Main Manuscript for

"Population-level age effects on the white matter structure subserving cognitive flexibility in the human brain"

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Abstract

Cognitive flexibility, a cognition crucial for adaptive behavior, involves multi-scale functioning across several neuronal organization levels. While the neural underpinnings of flexibility have been studied for decades, limited knowledge exist about the structure and differentiation of the white matter subserving brain regions implicated in cognitive flexibility. Neural changes that occur over the lifespan have an impact in the brain's white matter organization and, thereby, may alter cognitive flexibility abilities. This study investigates the population-level relationship between cognitive flexibility and macromolecular properties of white matter across two periods of adulthood, aiming to discern how these associations vary over different life stages and brain tracts. A novel method to study age-effects in the brain's structure-function associations is proposed. First, the white matter structure implicated in cognitive flexibility was delineated by tracing in the Human Connectome Project tractography template the pathways subserving neural regions derived via meta-analysis of set-shifting. Then, a cohort analysis was performed to characterize related brain features using a subset of the UKBiobank MRI data which has a companion functional/behavioral dataset.[1] We found that (1)the wiring of cognitive flexibility is defined by specialized tracts, which present undifferentiated features early in adulthood, and significantly differentiated types in later life. (2)These MRI-derived properties are correlated with individual subprocesses of cognition which intimately relate to the latent construct of cognitive flexibility function (switch, inhibition, and updating).[2] (3)In late life, myelin-related homogeneity of specific white matter tracts implicated in cognitive flexibility declines as a function of chronological age—a phenomenon not observed in early life. Our findings support the age-related differentiation of white matter tracts implicated in cognitive flexibility as a natural substrate of brain adaptive function.

Significance Statement

Cognitive flexibility, a cognition that facilitates adaptation to environmental demands, involves complex brain processes. During the lifespan, brain changes affecting the brain's structural organization are theorized to impact cognitive flexibility. This study characterizes how the brain's connectivity is correlated with cognitive flexibility throughout adulthood. By analyzing macromolecular properties of white matter, this study found that certain parts of the brain's wiring related to cognitive flexibility become more distinct with advanced age. This age-related distinction of the wiring implicated in cognitive flexibility appears as a natural, underlying characteristic of the human brain which may impact specific aspects of thinking, like shifting between tasks or updating information.

Main Text

Introduction

Cognitive flexibility is an inherent ability important for human adaptive functioning and behavior.[1] This cognition is acquired during development and continues to evolve over the adult lifespan.[2,3] It plays a crucial role in various aspects of life, including coordination with other executive functions and behaviors.[4] Additionally, maintaining flexibility in later life may help mitigate cognitive decline associated with late-life aging. Furthermore, impairments in cognitive flexibility are common among several neurological and neuropsychiatric disorders, including anxiety and dementia.[6,7] Understanding effectors relevant to cognitive flexibility function during adulthood is important to elucidate intrinsic properties of the neural mechanisms of human adaptive thinking and behavior.

Cognitive flexibility involves brain-wide functioning at several neural organization levels, including degrees of regional neural liberality (e.g., the ability to switch processing assignment in synchronized pace with the functional network);[7,8] and shifts in network-wide properties of brain function (e.g., connectivity or eccentricity).[4,9,10] Over natural aging, neural organization changes both regionally – through synaptic pruning,[11] cortical myelination,[12] and related activity-dependent tailoring mechanisms,[13] and at brain-wide network levels through frequency-dependent integration (e.g., between-network connectivity).[14] Changes visible in the interconnecting white matter accompany these functional transitions.[15] The trajectory of white matter maturation over the natural lifespan is different for different brain tracts and neuropils,[16] which modifies how brain regions decentralize functional processing while increasing regional specialization.[13] This process has direct implication in the topography of functional networks, and in consequent cognitive functioning.

Imaging studies based on diffusion measures of structural alignment have shown that advanced age affects white matter tracts differently, with prefrontal tracts being the most affected in humans.[17] These studies frequently report age-related changes in white matter as detrimental alterations to tissue structure. On the other hand, histopathological studies, which consider staining specifically for macromolecular lipid density, have further noted that deep white matter and its projections into the cerebral cortex show highly differentiated arrangements with age—not necessarily reflecting pathology.[18] Sherin and Bartzokis have summarized that, in older adults, white matter fibers within bundles appear less dense, and show robust selective myelination along its projections and greater number of myelinated connections within the gyri. While among younger adults, fiber myelination is rather abundant and largely undifferentiated within the bundles. These cellular structural characteristics of brain white matter portrait a level of age-related adaptation of brain tissues. Models of natural differentiation of white matter with age have been proposed.[13] In an influential review, Bonetto et al. outlines the processes of activity dependent myelination as a natural

adaptive brain process which modifies the white matter in response to function—rather than functional changes being a consequence of it.

In this work, we compute features of white matter derived from MRI measures of macromolecular tissue properties (rather than diffusion), and investigate their association with cognitive flexibility function and age. A method to derive the population-level structure of cognitive flexibility and investigate age effects is proposed (**Fig.1**). This framework aims to investigate aspects of white matter differentiation in terms of its macromolecular characteristics by comparing MRI features derived from T1-weighted and T2 fluid attenuated inversion recovery (FLAIR) data to functional scores dimensionally. We focus on a brain representation of cognitive flexibility that is not explicitly associated with any pathology; thus, the structural and functional variability encompassed in the analyses is deemed that of natural aging processes. Specifically, we define the white matter tracts that are particularly implicated in cognitive flexibility function and test three related hypotheses: (1) that an intrinsic association exists between cognitive flexibility ability and the homogeneity of the white matter implicated in cognitive flexibility function; and (2) that this relationship differs between early and later adulthood. Furthermore, (3) we investigate if these associations exist in either life period in a tract-selective manner.

Results

White Matter Structure Implicated in Cognitive Flexibility

The Neurosynth meta-analysis (neurosynth.org)[19] using search terms associated with set-shifting identified 5124 regional neuro-activations reported from 120 neuroimaging studies were found to be significantly associated with set-shifting function within 95% CI. Synthesized studies included loadings between 0.647 and 0.038. The specificity of the term-search was estimated to be 0.885 for the term search when associations with abilities other than shifting were considered with effect sizes >2. These activations largely overlap with regions previously reported as implicated with cognitive flexibility among humans,[2] including the inferior frontal junction, anterior cingulate cortex, angular gurus, anterior insula, dorsolateral prefrontal cortex, and inferior parietal lobule.

An atlas-based parcellation analysis revealed that these Neurosynth-derived activations implicated with cognitive flexibility overlapped with 36 neural regions described in four distinct atlases of the human brain, including the posterior and caudal anterior cingulate cortices, superior and middle frontal gyri, and the caudal, superior, and middle frontal and orbitofrontal cortices, in addition to bilateral striatum, putamen, and caudate. The conglomerate of tracts that fed into these neural regions defines the white matter structure subserving cognitive flexibility function in the human brain. This interconnected wiring is composed of 32 white matter pathways described in the Human Connectome Project tractography atlas of the adult white matter (HCP1065),[20] which encompasses 82 possible segmentations in total (68 for bundles and 14 for cranial

nerves). The white matter structure of cognitive flexibility includes a few of the longest white matter pathways of the human brain (e.g., cingulum bundle, frontal and parietal aslant tracts, the uncinate and the left arcuate fasciculus, and the inferior, middle, and superior portions of the longitudinal fasciculus). **Figure 2** shows the neural regions found to be implicated in cognitive flexibility and its white matter structure. Additional details are described in **Table 1** along with the pertaining anatomical atlases.

Age Effects on Cognitive Flexibility Function

Functional performance in set-shifting, inhibitory control, and working memory tasks significantly differed between age-groups ($p<0.001$) (**Fig. 3**). Set-shifting abilities appeared to hold an inverse relationship with age, with a logarithmic decay appearance withing the 95% CI (**Fig. 3a** left). When evaluated within each age group (younger or older) by linear regression, a significant association was found between set-shifting abilities and age among older adults (β_1= -0.462, Ɛ = 0.118, t = -3.906, p<.001) but not among younger adults (p = 0.859) (Fig. 2a right panels). This result indicates that the decline in set-shifting function may be particularly relevant in late-life.

On the other hand, inhibitory control exhibited a non-linear relationship with age within the 95% CI (**Fig. 3b** left); with a significant linear association with age among younger adults (β_1= -0.892, Ɛ = 0.415, t = -2.149, p = 0.034), but non-significant curvilinear association among older adults (p = 0.735) (**Fig. 3b** right panels). This result indicates that inhibitory control abilities are likely invariant in later life.

Similar to set-shifting, working memory abilities exhibited a logarithmic decay with age withing the 95% CI (**Fig. 3c** left), with a significant linear decay among older adults (β_1= -0. 339, Ɛ = 0.136, t = -2.501, p=0.014), but not among younger adults (p = 0.814) (**Fig. 3c** right panels). This result indicates that information updating abilities, such as working memory, decline as a function of age in later life.

Age Effects on the White Matter Structure of Cognitive Flexibility

The macrostructural characteristics of each relevant tract were analyzed across younger and older adult groups, focusing on two main parameters: (i) increased mean in standardized T1w (*m*), and (ii) tail trends in distributions of myelin-related appearance, as indicated by the kurtosis of T1/T2-FLAIR ratios (*k*) (see **Fig. 4a-c**).[21] Elevated *m* values suggest higher macromolecular density within the tract, while lower *m* values indicate reduced tissue density. The interpretation of *k* revolves around the apparent homogeneity within the tract: higher kurtosis (leptokurtic trends) suggests greater uniformity with most data clustered around a central value, whereas lower kurtosis (platykurtic trends) implies a non-uniform appearance with data distributed towards the tails.

As a whole aggregate, the white matter structure implicated in cognitive flexibility exhibited significant age-group differences in both *m* and *k* (*m*: t(30)=9.26, p <0.001; *k*: t(27)=3.24, p=0.003). These results indicate that, on average, the white matter structure of cognitive flexibility is significantly more dense and more homogenous among younger adults (greater *m*, leptokurtic trend in *k*) than among older adults

(lower *m*, platykurtic trend in *k*). The distribution of both variables, the structure's phenotypical MRI appearance (i.e., *m*) and the trends of myelin-related homogeneity (i.e., *k*), is shown in **Fig. 4d**. The statistical dispersion of these variables qualitatively depicts within-group age effects, and indicates that, on average, the density and homogeneity of the entire structure of cognitive flexibility declines in the later decades of life.

Table 2 shows quantification of the age-group effects for each white matter tract in the structure of cognitive flexibility. Although the entirety of the structure of cognitive flexibility carries significant differences with age-group membership among adults, once parceled out, not all segmented pathways carried significant differences in density or homogeneity between age groups. In particular, age-group related variations in tract homogeneity were not detected in the left frontal and parietal aslant tracts, right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, and the left dentatorubrothalamic and the right reticulospinal tracts. These findings indicate that, on average, the overall tissue homogeneity across the structure subserving cognitive flexibility is significantly different within those two periods of human life, but age-group-specific variations are selective to specific brain pathways (stars in **Table 2**; CI: 95%), with several white matter bundles which are also implicated in sensory, motor, learning, and sensory processing not displaying detectable differences across age groups.

Additionally, a significant age effect on the entirety of the white matter structure was observed among older but not among younger adults. The myelin-related homogeneity *k* was found to be inversely correlated with chronological age among older adults ($r = -0.643$, $p<0.001$, CI: 95%). This indicates that the WM integrity of these aggregated brain structures decreases with increasing age later in life. This relationship remained nearly unchanged when biological sex was considered ($r = -0.596$ and $r = -0.604$, $p<0.001$, for males and females, respectively).

Relationship between brain function and the structure of cognitive flexibility

Three distinct functions related to cognitive flexibility were considered: dimensional set-shifting, inhibitory control, and working memory.[1] The association between brain function and the white matter characteristics of the structure implicated in cognitive flexibility was evaluated for each brain pathway using Bayesian-Pearson correlations reported at $BF_{10}>100$ and 95% CI. These relationships were evaluated within age groups. **Figure 5** shows the white matter pathways that were found to present function-correlated appearance within each life period colored by functional construct (singular constructs or shared among multiple constructs). Tract-selective associations are detailed below for each age group.

Among younger adults, inhibitory control (e.g., t-score of performance in the flanker inhibitory control task) was the only domain exhibiting a significant direct association with white matter integrity. Specifically, *m* computed for the right uncinate fasciculus (UF) inversely correlated with inhibition ability (m_{UF} right: $r = -0.202$, $p=0.043$). Tract homogeneity (i.e., *k* values) was not significantly correlated with task

performance among younger adults. These results indicate that variability in white matter structure that exist in earlier adulthood were not observed to be significant explanatory variables of functional performance.

Among older adults, several distinct tracts carried significant correlations with brain functions. Performance in a set-shifting task was observed to negatively correlate with the appearance of the arcuate fasciculus (AF) bilaterally (m_{AF} right: r = -0.487, p<0.001; m_{AF} left: r = -0.488, p<0.001) and a unilateral, negative correlation was found between dimensional set-switching function and the left UF (k_{UF} left: r = -0.221, p = 0.003). Additionally, the homogeneity of the corticothalamic projection fibers (ChT) was found to carry a significant left-lateralized correlation with dimensional set-switching function (m_{Cth} left: r = -0.119, p = 0.048). Given the large degree of connectivity of the cingulum bundle—a white matter pathway that extends throughout all cerebral lobes, its white matter features were expected to correlate with flexibility function. However, curiously, performance in the set-switching task did not correlate significantly with the homogeneity of the cingulum bundle in isolation (k_{Cing} left: BF_{10} =0.776; and right: BF_{10} =0.120). Furthermore, significant correlations with functional scores were not observed for the right UF (*m*: BF_{10} =1.159, *k*: BF_{10} =0.191), nor for the CC (*m*: BF_{10} =1.269, *k*: BF_{10} =0.199) among older adults. These findings indicate that age effects that occur later in life are selective to specific tracts and affect one's dimensional set-switching abilities.

Performance in an inhibitory control task was found to be significantly correlated with the homogeneity of the association fibers of the corpus callosum (CC) in older adults (m_{CC}, r = -0.465, p < 0.001) and bilaterally with the ChT projections (m_{Cth} right: r = -0.477, p < 0.001; left: r = -0.479, p < 0.001). Additionally, a significant left-lateralized association was observed between inhibitory control and an increase (positive correlation) in homogeneity across the left cingulum bundle among older adults (k_{Cing} left: r = 0.157, p=0.011). These findings indicate that, in later life, inhibitory control function finds broader, de-centralized correlates with brain structure, including both hemispheres amply.

A single significant correlation with white matter integrity was observed for working memory abilities among older adults. Performance in a working memory task was positively correlated with homogeneity of fibers of the CC among older adults (k_{CC}, r = 0.172, p = 0.007). This result indicates an unspecific, but rather global, link exists between information updating abilities, such as working memory, and the brain's white matter in later life.

Discussion

Our findings support the life-period related differentiation of white matter tracts implicated in cognitive flexibility as a natural substrate of brain function. We found that (1) the wiring of cognitive flexibility is defined by a collection of specialized tracts, which present undifferentiated characteristics early in adulthood and significantly differentiated features in later life; (2) these macromolecular, myelin-related white matter properties are correlated with individual subprocesses of cognition which are intimately related

to the latent construct of cognitive flexibility function (i.e., dimensional switch, inhibition, updating)[1]; and (3) in the later decades of life, the myelin-related homogeneity of specific white matter tracts implicated in cognitive flexibility declines as a function of chronological age.

In this study, we used a novel data-driven approach to segment the average white matter structure subserving brain regions of cognitive flexibility using a white matter template of the human brain (i.e., the HCP1065 tractography based atlas). Figure 1 presents a diagram of the method, and the primary code used in this analysis is available as an open resource (github.com). Through a meta-analysis in Neurosynth (neurosynth.org), we defined the neural regions reportedly implicated in cognitive flexibility tasks, and then traced the structure wiring these brain regions using the HCP1065 template of quantitative anisotropy in white matter. This approach allowed us to analyze brain regions and tracts of specific interest to cognitive flexibility function while evaluating age effects and associations with functional domains. Furthermore, this method allowed us to evaluate age-effects across the entirety of the delineated structure and in a tract-selective manner. Importantly, here we present data that emphasizes the value of evaluating white matter structures in the context of specific brain functions.

White matter features are investigated in terms of MRI-derived quantities that assess macromolecular tissue properties (T1w, T2-FLAIR). This approach centers the work on consideration of age- and function-related variations in homogeneity within white matter bundles, rather than structural alignment or coherence, which can be assessed by diffusion-based measures (e.g., fraction of anisotropy, radial diffusivity). Commonly, radiologic evaluations of these MRI modalities point to hypo- or hyperintensities as degenerative features, and the appearance of white matter hyperintensities in T2-FLAIR is observed in pathology and brain injury.[22] Several studies focused on the coherence of white matter axons, which is a parameter measured by diffusion magnetic resonance imaging (MRI), document correlations between white matter thinning (reduced tissue coherence, reduced fraction of anisotropy [FA]) and neuropathology or decline in functional scores. Specifically in the context of cognitive flexibility, in vivo diffusion studies have documented that changes in parameters of diffusivity within the white matter, such as myelin-related radial diffusivity and fraction of anisotropy, are correlated with advanced age in healthy aging adults.[23] And concomitant functional decline has been attributed to originate from these changes in global and tract-specific incoherence of white matter.[13] Although intriguingly parallel to the knowledge of (micro)structural features of age-related pathology that appear in cerebral tissue of some older adults, these findings are restricted by the limitations of diffusion imaging measures. It remains unclear whether diffusion magnetic resonance imaging (MRI) can distinguish between features of natural white matter differentiation and pathology. The data presented in this work considers associations between macromolecular tissue features, cognitive flexibility function, and age; and the findings limitations are discussed.

The MRI dataset utilized in this work was acquired in adults with no documented pathology or cognitive deficits, and the variability among the sample is attributed to natural age.[24] Here, homogeneity of the white matter bundles was evaluated in terms of the asymmetry of the T1w/T2-FLAIR ratio distribution,

therefore encompassing tissue irregularities that may exist due to (natural age-related) hypo- or hyperintensities along the bundles. The volume of white matter hyperintensity was not considered explicitly, and the consequent limitations are discussed. In this work, hyperintensities were considered implicitly through the measure of kurtosis of the T1w/T2-FLAIR distribution, *k*.

The process of natural aging is defined in the context of neurosciences as the time-related deterioration of structural and functional cellular processes which results in maturation of brain tissues.[25] Peters and Folger have documented the remarkable resemblance between age- and pathology-related features of neuronal bodies and myelin stacks, emphasizing the relevance of function-centered investigations in aging studies. Age-related changes in neural structure and function overlap with features of late-life pathophysiology, and may manifest at different degrees across the lifespan in the presence of other risk factors. This poses an added challenge to studies on the effects of age in brain structure and function. In this work, we pose that, by deriving white matter structures related to cognitive flexibility from meta-analysis derived functional patterns, we explicit white matter structures representative of population-level structure-function associations (see **Fig. 1**, left panel). We further apply these structures to an independent dataset (the UK Biobank subset) which includes MRI and functional/behavioral data from adults with no impairment or pathology (see **Fig. 1**, right panel). Lastly, we derive associations and the effects of age. Although this methodological approach has limited specificity to pathological processes, it revels age-related macromolecular features of white matter directly associated with cognitive flexibility function and the effects of age.

The homogeneity across the entirety of the resulting white matter structure was found to differ between early (e.g., age<45 years) and later adulthood (e.g., age>65 years). However, not all tracts within the structure showed significant age-group differences (CI=95%) as shown in **Table 2**. These findings were computed after testing for equality of variances per tract (i.e., Lavene's $p>0.05$), and highlight that the white matter structure of cognitive flexibility differs in different periods of adult life, with older adults carrying a significantly less dense and homogeneous type across select tracts and appearing more left-lateralized (see **Fig. 5**).

The correlation between white matter homogeneity and function is also different in the different periods of life. We found that, among younger adults, the density and homogeneity of specialized tracts is not associated with the network-level functions of dimensional switch, nor with updating—but an inverse association does exist between the appearance of the right uncinate fasciculus and inhibitory control. On the other hand, among older adults, a left-lateralized pattern involving a few projection, association, and commissural fibers was found to correlate with the specific functions. These findings are consonant with the elevated functional network manifold eccentricity (i.e., a graph measure of how diffuse or decentralized networks are) found by Setton et al. 2023 in the same dataset.[14] Using multi-echo resting state BOLD series associated with this dataset,[1] the study found that canonical functional networks that are related to cognitive flexibility (e.g., default-mode, dorsal attention, fronto-parietal) are physiologically more integrated among

older adults, with particular components gaining greater functional specialization later in life. Our findings on the age-related specialization of these same subject's white matter further corroborate an argument for a fundamental myelin-related mechanism of brain aging that may exist in synchrony with functional aging.

The patterns of white matter aging and their relationship to function have been charted across the lifespan.[2,16] Grydeland et al. have shown that white matter ages differently in different areas of the brain, presenting either an inverted U-shaped dependence with chronological age or a long-lasting linear and positive relationship with aging (indicating myelination increases in some areas as one ages). Both these association types go hand-in-hand with cognitive performance.[3,5,6] Here, we show that age effects also exist at the system-structure level. For the structure of cognitive flexibility, it appears that the orchestrated differentiation of white matter tracts in the later periods of life describes structural regionalization and its consequent functional performance.

Limitations

A relevant limitation of our analysis is that these correlations were observed considering data collected in normative subjects and thus have limited extension to interpretation of clinical samples with deficits in cognitive flexibility. Moreover, here we investigated age effects across age groups and the effects of age within age groups using a cross-sectional sample. Therefore, these findings have limited sensitivity to individual variability in age-related features and their association with brain function. Additional studies are necessary to determine if the slope of decline in myelin-related homogeneity is an interesting predictor of functional impairment or risk and to further understand if tract-selective associations can explain functional deficits.

The fraction of radiologically visible white matter hyperintensity present within each white matter bundle was not considered explicitly in this work, thus limiting the specificity of our findings. Given that (i) hypo- or hyperintensities modify the skewness of the distribution of T1w/T2-FLAIR ratio, (ii) the dataset is composed of MRIs acquired in a normative sample, our findings are linked to white matter normative age-related features that appear at the population-level; and are limited to discern age effects from potential early signs of age-related pathology. Additional studies focused on measures specific to pathology are necessary to investigate the role of macromolecular hyperintensities in age-related decline.

A limited evaluation of cognitions was conducted in this study. Cognitive flexibility as measured by set-shifting and two related cognitions, inhibition and updating, were considered. Although a significant age-related, tract-specific distinction was found for the link between white matter homogeneity and function among these cognitions, a larger-scale investigation would be necessary to identify if this function-related differentiation of white matter is a generalized phenomenon across other functions.

Additionally, it possible that the functional patterns of cognitive flexibility among older adults may significantly differ from that of younger adults in the context of age-related reorganization for instance. In this work, meta-analysis was employed to derive the population-level functional pattern of interest; but it is possible that an intrinsic age-related difference exists between the ROIs of interest for cognitive flexibility

among older versus younger adults. Additional studies on age-related changes in functional topology in combination with diffusion MRI, performed at the individual level are necessary to investigate this limitation.

Furthermore, our study was limited to evaluation of white matter tracts that can be reliably segmented in anatomical images of the brain. For example, the anterior commissure was identified in the tractography as part of the average white matter structure of cognitive flexibility in humans. However, its segmentation was not feasible using anatomical images of the dataset due to poor voxel resolution (i.e., 1-2 mm), and therefore, its role and age effects remain elusive. Here we used a limited sample of the UK Biobank MRI dataset, granting that replicability of our findings in other samples is necessary. Analysis of additional datasets may enrich the understanding of age effects on macromolecular features of white matter that are related to cognitive flexibility. And additional studies, including delineation of the brain's fine tractography performed at the individual level, have the potential to substantiate the understanding of the specific roles that white matter tracts play in sustaining and changing cognitive flexibility function.

Materials and Methods

Brain Structure Implicated in Cognitive Flexibility

Meta-analysis

Neurosynth (Neurosynth.org) is a platform designed for automated, large-scale meta-analysis, which synthesizes brain map data from thousands of studies banked in the database. Our results reflect a limited search conducted early in 2024 when the database was reported to encompass data from 14,371 studies and 1,334 searchable terms.[19] To identify brain regions that are reported in neuroimaging studies to be active during dimensional set-shifting tasks, we used the term 'switching'. Noticeably, searchable terms available in the database are naturally limited by the existing literature archive which has consistently used 'switching' to describe dimensional set-shifting in neuroimaging studies. In this work, we aim to encompass those brain processes. Set-shifting is a component of the broader functional class of executive functioning, which also involves inhibitory control and information-updating abilities.[1] Here, the single term 'switching' was used aiming to evoke studies reporting brain function associated primarily with set-shifting.

Two brain maps and the under-layered anatomical volume (i.e., Montreal Neurological Institute MNI template) were obtained from the search in Neurosynth, including the uniformity test map and the association test map. Both maps are corrected for false discovery rate (FDR) with an expected FDR = 0.01. The uniformity map consists of all brain voxels reported in neuroimaging studies to be correlated with dimensional switching abilities. The association test map consists of voxels reported as also being correlated with other abilities, such as the term 'language' in a language-switching task, for example. The resulting specificity (S) of the term-search was computed as: $S = 1 - (N_a / N_u)$, where the ratio between the total number of voxels present in the association map (N_a) and the total number of voxels present in the uniformity test

map (N_u) are obtained. An arbitrary threshold of effect sizes >2 was applied to the association test map to remove spurious associations while estimating the sensitivity of the term-search. This threshold is set in Neurosynth to modify the association test map only (not the neural activations from meta-analysis). Voxels that are implicated in the 'shifting' term search may also be implicated in other searchable terms (e.g., learning). The effect size threshold controls the relative magnitude of association between a voxel and the term 'shifting' specifically, in comparison with the magnitude of association between the same voxel and other search terms in the database. A threshold of effect sizes >2 was chosen to estimate the specificity of the search in terms of voxels that are at least twice more likely to associate with the term 'shifting' specifically.

Using MRIcron (www.nitrc.org/projects/mricron), a list of MNI coordinates was extracted for all voxels in the meta-analysis uniformity map. A systematic search, including four distinct atlases of the human brain, was conducted to identify cortical and subcortical regions corresponding to the extracted coordinates. The Brainnectome (atlas.brainnetome.org), the Atlasing of the Basal Ganglia 'ATAG_basal_ganglia' (www.nitrc.org/projects/atag), FreeSurfer Desikan-Killiani cortical parcellation 'FreeSurfer_DKT_cortical' (surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation) and subcortical segmentation 'FreeSurfer_DKT_subcortical' (surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferVersion3) encompassed coordinates for all the listed regions.

Structural alignment to function

The Human Connectome Project 2 mm isotropic template of the white matter 'HCP1065_tractography' (brain.labsolver.org/hcp_template.html) was used to define the brain tracts underlying neural regions implicated in cognitive flexibility. In this work, we refer to this collection of tracts as the structure of cognitive flexibility. The HCP1065 tractography data is a group-average constructed from a total of 1,065 subjects, which was acquired using a multishell diffusion scheme with b-values equal to 990, 1985, and 2980 s/mm^2 with 90 diffusion sampling per b-shell. The in-plane resolution and the slice thickness were both equal to 1.25 mm. The diffusion-weighted images were resampled at 2.0 mm isotropic during q-space diffeomorphic reconstruction (QSDR)[26] reconstruction to obtain a map of the spin distribution function.[27] The final white matter template consisted of a 2 mm isotropic map of quantitative anisotropy (QA) values.

Fibers were reconstructed from the QA template in DSI-Studio (dsi-studio.labsolver.org),[28,29] using mean diffusion distance of 1.25 mm, three orientations per fiber, angular cut-off of 45, step size of 1.0 mm, minimum length of 5 mm, spin density function smoothing of 0.0, maximum length of 400 mm, and a QA threshold set to 0.1 (i.e., selection based on the diffusion signal density in the colony-stimulating factor). Tracts with lengths shorter than 5 or longer than 400 mm were discarded, and 25 topology pruning iterations were used to trace 10,000,000 streamlines from the template.

We then pursued a parallel approach for alignment of functional and structural data as previously reported.[30,31] Anatomical regions identified in the meta-analysis uniformity map were separated into two separate files containing cortical or subcortical regions of interest. Each were loaded into DSI-Studio atop of the QA template of average adult white matter and dilated to expand the region labels across the grey-white matter boundary. Neural regions in the cortical ribbon were dilated 8 mm, and voxels located in subcortical structures were dilated 4 mm because the gray-white matter interface in subcortical structures is demonstrably thinner. Dilation-filled voxels contained only voxels outside regions of interest. Tracts obtained from the whole brain tractography were converted from endpoints to regions of interest. Streamlines not terminated in the meta-analysis-derived regions of interest were deleted. Finally, the HCP1065 atlas of white matter parcellations was used for recognition and clustering of the remaining streamlines into anatomical brain tracts. The identified brain tracts compose the average structure of white matter implicated in cognitive flexibility function among adult humans.

Comparative Cohort Analyses

To investigate the effects of age in the white matter structure implicated in cognitive flexibility and its relationship to brain function, we computed myelin-related MRI features of white matter density and homogeneity for a subset of the UKBiobank MRI data (n=301), which has a companion functional and behavioral dataset[24] and a collection of related multi-component functional connectivity attributes previously mapped.[14] Limited functional, behavioral, and MRI data (T1w, T2-FLAIR, functional MRI) is available for this dataset in OpenNeuro (openneuro.org/datasets/ds003592/versions/1.0.13).

Dataset

The dataset is comprised of discrete samples of 301 healthy younger and older adults who have been characterized by behavioral, self-report, and functional and structural brain MRI assessments. The distribution of age within each age group were tested for normality by computing the kurtosis and skewness over the age variables. The group of younger adults had a mean age equal to 22±3 years (43% male; 57% female), and older adults had a mean age equal to 68±6 years (45% male; 54.2% female; 0.8% non-reported biological sex). Additional demographic characteristics and description of their original MRI data have been reported previously.[24]

Task-based measures related to cognitive flexibility

Set-shifting, inhibitory control, and information updating (evaluated through a working memory task) are abilities with membership within the broader cognitive category of executive functioning. In this work, we focused on assessing cognitive flexibility through the primary component of dimensional switching, which is closely related to set-shifting and also relies on inhibition and updating. To investigate the associations between white matter features and brain function using behavioral scores, we selected three

tasks from the NIH Toolbox (www.nihtoolbox.org) cognitive battery available in the dataset. The dimensional change card sorting (DCCS), flanker inhibitory control, and list sorting working memory (LSWM) tasks were used. Normalized t-scores computed from task performance are available for the dataset and were used as individual measurements of function.

Age effects on functional performance

The behavior of the task score data across the entire age range was evaluated qualitatively (without model), and the outcome plots express distributions within 95% CI. The distribution of performance scores in each task per age group was tested for inequality using an independent sample t-test. Within each age group, the relationship between age and performance in set-shifting, inhibitory control, and working memory tasks was assessed in JASP by linear regression using a forward model $y = \beta_0 + x.\beta_1 + \varepsilon$, where β_0 is the intercept, β_1 is the model coefficient, and ε is the standard error. T-statistics and p-values are reported at significance level $p \leqq 0.05$, and the influence of sex as a factor was tested. Missing cases were handled listwise.

MRI features

MRI features of macrmolecular properties of the white matter were computed for all subjects included in the UK Biobank MRI dataset. Anatomical data weighted in T1 and fluid attenuated inversion recovery T2 (T2-FLAIR) underwent orientation alignment using afni (afni.nimh.nih.gov) '3dresample –prefix' function.[32] T2-FLAIR images were resampled to match spatial resolution with T1w using Matlab (www.mathworks.com) 'imresize3' function. Volumes were then co-registered using FLIRT, a linear triangulation method in FSL (fsl.fmrib.ox.ac.uk/fsl), skull stripped using FSL 'bet2' function, and masks of brain tissue and non-brain tissue were saved.[33] Image intensities were standardized using a non-brain-tissue based equalization method,[34] which computes intensity corrections using the intensity distribution of stripped tissue (e.g., non-brain tissue). The standardization was then applied to brain tissue voxel-wise using a z-score criteria, which is computed in respect to the standard intensity distribution of the ICBM152 anatomical brain atlas, including the cerebellum. Intensity in T2-FLAIR was checked for field bias using a standard ghosting criteria.[35] A point-by-point map of T1/T2-FLAIR ratio was then computed for each subject.[21] Using Matab 'imregister' function which employs an 'affine3' method for volumetric overlay, the HCP1065 anatomical template of the brain was warped to each individual subject's T1w space, keeping the subject's anatomy intact; the transformation matrix was then applied to the atlas' parcellation mask. An atlas-based parcellation mask of the white matter was then applied to extract properties of 68 anatomical parcels from each subject's brain (cranial nerves were not considered). In the case of a parcel overlay post affine transformation, voxel membership was selected randomly.

Parcel-specific mean intensity in T1w (*m*) was computed as a measure of comparable macromolecular density with greater *m* signifying greater macromolecular density along each tract, and the

counterpart of lower *m* signifying reduced tissue density.[36] *m* was calculated as the mean value in a distribution of standardized T1w values obtained from voxels within each white matter parcel. Parcel-specific kurtosis of the T1/T2-FLAIR ratio was computed as a myelin-related measure of tissue homogeneity throughout each white matter structure. The related biological interpretation of *k* is that greater apparent homogeneity is associated with greater kurtosis (e.g., leptokurtic trends), or having most of the data centered around a common value; whereas lower kurtosis (i.e., platykurtic trends), or carrying more data in the tails of the distributions, are interpreted as nonhomogeneous appearance along each brain pathway.[37] *k* was not computed for subjects with no T2-FLAIR data. Measures representative of global features of the white matter implicated in cognitive flexibility, *m* and *k*, were also computed for the conglomerate of white matter tracts. *m* and *k* were calculated as the mean and kurtosis of a larger distribution (not tract-specific) containing data from voxels of all 32 implicated bundles. Whole-aggregate *m* and *k* represent the mean T1w (post standardization) and the kurtosis of T1w/T2-FLAIR across the entire white matter structure subserving cognitive flexibility function.

Age Effects on White Matter

The effects of age were evaluated for each white matter parcel (i.e., brain pathway) at age-group level using independent samples Student's t-test in JASP (jasp-stats.org). Missing values were handled by excluding cases per dependent variable. Levene's test was run to check homogeneity of variances, and interpretation was given to probability values $p > 0.05$. Furthermore, the effects of age were also evaluated for each parcel among subjects within each age group using Bayesian-Pearson correlation method in JASP.[38] Pearson's rho was used to estimate population correlation coefficient, no valence was assumed, and a Bayes factor equal 10 (BF_{10}) was chosen for likelihood boundary.

Brain Structure and Function Relationships

Associations between behavioral task performance and MRI features of each brain parcel were examined using Bayesian-Pearson correlation method in JASP.[38] Pearson's rho was used to estimate population correlation coefficient, no valence was assumed, and a Bayes factor equal 10 (BF_{10}) was chosen for likelihood boundary.

Data, Materials, and Software Availability

All code utilized for analysis is available on GitHub and can be found at this link: https://github.com/TatianaWolfe/NeuroAge_v5. Subjects' original images and functional and behavioral data are available in OpenNeuro and can be found at this link: 200219.

Acknowledgments

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Figures and Tables

Figure 1.

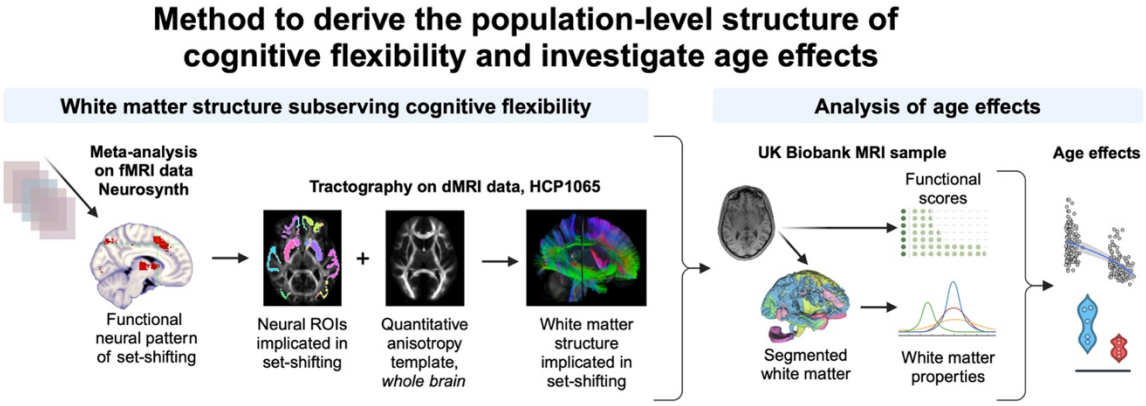

Figure 1 - Methodological approach to investigate age effects in brain white matter structures implicated in cognitive flexibility function. First, the functional neural pattern is identified by meta-analysis using neurosynth (left) as a collection of imaging voxels reportedly implicated in set-shifting function in human experiments. These voxels derived from functional magnetic resonance imaging (fMRI) data are then considered neural regions of interest (ROIs), which serve as input for diffusion-based tractography (center). The Human Connectome Project (HCP) 1065 template of diffusion MRI (dMRI) quantitative anisotropy is used to trace the white matter structure interconnecting set-shifting ROIs. Tracts are anatomically identified using cluster recognition in DSI-studio. The collection of tracts identified as implicated in set-shifting function composes the structure of cognitive flexibility referred in this work. Next, a comparative cohort analysis is conducted using a subset of the UK Biobank imaging data (n=301), which has a companion table of cognitive and behavioral scores for set-shifting and related functions. Following segmentation of white matter bundles at the individual level among the sample, two macrostructural properties of the white matter are computed (right): the mean intensity in standardized T1w MRI (*m*), and the kurtosis of the distribution of T1w/T2-FLAIR ratio (*k*). These properties are computed per subject, for each white matter bundle individually and for the whole aggregate. Lastly, the effects of age are quantified by modeling the relationship between the image-derived macrostructural properties of white matter, functional scores, and age or age-group.

Figure 2.

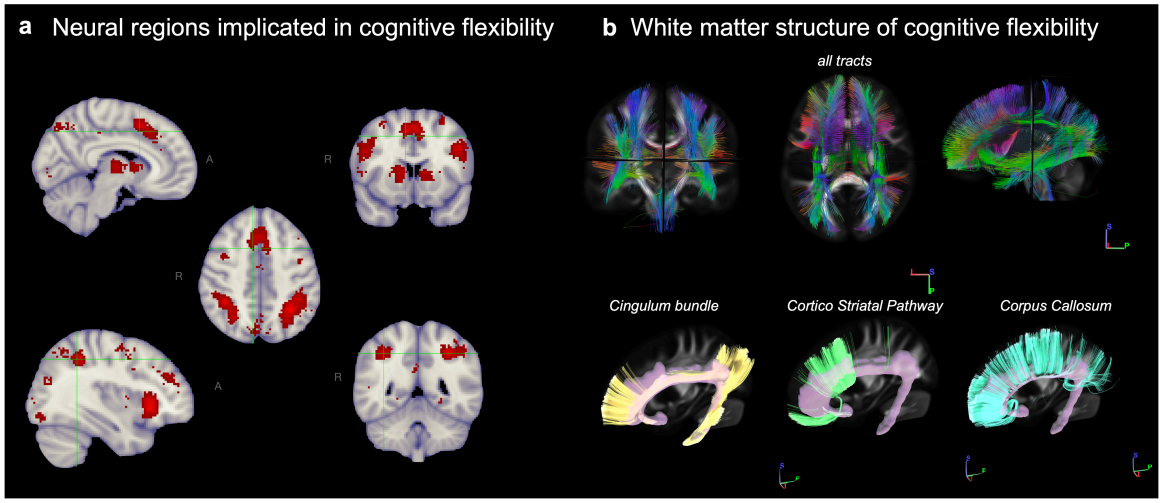

Figure 2 - a. Neural regions active during cognitive flexibility tasks (e.g., set-shifting; 95% CI) include the cingulate cortex, several areas of the orbito-frontal and frontal cortex, in addition to the putamen, caudate, and striatum. The complete list of implicated regions derived from term meta-analysis can be found in **Table 1**. **b.** The underlying white matter structure of cognitive flexibility function (top row) was found to be composed of 38 independent tracts also listed in **Table 1**. The intricacy of this wiring is illustrated by the common convergency of the left cingulum bundle, the cortico-striatal pathway, and the corpus callosum into distinct regions of the cingulate, prefrontal, and frontal cortex, and across the various neural areas of cognitive flexibility. Twenty million tracts were traced by QSDR reconstruction (DSI-studio.labsolver.org)[10] using the quantitative anisotropy tractography data from the Human Connectome Project atlas of the adult white matter.

Figure 3.

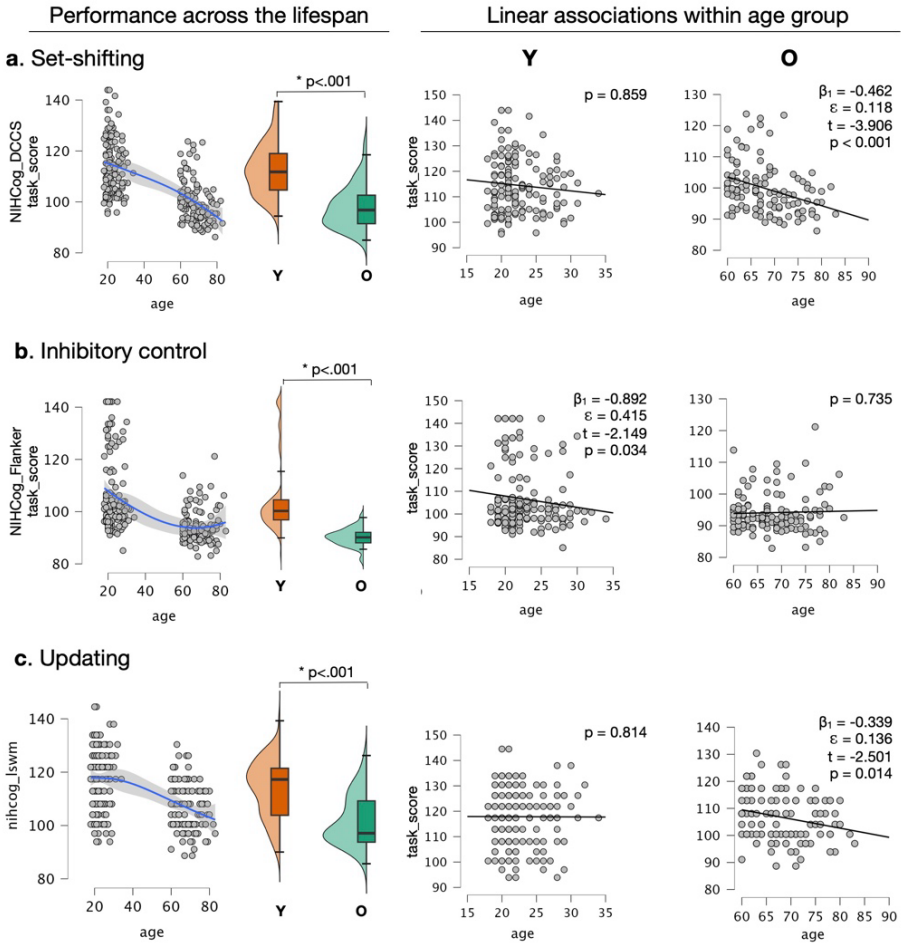

Figure 3 – The consonance between brain process related to cognitive flexibility function and age. **a.** Set-shifting abilities exhibited a logarithmic relationship (left panel; CI: 95%) across age ranges of earlier and later adulthood, significantly differing between groups (center panel box plots; $p<0.001$). Among older adults, set-shifting exhibited a significant linear relationship with age (β_1= -0.462, Ɛ = 0.118, t = -3.906, $p<.001$) but not among younger adults ($p = 0.859$). **b.** Inhibitory control abilities exhibited a hammock-shaped relationship (left panel, CI: 95%) across the same age ranges, similarly differing between the older and younger age groups (center panel box plots; $p<0.001$). A linear association between age and inhibitory control function was found only among younger adults (β_1= -0.892, Ɛ = 0.415, t = -2.149, $p = 0.034$), but not among older adults ($p = 0.735$). **c.** Working memory abilities exhibited overall behavior similar to set-shifting, varying significantly between age groups (left panel; $p<0.001$), and presenting an inverse linear association with age among older adults (β_1= -0. 339, Ɛ = 0.136, t = -2.501, $p=0.014$), but not among younger adults ($p = 0.814$). These results explicit the nature of function-specific associations between biological age and human abilities, further emphasizing intrinsic relationships that exist across the age strata.

Figure 4.

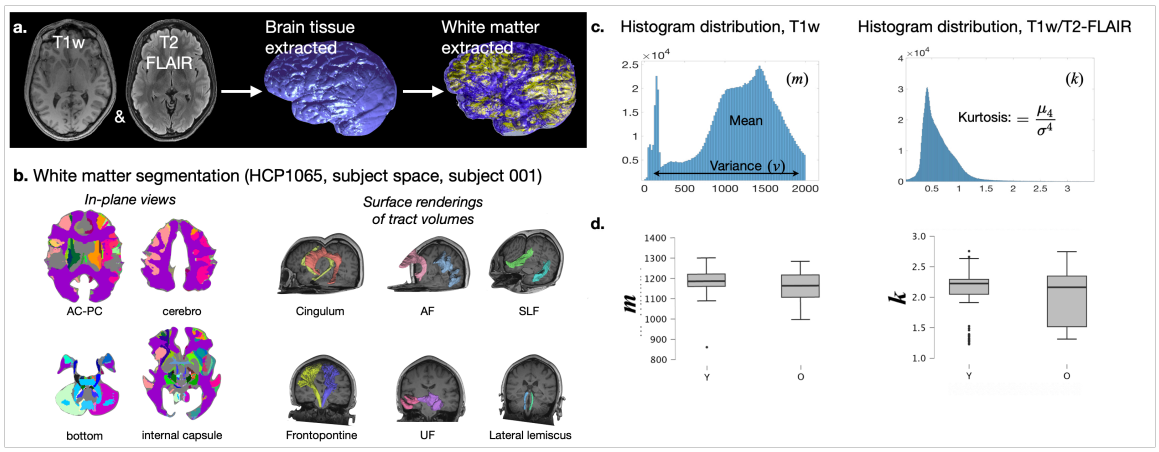

Figure 4 – a. Extracted brain white matter showing the representativeness of the encased volume. **b.** Region segmentation of white matter in subject's native space showing the HCP1065 atlas-based parcels in consecutive axial planes (top) and their surface rendering (bottom). **c.** Distributions of image-derived parameters of macrostructural integrity for a representative case. *m*: region-specific T1w mean; *k* region-specific kurtosis of the T1w/T2-FLAIR ratio. **d.** As a whole, the homogeneity of the white matter structure of cognitive flexibility significantly differs among younger and older adults ($t(30)=9.26$, $p<0.001$ for *m,* and $t(27)=3.24$, $p=0.003$ for *k*).

Figure 5.

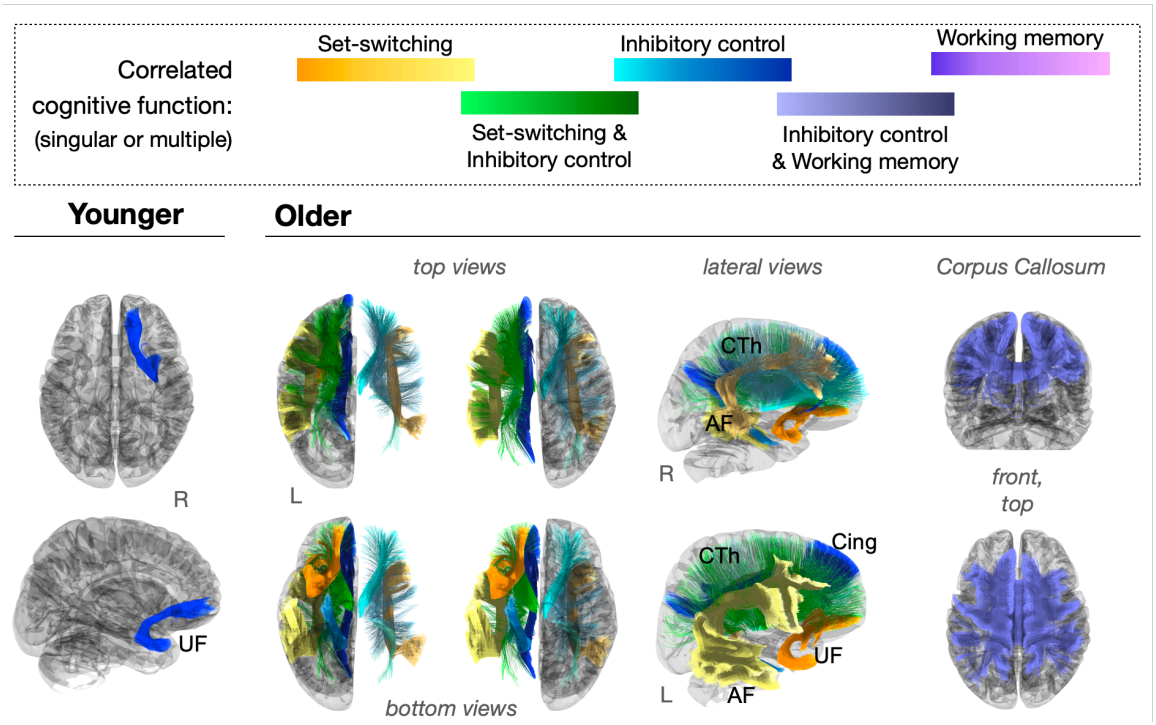

Figure 5 – Age effects on brain tracts that present function-correlated appearance in MRI. A subcollection of brain tracts among those with membership in the circuit of cognitive flexibility show significant correlations between white matter homogeneity and functional performance in older adults but not in younger adults. This finding indicates that age-related changes in cognitive flexibility function are reflected in the integrity of specific white matter compartments. Tract colors indicate the correlated cognitive function. AF: arcuate fasciculus; UF: uncinate fasciculus; CTh: corticothalamic projections; Cing.: cingulum bundle.

Table 1. Neural regions of cognitive flexibility and its integrating white matter structure

Neural Regions	Atlas Membership	White Matter Pathways	Atlas label
Striatum_L	ATAG basal ganglia	Cortico_Striatal_Pathway_L	2
Striatum_R	ATAG basal ganglia	Cortico_Striatal_Pathway_R	3
left_superior_temporal	FreeSurfer DKT_cortical	Cortico_Spinal_Tract_L	4
right_superior_temporal	FreeSurfer DKT_cortical	Cortico_Spinal_Tract_R	5
left_superior_parietal	FreeSurfer DKT_cortical	Corticothalamic_Pathway_L	6
right_superior_parietal	FreeSurfer DKT_cortical	Corticothalamic_Pathway_R	7
left_inferior_parietal	FreeSurfer DKT_cortical	Corticopontine_Tract_L	10, 12, 16 (bundled)
right_inferior_parietal	FreeSurfer DKT_cortical	Corticopontine_Tract_R	11, 13, 17 (bundled)
left-Putamen	FreeSurfer_DKT_subcortical	Arcuate_Fasciculus_L	20
right-Putamen	FreeSurfer_DKT_subcortical	Cingulum_L	22
left-Caudate	FreeSurfer_DKT_subcortical	Cingulum_R	23
right-Caudate	FreeSurfer_DKT_subcortical	Extreme_Capsule_L	24
left_posterior_cingulate	FreeSurfer DKT_cortical	Extreme_Capsule_R	25
right_posterior_cingulate	FreeSurfer DKT_cortical	Frontal_Aslant_Tract_L	26*
left_superior_temporal	FreeSurfer DKT_cortical	Frontal_Aslant_Tract_R	27*
right_superior_temporal	FreeSurfer DKT_cortical	Parietal_Aslant_Tract_L	26*
left_caudal_anterior_cingulate	FreeSurfer DKT_cortical	Parietal_Aslant_Tract_R	27*
right_caudal_anterior_cingulate	FreeSurfer DKT_cortical	Inferior_Fronto_Occipital_Fasciculus_L	28
SFG_L_7_2	Brainnectome	Inferior_Fronto_Occipital_Fasciculus_R	29
SFG_R_7_2	Brainnectome	Inferior_Longitudinal_Fasciculus_L	30
SFG_L_7_4	Brainnectome	Inferior_Longitudinal_Fasciculus_R	31
SFG_R_7_4	Brainnectome	Middle_Longitudinal_Fasciculus_L	32
MFG_L_7_2	Brainnectome	Middle_Longitudinal_Fasciculus_R	33
MFG_R_7_2	Brainnectome	Superior_Longitudinal_Fasciculus2_L	34
left_lateral_orbitofrontal	FreeSurfer DKT_cortical	Superior_Longitudinal_Fasciculus2_R	35
left_medial_orbitofrontal	FreeSurfer DKT_cortical	Uncinate_Fasciculus_L	38
left_rostral_middle_frontal	FreeSurfer DKT_cortical	Uncinate_Fasciculus_R	39
left_superior_frontal	FreeSurfer DKT_cortical	Vertical_Occipital_Fasciculus_L	40
left_caudal_middle_frontal	FreeSurfer DKT_cortical	Anterior_Commissure	42
right_caudal_middle_frontal	FreeSurfer DKT_cortical	Corpus_Callosum	43
right_medial_orbitofrontal	FreeSurfer DKT_cortical	Dentatorubrothalamic_Tract_L	62
left_lateral_orbitofrontal	FreeSurfer DKT_cortical	Dentatorubrothalamic_Tract_R	63
right_lateral_orbitofrontal	FreeSurfer DKT_cortical	Reticulospinal_Tract_L	64
ight_rostral_middle_frontal	FreeSurfer DKT_cortical	Reticulospinal_Tract_R	65
right_superior_frontal	FreeSurfer DKT_cortical		
left_medial_orbitofrontal	FreeSurfer DKT_cortical		

* Anatomical parcels of fiber bundles which were modeled as bundles in the comparative analysis.

Table 2.

Table 2 – Age-group effects on myelin-related homogeneity per white matter tract in the structure of cognitive

Atlas numeric label (HCP)	Younger (n = 180)				Older (n = 121)				Group Differences (Independent Samples T-Test)							
									m				k			
	Valids	m (coef. var)	Valids	k (coef. var)	Valids	m (coef. var)	Valids	k (chef. var)	t	df	p		t	df	p	
2	178	112.0 (.380)	139	0.295 (.417)	119	85.8 (.564)	109	0.272 (.558)	1.288	245	0.199		4.929	295	< .001	*
3	179	149.8 (.355)	140	0.439 (.404)	120	115.1 (.548)	110	0.371 (.515)	2.915	247	0.004	*	5.12	297	< .001	*
4	180	156.8 (.356)	139	0.464 (.543)	120	128.6 (.536)	110	0.400 (.505)	2.18	248	0.030	*	3.891	298	< .001	*
5	179	114.9 (.526)	140	0.510 (.649)	120	98.8 (.735)	110	0.405 (.733)	2.609	247	0.010	*	2.082	297	0.038	*
6	180	149.7 (.434)	139	0.391 (.559)	120	125.2 (.634)	110	0.394 (.754)	-0.117	248	0.907		2.923	298	0.004	*
7	179	182.2 (.363)	139	0.427 (.385)	120	142.9 (.559)	110	0.402 (.520)	2.825	247	0.005	*	4.618	297	< .001	*
10, 12, 16	178, 178	123.5 (.363)	138, 138	0.334 (.362)	120	117.0 (.453)	109	0.302 (.562)	1.772	246	0.078		3.735	296	< .001	*
11, 13, 17	179, 176	136.4 (.354)	139, 136	0.398 (.374)	120	129.4 (0.654)	110	0.411 (.347)	3.137	247	0.002	*	5.157	297	< .001	*
20	178	74.2 (.725)	139	0.414 (0.985)	119	92.0 (.654)	110	0.595 (.990)	-2.857	245	0.005	*	-2.659	295	0.008	*
22	179	248.1 (.422)	139	0.538 (.450)	120	208.3 (.620)	110	0.473 (.606)	1.936	247	0.054		2.932	297	0.004	*
23	179	172.8 (.360)	139	0.484 (.387)	120	134.2 (.557)	110	0.411 (.520)	2.93	247	0.004	*	4.84	297	< .001	*
24	179	166.6 (.360)	139	0.471 (.376)	120	130.4 (.555)	109	0.404 (.528)	2.704	247	0.007	*	4.703	297	< .001	*
25	179	162.6 (.361)	139	0.473 (.381)	120	138.1 (.538)	110	0.423 (.525)	1.958	247	0.051		3.175	297	0.002	*
26*	178	148.5 (.417)	138	0.424 (.447)	119	134.8 (.555)	110	0.399 (.591)	0.912	245	0.363		1.714	295	0.088	
27*	180	164.9 (.374)	140	0.491 (.421)	120	134.8 (.556)	109	0.427 (.560)	2.275	248	0.024	*	3.8	298	< .001	*
26*	178	148.5 (.417)	138	0.424 (.447)	119	134.8 (.555)	110	0.399 (.591)	0.912	245	0.363		1.714	295	0.088	
27*	180	164.9 (.374)	140	0.491 (.421)	120	134.8 (.556)	109	0.427 (.560)	2.275	248	0.024	*	3.8	298	< .001	*
28	180	178.8 (.375)	140	0.488 (.390)	120	151 (.553)	108	0.447 (.537)	1.491	248	0.137		3.177	298	0.002	*
29	178	195.9 (.402)	138	0.530 (.420)	119	180.2 (.605)	109	0.517 (.597)	0.411	245	0.682		1.438	295	0.152	
30	178	149.3 (.506)	138	—	119	138 (.661)	109	0.400 (.659)	—	—	—		1.162	295	0.246	
31	178	105.0 (.458)	138	0.323 (.482)	119	78.3 (.563)	109	0.258 (.543)	3.374	245	< .001	*	4.844	295	< .001	*
32	178	64.6 (.538)	138	0.224 (.765)	119	48.1 (.726)	109	0.225 (.943)	-0.007	245	0.995		4.018	295	< .001	*
33	178	175.6 (.370)	138	0.442 (.409)	119	149.7 (.575)	110	0.393 (.542)	1.921	245	0.056		2.932	295	0.004	*
34	178	173.8 (.378)	138	0.421 (.618)	119	154.1 (.569)	110	0.418 (.643)	0.097	245	0.923		2.201	295	0.029	*
35	179	170.2 (.365)	139	0.458 (.386)	120	138.1 (.555)	109	0.396 (.533)	2.544	247	0.012	*	3.979	297	< .001	*
38	180	191.7 (.379)	140	0.514 (.511)	120	163.6 (.566)	108	0.462 (.556)	1.567	248	0.118		2.942	298	0.004	*
39	178	158.0 (.381)	138	Inf (NaN)	119	134.4 (.558)	0	0.470 (.647)	NaN				3	295	0.003	*
40	178	162.4 (.404)	138	0.558 (.585)	119	137.3 (.564)	109	0.516 (.702)	0.955	244	0.340		3	295	0.003	*
43	178	129.8 (.368)	138	0.606 (.618)	119	109.4 (.545)	0	0.577 (.748)	0.552	245	0.581		3.263	295	0.001	*
62	178	101.7 (.528)	138	0.347 (.557)	119	100.5 (.572)	0	0.374 (.596)	-1.03	245	0.304		0.176	295	0.860	
65	178	76.4 (.454)	138	—	119	74.9 (.579)	110	0.304 (.529)	—	—	—		0.325	295	0.745	

* Significantly differs among age groups.

† Variations in the number of valid cases per parcel-specific variables (e.g., *m* or *k*) stem from bootstraps in parcellation method, absence of T2-FLAIR scan in the dataset.