0.13** | 0.00 |
| *FW-Corrected FA* | | | | | |
| All Tracts | −0.10 | 0.04 | **−0.10** | **−0.23** | −0.12 |
| Cingulum | −0.09 | −0.01 | −0.09 | 0.02 | 0.02 |
| Fornix | **−0.14** | 0.01 | −0.03 | −0.06 | 0.02 |
| IFG Opercularis | −0.10 | −0.02 | **−0.16** | **−0.21** | **−0.12** |
| IFG Orbitalis | **−0.11** | 0.07 | −0.05 | **−0.24** | **−0.20** |
| IFG Triangularis | **−0.13** | 0.01 | **−0.12** | **−0.17** | −0.10 |
| Inferior Longitudinal Fasciculus | −0.02 | 0.04 | 0.00 | **−0.20** | **−0.14** |
| Inferior Temporal Gyrus | 0.06 | 0.02 | −0.05 | **−0.22** | **−0.23** |
| Medial Frontal Gyrus | **−0.15** | 0.07 | **−0.12** | **−0.17** | −0.02 |
| Middle Frontal Gyrus | **−0.15** | 0.02 | **−0.12** | **−0.11** | −0.02 |
| Superior Longitudinal Fasciculus | −0.07 | 0.04 | −0.06 | **−0.15** | −0.10 |
| Uncinate Fasciculus | −0.08 | 0.03 | −0.05 | **−0.10** | −0.02 |
| *FW-Corrected MD* | | | | | |
| All Tracts | **−0.16** | 0.04 | −0.05 | −0.01 | 0.07 |
| Cingulum | −0.07 | −0.03 | −0.07 | −0.03 | 0.00 |
| Fornix | −0.18 | 0.04 | −0.05 | 0.01 | 0.07 |
| IFG Opercularis | −0.09 | 0.03 | −0.07 | −0.05 | −0.05 |
| IFG Orbitalis | **−0.10** | 0.04 | −0.06 | **0.15** | 0.10 |
| IFG Triangularis | −0.10 | 0.04 | −0.05 | −0.05 | −0.09 |
| Inferior Longitudinal Fasciculus | −0.06 | 0.00 | 0.01 | −0.03 | 0.03 |
| Inferior Temporal Gyrus | 0.03 | 0.05 | 0.00 | 0.03 | −0.01 |
| Medial Frontal Gyrus | **−0.13** | 0.05 | −0.03 | 0.03 | 0.08 |
| Middle Frontal Gyrus | **−0.15** | 0.04 | −0.09 | 0.02 | 0.02 |
| Superior Longitudinal Fasciculus | −0.06 | 0.04 | 0.02 | −0.05 | −0.02 |
| Uncinate Fasciculus | −0.04 | 0.02 | −0.06 | **0.12** | 0.08 |

*Note:* Each row represents a separate regression model (corresponding to Table 2) where the latent executive function factors are regressed on that white matter microstructure measure and the covariates. Dichotomous variables were used for diabetes and hypertension (0 = no, 1 = yes). The orthogonal 'Scanner' contrasts capture differences among scanners (Contrast 1) and software within one of the scanners (Contrast 2). Significant associations are indicated in bold ($p < .05$; no multiple test correction).

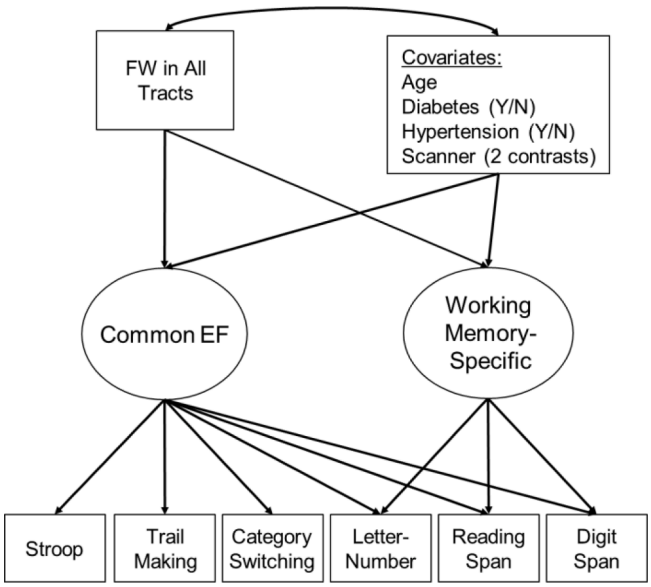


**Fig. 3.** Example of the primary regression analyses where executive function (EF) latent factors are regressed on free water (FW) or white matter microstructure measures (FW across all white matter tracts in this example) and covariates (displayed in a single box for simplicity). All covariates except age were dichotomous or orthogonal contrasts.

$FA_{FWcorr}$ or $MD_{FWcorr}$ in some tracts.

These results are consistent with two recent studies that have suggested EFs are associated with FW (but not $FA_{FWcorr}$ or $MD_{FWcorr}$) in older adult samples (Archer et al., 2020; Maillard et al., 2019). These prior studies focused on samples with high rates of MCI (~50 %) and our study extends these findings to a slightly younger sample with a substantially lower prevalence of MCI. Importantly, after excluding individuals with MCI (13.7 % of the sample), the associations between Common EF and FW described above were nonsignificant, suggesting individuals with MCI may be driving many of the observed FW associations, though there was some evidence that Common EF remained associated with FW in the cingulum and uncinate (based on raw *p*-values). Thus, it is possible that widespread associations between Common EF and FW are primarily observed in samples with some MCI/AD cases.

Another explanation for the lack of significance of many tracts after excluding MCI cases is reduced power in the smaller cognitively normal sample (with restricted range in scores). However, associations between Common EF and FW were about half the magnitude as they were when including participants with MCI (Table 2 vs Table 4), suggesting that the differences are not simply due to reduction in sample size. Thus, EF may be modestly related to FW in cognitively normal individuals, with associations observed potentially for frontally-connected tracts (e.g., the uncinate and cingulum) in normal aging. This is consistent with the notion that FW metrics primarily capture neurodegeneration (Pasternak et al., 2012), with individual differences in FW not being strongly associated with cognitive abilities until after some neurodegeneration has taken place. Another recent study of cognitively normal older adults revealed similar negative associations between FW and fluid cognition (which included multiple EF tasks) in some, but not all, white matter tracts (including the cingulum and SLF) and no associations with $FA_{FWcorr}$ in any of the candidate tracts (Gullett et al., 2020). Therefore, associations between Common EF and FW may be relatively restricted to certain brain regions in adulthood and normal aging, but expand to others with age and/or early AD pathology. In either case, associations appear unique to FW rather than $FA_{FWcorr}$ or $MD_{FWcorr}$ metrics.

Because this was one of the first studies to examine these associations at the level of latent factors, we were also able to examine associations

**Table 4**
Associations between executive function and white matter microstructure in cognitively normal subjects (N = 411).

| Independent Variable | Free Water | | | $FA_{FWcorr}$ | | | $MD_{FWcorr}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* | *p* | *p* (FDR) | β | p | *p* (FDR) | *β* | *p* | *p* (FDR) |
| *Common EF* | | | | | | | | | |
| All Tracts | −0.15 | 0.113 | 0.247 | 0.05 | 0.793 | 0.891 | −0.06 | 0.432 | 0.740 |
| Cingulum | −0.27 | 0.005 | 0.062 | −0.06 | 0.797 | 0.891 | 0.05 | 0.670 | 0.869 |
| Fornix | −0.09 | 0.428 | 0.467 | −0.01 | 0.891 | 0.891 | 0.03 | 0.797 | 0.869 |
| IFG Opercularis | −0.14 | 0.071 | 0.213 | 0.07 | 0.233 | 0.792 | −0.07 | 0.428 | 0.740 |
| IFG Orbitalis | −0.14 | 0.065 | 0.213 | −0.05 | 0.658 | 0.891 | 0.02 | 0.894 | 0.894 |
| IFG Triangularis | −0.12 | 0.268 | 0.325 | −0.02 | 0.264 | 0.792 | −0.03 | 0.722 | 0.869 |
| Inferior Longitudinal Fasciculus | −0.09 | 0.210 | 0.315 | −0.10 | 0.260 | 0.792 | −0.13 | 0.111 | 0.454 |
| Inferior Temporal Gyrus | −0.11 | 0.643 | 0.643 | −0.06 | 0.154 | 0.792 | −0.15 | 0.151 | 0.454 |
| Medial Frontal Gyrus | −0.11 | 0.271 | 0.325 | 0.02 | 0.870 | 0.891 | −0.13 | 0.087 | 0.454 |
| Middle Frontal Gyrus | −0.15 | 0.137 | 0.247 | 0.02 | 0.481 | 0.891 | −0.06 | 0.744 | 0.869 |
| Superior Longitudinal Fasciculus | −0.11 | 0.144 | 0.247 | 0.04 | 0.776 | 0.891 | −0.09 | 0.138 | 0.454 |
| Uncinate Fasciculus | −0.19 | 0.023 | 0.141 | 0.10 | 0.403 | 0.891 | 0.10 | 0.383 | 0.740 |
| *Working Memory-Specific* | | | | | | | | | |
| All Tracts | −0.08 | 0.486 | 0.839 | 0.22 | 0.018 | 0.054 | 0.06 | 0.547 | 0.772 |
| Cingulum | 0.00 | 0.986 | 0.986 | 0.22 | 0.231 | 0.323 | 0.08 | 0.420 | 0.772 |
| Fornix | −0.04 | 0.629 | 0.839 | 0.06 | 0.541 | 0.591 | 0.08 | 0.152 | 0.772 |
| IFG Opercularis | −0.11 | 0.340 | 0.839 | 0.16 | 0.252 | 0.323 | 0.09 | 0.388 | 0.772 |
| IFG Orbitalis | 0.00 | 0.981 | 0.986 | 0.25 | 0.149 | 0.255 | −0.02 | 0.871 | 0.871 |
| IFG Triangularis | −0.08 | 0.560 | 0.839 | **0.25** | **0.011** | **0.042** | 0.08 | 0.528 | 0.772 |
| Inferior Longitudinal Fasciculus | −0.06 | 0.575 | 0.839 | **0.26** | **0.002** | **0.027** | 0.05 | 0.665 | 0.772 |
| Inferior Temporal Gyrus | −0.11 | 0.550 | 0.839 | 0.24 | 0.064 | 0.127 | 0.05 | 0.702 | 0.772 |
| Medial Frontal Gyrus | −0.03 | 0.796 | 0.955 | 0.16 | 0.269 | 0.323 | 0.10 | 0.397 | 0.772 |
| Middle Frontal Gyrus | −0.06 | 0.615 | 0.839 | 0.19 | 0.056 | 0.127 | 0.10 | 0.708 | 0.772 |
| Superior Longitudinal Fasciculus | −0.10 | 0.323 | 0.839 | **0.28** | **0.008** | **0.042** | 0.04 | 0.661 | 0.772 |
| Uncinate Fasciculus | 0.07 | 0.551 | 0.839 | −0.02 | 0.862 | 0.862 | −0.07 | 0.570 | 0.772 |

*Note:* Each value represents a separate model where Common EF and Working Memory-Specific latent factors were regressed on that white matter microstructure measure, controlling for covariates (age, diabetes & hypertension status, and scanner). Bold indicates values that are statistically significant (uncorrected *p*-values < 0.05). IFG = Inferior Frontal Gyrus.

**Table 5**
Results of moderation analyses involving cognitive reserve.

| Association | Main Effect: Free Water | | Main Effect: Cognitive Reserve | | Interaction Term: (Free Water * Cognitive Reserve) | | |
|---|---|---|---|---|---|---|---|
| | *β* | *p* | *β* | *p* | *β* | *p* | *p* (FDR) |
| *Common EF and Free Water* | | | | | | | |
| All Tracts | −0.15 | 0.208 | **0.62** | **<0.001** | 0.03 | 0.661 | 0.782 |
| Cingulum | **−0.23** | **0.024** | **0.58** | **<0.001** | 0.05 | 0.608 | 0.782 |
| Fornix | **−0.17** | **0.017** | **0.62** | **<0.001** | −0.05 | 0.243 | 0.782 |
| IFG_Opercularis | −0.14 | 0.265 | **0.59** | **<0.001** | 0.02 | 0.602 | 0.782 |
| IFG_Orbitalis | **−0.18** | **0.003** | **0.58** | **<0.001** | 0.07 | 0.361 | 0.782 |
| IFG_Triangularis | −0.11 | 0.586 | **0.41** | **<0.001** | 0.16 | 0.518 | 0.782 |
| Medial_Frontal_Gyrus | −0.15 | 0.560 | **0.60** | **<0.001** | 0.06 | 0.828 | 0.828 |
| Middle_Frontal_Gyrus | −0.15 | 0.307 | **0.61** | **<0.001** | 0.03 | 0.623 | 0.782 |
| SLF | −0.15 | 0.174 | **0.53** | **<0.001** | 0.02 | 0.711 | 0.782 |
| Uncinate Fasciculus | **−0.19** | **0.024** | **0.64** | **<0.001** | 0.05 | 0.352 | 0.782 |
| *Working Memory-Specific and $FA_{FWcorr}$* | | | | | | | |
| IFG Triangularis | **0.36** | **0.000** | −0.36 | 0.121 | −0.09 | 0.274 | 0.782 |

*Note:* Each row represents a separate model where Common EF and Working Memory-Specific Latent factors were regressed on that white matter microstructure measure, controlling for covariates (age, diabetes & hypertension status, and scanner). Additionally, EF factors were regressed on the indicator of cognitive reserve (age 20 general cognitive ability) and an interaction term was included (AFQT * FW). IFG = Inferior Frontal Gyrus.

between variance unique to working memory tasks not already captured by Common EF (i.e., the Working Memory-Specific factor). Results in the full sample (including individuals with MCI) were consistent with an earlier study of younger adults in which working memory updating-specific ability was not associated with white matter microstructure (Smolker et al., 2018), though the FA and MD metrics were not corrected for FW in this prior study. However, the Working Memory-Specific factor was associated with $FA_{FWcorr}$ in the IFG-Triangularis in the primary analysis (including participants with MCI) and with $FA_{FWcorr}$ in three tracts (IFG-Triangularis, inferior and superior longitudinal fasciculus) after excluding participants with MCI.

It will be important to further examine these novel associations with working memory-specific to understand these positive associations with $FA_{FWcorr}$, including why some associations were only observed in cognitively normal subjects. Importantly, there was little evidence for group-level differences in $FA_{FWcorr}$ across cognitively normal and MCI subjects (see Table S3), suggesting the lack of association in the full sample was not driven by MCI subjects having lower $FA_{FWcorr}$. Rather, the individual differences captured by microstructural measures may be more subtle and shed light into individual variability in normal aging. That is, while FW metrics capture neurodegeneration or axonal degradation (and therefore relate to cognitive ability after some atrophy has taken place), microstructural measures may tell us more about normal function and/or may possibly be of use in predictive studies. This would be consistent with prior work showing FW was strongly associated with neurodegeneration (e.g., hippocampal volume) but $FA_{FWcorr}$ in the fornix interacted with hippocampal volume to predict future executive function decline (Archer et al., 2020). Regardless, these findings

highlight the importance of considering the role of MCI in these associations and separately evaluating cognitive correlates of white matter microstructure within cognitively normal individuals. Furthermore, because earlier work has suggested that working memory-specific operations may be more associated with subcortical brain regions such as gating in the basal ganglia (Friedman and Miyake, 2017), it will be interesting to further probe these associations with FW and white matter in other tracts beyond those cortical tracts examined here.

Another goal of the study was to examine whether an indicator of cognitive reserve (age 20 general cognitive ability) moderates associations between EFs and white matter microstructure. For example, earlier work in this VETSA sample has demonstrated that individuals with low general cognitive ability at age 20 demonstrated stronger associations between hippocampal volume and memory at mean age 56 (Vuoksimaa et al., 2013). The present results indicated no evidence for such interactions for Common EF. It is possible that moderating effects of cognitive reserve are only apparent in the context of disease- or age-related pathology. Although FW in all tracts was significantly associated with age, the cross-sectional nature of this study makes it difficult to determine whether this association reflects age-related neuropathology or instead reflects pre-existing individual differences or other factors beyond age-related neuropathology. Indeed, white matter abnormalities have been observed in wave 2 of VETSA (mean age 62) (Fennema-Notestine et al., 2016; Sanderson-Cimino et al., 2021), suggesting some pathology was present in at least some subjects, yet a significant interaction with age 20 cognitive ability was not observed. Alternatively, or additionally, moderation of $FA_{FWcorr}$ and $MD_{FWcorr}$ by cognitive reserve may be possible in samples with greater rates of impairments (MCI or AD), as EFs appear more related to these measures in AD patients (Ji et al., 2017).

While associations between EF factors and FW differed after removing MCI subjects from these analyses (i.e., Table 2 vs Table 4), there were no group differences between MCI and cognitively normal subjects on our index of young adult cognitive reserve ($p$ =.263). The fact that our MCI subjects had comparable levels of young adult cognitive reserve to cognitively normal subjects, but appeared to show much stronger associations between Common EF and FW, adds further support to the idea that associations between EF and FW differ in normal versus pathological aging. It may therefore be interesting to examine moderating effects of cognitive reserve within samples of MCI cases only, though it will be necessary to do so in a sample with a greater number of MCI subjects.

### 8.1. Strengths and weaknesses

The comprehensive assessment of EFs in VETSA allowed for examination of associations between EF and white matter microstructure using a latent variable approach that isolated Common EF variance from Working Memory-Specific variance at a time in early old age where most individuals were cognitively normal. This study also represents one of the first examinations into the role of cognitive reserve in these associations. Some weaknesses of the study include the fact that all participants are men, and the vast majority are non-Hispanic and White. It will be important to evaluate these associations in more diverse samples.

Additionally, we used established white matter tract templates (Archer, Vaillancourt, & Coombes, 2018) and a recently-available white matter tract atlas that provides strong coverage of the brain, replicating prior associations between EF and FW in older adults (Archer et al., 2020). While our results showed consistent associations between the Common EF factor and extracellular (FW) but not intracellular metrics ($FA_{FWcorr}$ and $MD_{FWcorr}$), it is still unclear what specific cellular processes contribute to each variable. Better understanding the cognitive correlates of FW, $FA_{FWcorr}$, and $MD_{FWcorr}$ will help shed light on the nature of these measures, and their role as predictors and indicators of aging, but additional studies are also needed to quantify what gives rise to individual differences in these measures.

Finally, this study is cross-sectional and cannot speak to whether these associations reflect pre-existing associations between Common EF and FW, or if these effects are specific to aging. Findings from one existing study suggest that baseline levels of FW are also associated with longitudinal changes in EF, though this sample was at about 10 years older than the present sample and most individuals were diagnosed with MCI or dementia (Maillard et al., 2019). In our study, age was consistently associated with all free water measures (and some white matter measures), suggesting that the free water measures examined here are sensitive to age. The correlations with age may actually be relatively low estimates given the narrow age range of our sample (~10 years). In any case, it will be necessary to examine these associations in early adulthood and middle age to inform whether associations between FW and EF reflect age-related changes in EF or perhaps whether they account for individual differences in EF across the lifespan.

### 8.2. Concluding remarks

EF are complex cognitive control abilities that are highly relevant to aging. This study sheds light on the neural underpinnings of common and specific components of EF by demonstrating that FW measures across many cortical white matter tracts are associated with individual differences in Common EF abilities. By contrast, working memory-specific abilities were associated with $FA_{FWcorr}$, but only after excluding individuals with MCI from the analyses. Associations between Common EF ability and FW were not moderated by cognitive reserve in the current investigation, but it will be important to consider whether these factors may contribute more strongly to associations between EFs and white matter in later stages of aging or progression toward cognitive decline or dementia.

### CRediT authorship contribution statement

**Daniel E. Gustavson:** Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Derek B. Archer:** Data curation, Visualization, Writing – original draft, Writing – review & editing. **Jeremy A. Elman:** Data curation, Writing – review & editing. **Olivia K. Puckett:** Data curation, Writing – review & editing. **Christine Fennema-Notestine:** Data curation, Methodology, Writing – review & editing. **Matthew S. Panizzon:** Data curation, Writing – review & editing. **Niranjana Shashikumar:** Data curation, Writing – review & editing. **Timothy J. Hohman:** Methodology, Writing – review & editing. **Angela L. Jefferson:** Writing – review & editing. **Lisa T. Eyler:** Methodology, Writing – review & editing. **Linda K. McEvoy:** Methodology, Writing – review & editing. **Michael J. Lyons:** Funding acquisition, Writing – review & editing. **Carol E. Franz:** Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing. **William S. Kremen:** Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103279.

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