

Stable brain architecture but flexible dynamics: distinct structure - function coupling signatures link aging and genetic Alzheimer's risk to cognitive decline in 34,067 adults

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Abstract

Understanding how a stable structural connectome supports flexible cognition, especially in aging, is a fundamental question in neuroscience. While static structure-function coupling (SFC) is well-studied, the temporal variability of structure-function coupling, referred to as dynamic SFC (DSFC), remains poorly characterized, particularly in relation to aging and cognitive outcomes. Leveraging MRI data from 34,067 UK Biobank participants (ages 45-82), we characterized the distinct roles of SFC and DSFC in aging, cognition, and health. We found that SFC and DSFC followed spatially divergent aging trajectories: SFC declined primarily in sensorimotor systems, whereas DSFC decreased most prominently in higher-order networks. Both SFC and DSFC in higher-order networks were positively correlated with cognitive performance (e.g., fluid intelligence). However, the associations with mental and physical health diverged spatially between the two measures: reduced DSFC was predominantly linked to health burden in high-order default/limbic networks, whereas weakened SFC was primarily associated with health burden in low-order sensory-motor networks. Genetic analyses revealed that Alzheimer's risk, specifically APOE $\epsilon 4$ dosage, significantly reduced DSFC in higher-order cognitive networks and SFC in low-order visual cortex. Mediation analyses further suggested that SFC and DSFC partially mediated the associations of aging and APOE $\epsilon 4$ dosage with cognitive performance. These findings suggest that static and dynamic coupling capture complementary aspects of brain organization: static SFC reflects the degree of functional alignment with structural architecture, whereas DSFC captures temporal variability in this alignment. Together, our results highlight these dual mechanisms as crucial for maintaining cognitive flexibility, providing potential biomarkers for age-related neurodegeneration.

Introduction

One of the central challenges in neuroscience is understanding how a relatively stable structural connectome gives rise to flexible and adaptive brain functional dynamics, a key feature that supports complex behaviors and higher cognitive functions (Honey, Thivierge, & Sporns, 2010; Ju & Bassett, 2020; Park & Friston, 2013; Uddin, 2013). This characteristic is captured by structure-function coupling (SFC) (Fotiadis et al., 2024; Suárez, Markello, Betzel, & Misic, 2020), which quantifies the constraints that structural connectivity (SC) imposes on the synchrony of functional activity, or functional connectivity (FC) at the regional level (Fotiadis et al., 2023; Gu, Jamison, Sabuncu, & Kuceyeski, 2021; Preti & Van De Ville, 2019). The capacity of the brain to maintain functional organization within a structurally constrained architecture is associated with cognitive performance and health outcomes.

Given the foundational role of structure-function flexibility in cognitive performance, understanding how this relationship changes with aging is crucial for understanding cognitive decline and even general health deterioration in older adults. Although research has identified the multi-level impacts of aging on SC and FC, including white matter damage, myelin degradation of SC, and the breakdown of functional network modularity (Deery, Di Paolo, Moran, Egan, & Jamadar, 2023; Perez, Hernandez, Wulfekuhle, & Gratton, 2024) (Yang et al., 2023), the understanding of how SC and FC dynamically interact - and how this interaction changes with aging - remains in its early stages. While several studies demonstrated

developmental SFC changes during childhood and adolescence (Baum et al., 2020; Tooley et al., 2025; Vandewouw, Hunt, Ziolkowski, & Taylor, 2021; Z. Zhang et al., 2025), examinations of age-related changes across the broader lifespan are scarce (Zamani Esfahlani, Faskowitz, Slack, Mišić, & Betzel, 2022). These studies report that aging is associated with widespread reductions in SFC, particularly in unimodal sensory and motor cortices, with the most pronounced declines observed in the visual and sensorimotor areas, likely due to the loss of white matter myelination (Vandewouw et al., 2021; Zamani Esfahlani et al., 2022). Abnormalities in SFC have also been observed in aging-related brain diseases such as Alzheimer's disease (Cao et al., 2020; Dai et al., 2019; Sun et al., 2014), Parkinson's disease (Zarkali et al., 2021), and stroke (J. Zhang et al., 2017).

Despite these findings, most research has treated SFC as a static feature, largely overlooking its dynamic properties. Over the past decade, it has become increasingly clear that brain function is inherently dynamic, with functional connectivity exhibiting time-varying fluctuations that are non-random and organized (Allen et al., 2012; Hutchison et al., 2013; Preti, Bolton, & Van De Ville, 2016). Given the relative stability of brain structure, functional organization exhibits temporal variability that may reflect changes in the relationship between structural constraints and ongoing neural activity. Therefore, to fully understand the relationship between brain structure and function, it is essential to consider both the static and dynamic aspects of structure-function coupling. Some studies have already investigated the dynamic characteristics of structure-function coupling (Fotiadis et al., 2023; Z.-Q. Liu et al., 2022; Preti & Van De Ville, 2024; Z. Zhang et al., 2024) and found SFC was moderated by cognitive demands (Griffa, Amico, Liégeois, Van De Ville, & Preti, 2022) and state of consciousness (drowsiness) (Preti & Van De Ville, 2024), and greater temporal variability in structure-function coupling has been observed in higher-order networks involved in complex cognitive functions which show ageing related changes, such as attentional and memory tasks (Fotiadis et al., 2023; Z.-Q. Liu et al., 2022). While much of this research has focused on children and younger adults, there is a notable gap in our understanding of how these dynamics evolve across the lifespan, particularly in middle-to-late adulthood, how they contribute to cognitive decline and changes in health status, and what genetic and environmental factors influence them.

To address these gaps, we combined traditional SFC methods with dynamic analysis techniques, leveraging multimodal neuroimaging data from 34,067 participants (ages 45–82) in the UK Biobank to calculate both static SFC and dynamic SFC (DSFC) (Fig. 1). Our goal was to investigate how both SFC and DSFC evolve across the adult lifespan and how these dynamics change with aging from 45 to 82. Specifically, we aimed to answer three interrelated questions: (1) How do SFC and DSFC change across middle-to-late adulthood (ages 45–82), and do they follow distinct aging trajectories? (2) To what extent do SFC and DSFC differentially support cognitive function and relate to mental and physical health burden? (3) What genetic risk factors (e.g., APOE ϵ 4) and environmental or lifestyle factors modulate these coupling measures and their downstream cognitive effects? By integrating computational approaches with multimodal data encompassing neuroimaging, genetic, and deep phenotypic data in the largest sample to date, our study examines how static and dynamic aspects of structure-function

coupling vary across adulthood and how these measures are associated with cognition, health, and genetic risk factors.

Results

Static and Dynamic Structure-Function Coupling have distinct spatial patterns

To characterize the temporal variability of structure-function coupling (SFC), we computed dynamic structure-function coupling (DSFC) using a sliding-window approach. The window length was set to 30 TRs ($0.735 \text{ s} \times 30 = 22.05 \text{ s}$) with a step size of 5 TRs. Within each window, a functional connectivity (FC) matrix was estimated using Pearson's correlation across the resting-state fMRI signals of all 360 regions of interest (ROIs) using the Glasser parcellation (Matthew F. Glasser et al., 2016). The structural connectivity (SC) matrix quantifies anatomical connections based on the number of streamlines from probabilistic tractography between each pair of ROIs in the Glasser parcellation. For a given brain region, the SFC at each time window was quantified as the Spearman rank correlation between its functional- and structural-connectivity profile. Static SFC was defined as the mean SFC across all windows, whereas DSFC was defined as the standard deviation of SFC across windows, reflecting temporal variability in structure-function coupling. We computed SFC and DSFC values for each of the seven canonical functional networks defined by the Yeo 7 network parcellation: the visual network (VN), sensorimotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FPN), and default mode network (DMN).

At the group level, we first averaged SFC and DSFC across individuals (Fig. 2A) and then organized the seven canonical functional networks into four quadrants based on their mean SFC and DSFC values (Fig. 2B). The VN and DAN exhibited the highest static SFC, while the FPN showed the highest DSFC. The VN and DAN tended to exhibit high SFC with low DSFC, while the LN showed low coupling and low dynamics. The FPN was characterized by high SFC and high DSFC, while the DMN, VAN, and SMN generally fell in between, exhibiting medium SFC and medium DSFC. The validation analyses showed that the spatial organization and individual-level variability of SFC/DSFC remained consistent across different structural connectome measures, parcellation, and time window size (see *Robustness and reproducibility analyses*).

SFC and DSFC show distinct aging effects

To examine the impact of aging on SFC and DSFC, we employed linear mixed models (LMMs) to assess the associations between age and structure-function coupling measures across brain networks. Both SFC and DSFC showed significant age-related reductions, although they exhibited distinct spatial patterns (Fig. 2C). The decline in SFC was most pronounced in the sensorimotor network (SMN: standardized $\beta = -0.204$, $t = -36.30$, $p < 0.001$). In contrast, DSFC demonstrated more pronounced age-

related associations, with the largest reductions observed in higher-order networks, including the limbic network (LN: $\beta = -0.224$, $t = -40.91$, $p < 0.001$), default mode network (DMN: $\beta = -0.196$, $t = -35.71$, $p < 0.001$), and frontoparietal network (FPN: $\beta = -0.155$, $t = -27.73$, $p < 0.001$) (Table S2&3). To examine potential nonlinear age effects, we additionally included a quadratic age term in the model. Although several networks showed significant quadratic age associations, these effects were substantially smaller than the linear age effects (standardized β range: -0.041 to -0.012 for SFC and -0.033 to -0.012 for DSFC), indicating that age-related alterations in SFC and DSFC were predominantly characterized by approximately linear declines with modest nonlinear deviations. These findings suggest that aging is associated with reduced structure-function coupling in sensorimotor systems and reduced temporal variability of structure-function coupling in higher-order brain networks.

SFC and DSFC are associated with distinct cognitive and health phenotypes

To further characterize the relationships between SFC, DSFC, and phenotypic traits, we employed linear mixed-effects models (LMMs) to examine associations between coupling measures and cognitive, mental health, and physical health variables from the UK Biobank (phenotypic list in Table S1). All analyses were corrected for multiple comparisons using family-wise error (FWE) correction across networks and phenotypes.

SFC and DSFC showed distinct but partially overlapping associations with cognitive performance (Fig. 3A). Stronger SFC within higher-order cognitive networks was associated with better fluid intelligence, including the frontoparietal network (FPN: $\beta = 0.033$, $t = 5.65$, $p < 0.001$) and default mode network (DMN: $\beta = 0.039$, $t = 6.86$, $p < 0.001$). Similar associations were observed for matrix pattern completion performance (FPN: $\beta = 0.053$, $t = 7.67$, $p < 0.001$; DMN: $\beta = 0.045$, $t = 6.51$, $p < 0.001$). In comparison, DSFC demonstrated broader associations with cognitive performance across multiple higher-order networks. For fluid intelligence, significant positive associations were observed in the dorsal attention network (DAN: $\beta = 0.053$, $t = 9.26$, $p < 0.001$), ventral attention network (VAN: $\beta = 0.050$, $t = 8.78$, $p < 0.001$), limbic network (LN: $\beta = 0.050$, $t = 8.90$, $p < 0.001$), FPN ($\beta = 0.028$, $t = 5.00$, $p < 0.001$), and DMN ($\beta = 0.036$, $t = 6.43$, $p < 0.001$). Similar DSFC associations were observed for puzzle-solving performance and working memory measures (Table S4&5). Region-level analyses further demonstrated that these associations involved distributed regions, including temporal cortices, insula, inferior frontal regions, and temporoparietal junctions (Fig. 3B&C).

SFC and DSFC also exhibited distinct spatial patterns in relation to health-related phenotypes. Lower SFC, particularly within sensorimotor and visual networks, was associated with greater health burden. For example, higher numbers of self-reported non-cancer illnesses were associated with lower SFC in the visual network (VN: $\beta = -0.065$, $t = -11.20$, $p < 0.001$) and sensorimotor network (SMN: $\beta = -0.036$, $t = -6.26$, $p < 0.001$). Similarly, the number of treatments or medications taken was negatively associated with SFC in the SMN ($\beta = -0.059$, $t = -9.97$, $p < 0.001$). In contrast, reduced DSFC in higher-order networks

was associated with poorer health and affective phenotypes, including overall health rating (DMN: $\beta = -0.038$, $t = -7.07$, $p < 0.001$; LN: $\beta = -0.034$, $t = -6.28$, $p < 0.001$), nervous feelings (DMN: $\beta = -0.089$, $t = -6.50$, $p < 0.001$), and treatment/health burden (LN: $\beta = -0.040$, $t = -6.88$, $p < 0.001$) (Table S4&5).

Together, these findings indicate that static and dynamic structure-function coupling measures show distinct spatial associations with cognitive and health-related phenotypes. While SFC associations were more prominent in sensorimotor and structural constraint-related patterns, DSFC showed broader associations with higher-order cognitive and affective domains.

Successful aging-related characteristics are associated with age-related differences in structure-function coupling

Given the associations of SFC and DSFC with cognitive performance and health-related phenotypes, we further examined whether successful aging-related characteristics were associated with differences in age-related coupling trajectories. Using LMMs, we tested age-by-successful-aging indicator interactions for cognitive performance (fluid intelligence) and health burden (number of treatments/medications taken). For the cognitive aging indicator, higher fluid intelligence was associated with modestly less negative age-related changes in SFC within the ventral attention network (VAN: $\beta = 0.015$, $t = 2.69$, $p = 0.007$) and DSFC within the default mode network (DMN: $\beta = 0.011$, $t = 2.10$, $p = 0.036$), although these effects were small and did not remain significant after stringent correction for multiple network comparisons (Table S6). For the health-related aging indicator, greater medication/treatment burden was associated with steeper age-related reductions in DSFC across several networks, including the sensorimotor network ($\beta = -0.020$, $t = -3.35$, $p < 0.001$), dorsal attention network ($\beta = -0.021$, $t = -3.59$, $p < 0.001$) and ventral attention network ($\beta = -0.017$, $t = -2.92$, $p = 0.003$) (Fig. 3B&C). These findings suggest that higher health burden is associated with greater age-related alterations in dynamic structure-function coupling.

Environmental and Lifestyle Modulators of SFC and DSFC

Similar LMMs were used to examine associations between SFC/DSFC and environmental and lifestyle factors, including smoking, alcohol consumption, physical activity, sleep, social support, and early-life traumatic experiences. All analyses were FWE corrected for multiple comparisons across networks and phenotypes. Compared with cognitive and health-related phenotypes, environmental and lifestyle factors showed relatively modest associations with SFC/DSFC (Fig. 4A). Among these factors, smoking status showed the strongest associations with SFC, with negative associations observed in the DAN ($\beta = -0.046$, $t = -8.38$, $p < 0.001$) and FPN ($\beta = -0.036$, $t = -6.62$, $p < 0.001$). Early-life traumatic experiences were primarily associated with reduced SFC in the SMN, including avoidance of activities or situations due to stressful experiences ($\beta = -0.036$, $t = -5.51$, $p < 0.001$) and repeated disturbing thoughts related to stressful experiences ($\beta = -0.030$, $t = -4.68$, $p < 0.001$). In addition, longer sleep duration (≥ 9 hours) was associated with lower SMN SFC ($\beta = -0.122$, $t = -5.36$, $p < 0.001$) (Fig. 4B, Table S7&8).

Given this strong association, mediation analysis was performed to investigate whether SFC mediates the impact of smoking on cognition. The results indicated that smoking potentially impairs future cognitive performance by diminishing SFC in the superior parietal lobule and frontal eye fields (FEF) (indirect effect explained = 10.4%, $z = -4.91$, $p < 0.001$) (Fig. 4C). In contrast, DSFC was more closely aligned with early-life health indicators (e.g., birth weight) and household income, although these associations were generally weaker than those observed for SFC (Fig. 4A). The most significant effects included increased DSFC within the DMN associated with higher income ($t = 4.72$, $p = 2.37e-6$) and increased DSFC in SMN related to higher birth weight ($t = 4.73$, $p = 2.24e-6$). Furthermore, mediation analysis suggested that higher income may enhance future cognitive performance by improving DSFC in right posterior cingulate cortex (PCC), inferior frontal gyrus (IFG), and orbitofrontal cortex (OFC) (indirect effect explained = 0.8%, $z = 3.89$, $p < 0.001$) (Fig. 4C and Table S9), albeit with a smaller effect size.

Genetic Architecture of Structure-Function Coupling

Apart from the external influences of environment and lifestyle, we investigated whether individual differences in SFC and DSFC were also regulated by internal genetic factors. To explore the molecular genetic mechanisms underlying SFC and DSFC, we conducted network-level genome-wide association analyses (GWAS) to identify single nucleotide polymorphisms (SNPs) significantly associated with these measures, where statistical significance was defined using the conventional genome-wide threshold of $p < 5e-8$ (Jannot, Ehret, & Perneger, 2015). Our results revealed no genome-wide significant SNPs, suggesting that individual differences in both SFC and DSFC were likely driven by the polygenic accumulation of numerous small-effect variants, rather than by any single locus of major effect.

Polygenic Risk for Alzheimer's Disease Selectively Affects Coupling Dynamics

Due to the limited explanatory power of individual SNPs observed in the GWAS analyses, we subsequently employed polygenic risk score (PRS) analyses to investigate cumulative genetic associations with SFC and DSFC. We examined associations between coupling measures and 87 PRSs, including 39 standard PRSs related to physical, mental, and neurological disorders and 51 enhanced PRSs associated with physiological quantitative traits (Thompson et al., 2022, 2024). Among the examined PRSs, Alzheimer's disease (AD) PRS showed the most widespread associations with dynamic structure-function coupling. Higher AD genetic risk was associated with lower DSFC across multiple networks, including the SMN ($\beta = -0.025$, $t = -4.57$, $p < 0.001$), VAN ($\beta = -0.028$, $t = -5.14$, $p < 0.001$), LN ($\beta = -0.026$, $t = -4.96$, $p < 0.001$), FPN ($\beta = -0.029$, $t = -5.48$, $p < 0.001$), and DMN ($\beta = -0.026$, $t = -4.86$, $p < 0.001$) (Fig. 5A&D). In comparison, AD PRS showed a weaker association with static coupling, with a significant negative association observed only in the visual network (VN: $\beta = -0.028$, $t = -5.01$, $p < 0.001$). Schizophrenia PRS was also associated with reduced SFC in the VN ($\beta = -0.027$, $t = -4.89$, $p < 0.001$), while atrial fibrillation PRS showed associations with DSFC in the VAN ($\beta = -0.022$, $t = -4.03$, $p < 0.001$) and FPN ($\beta = -0.024$, $t = -4.42$, $p < 0.001$) (Table S10&11). These findings indicate that genetic liability for

AD is associated with widespread alterations in dynamic structure-function coupling, particularly within higher-order association networks. However, these results should be interpreted as genetic associations rather than evidence that AD risk directly alters coupling dynamics.

Impact of APOE ϵ 4 Dosage on SFC and DSFC Trajectories

Given the specific strong correlation between AD polygenic risk and DSFC, we sought to further identify the specific genetic drivers of this association. Based on the most recent meta-analysis (Andrews et al., 2023), we extracted 81 SNPs from 21 candidate loci (Table S12). Using LMMs controlling for standard covariates and 20 genetic principal components (PCs), we identified significant associations between the APOE rs429358-C allele and lower structure–function coupling across multiple canonical brain networks across multiple canonical brain networks (C.-C. Liu, Kanekiyo, Xu, & Bu, 2013) (Table S13). Notably, the associations were predominantly observed for DSFC, involving the sensorimotor, ventral attention, limbic, frontoparietal, and default mode networks, whereas only limited effects were observed for SFC.

We further quantified the association between APOE ϵ 4 dosage and structure-function coupling across large-scale brain networks. Higher APOE ϵ 4 dosage was associated with lower SFC in specific networks, most prominently in the visual network (VN: $\beta = -0.036$, $t = -5.45$, $p < 0.001$). Additional negative associations were observed in the limbic network (LN: $\beta = -0.021$, $t = -3.33$, $p < 0.001$) and default mode network (DMN: $\beta = -0.022$, $t = -3.43$, $p < 0.001$). In contrast, APOE ϵ 4 dosage showed broader associations with DSFC alterations, with lower DSFC observed across multiple networks, including the sensorimotor network (SMN: $\beta = -0.032$, $t = -4.90$, $p < 0.001$), dorsal attention network (DAN: $\beta = -0.020$, $t = -3.13$, $p = 0.002$), ventral attention network (VAN: $\beta = -0.033$, $t = -5.13$, $p < 0.001$), limbic network (LN: $\beta = -0.032$, $t = -5.20$, $p < 0.001$), frontoparietal network (FPN: $\beta = -0.034$, $t = -5.46$, $p < 0.001$), and default mode network (DMN: $\beta = -0.026$, $t = -4.26$, $p < 0.001$) (Table S14&15). These findings indicate that APOE ϵ 4 dosage is associated with widespread alterations in dynamic structure-function coupling, particularly across higher-order association networks.

SFC and DSFC Partially Mediate the Effects of Aging and Genetic Risk on Cognitive Function

To investigate whether SFC and DSFC acted as mediators linking genetic factors (APOE ϵ 4 dosage) and age to cognitive outcomes (fluid intelligence), we conducted a statistical mediation analysis to examine indirect associations between age/APOE ϵ 4 dosage, coupling measures, and fluid intelligence. We defined the mediators as the average SFC (or DSFC) values extracted from brain regions whose SFC (or DSFC) significantly associated with age, ϵ 4 allele dosage, and cognitive performance (the intersection regions), as these regions were expected to provide the most informative substrate for mediation.

Our results revealed significant mediation effects: SFC in the occipital lobe, along with DSFC in the inferior frontal gyrus and dorsal anterior cingulate cortex, showed significant statistical indirect effects

linking age and APOE ϵ 4 dosage with fluid intelligence scores. Specifically, the mediation effects were as follows: For SFC, the indirect effect of age was significant ($\beta = -2.1 \times 10^{-3}$, 95% CI $[-2.67 \times 10^{-3}, -1.5 \times 10^{-3}]$, $z = -7.24$, $p = 4.39 \times 10^{-13}$), explaining 7% of the total variance; the indirect effect of APOE ϵ 4 dosage was also significant ($\beta = -1.06 \times 10^{-2}$, 95% CI $[-1.48 \times 10^{-2}, -6.81 \times 10^{-3}]$, $z = -5.22$, $p = 1.8 \times 10^{-7}$), explaining 12% of the total variance (Table S16).

For DSFC, the indirect effect of age was $\beta = -5.3 \times 10^{-4}$ (95% CI $[-8 \times 10^{-4}, -3 \times 10^{-4}]$, $z = -4.04$, $p = 5.24 \times 10^{-5}$), explaining 1.8% of the variance; the indirect effect of APOE ϵ 4 dosage was $\beta = -4.37 \times 10^{-3}$ (95% CI $[-7 \times 10^{-3}, -2 \times 10^{-3}]$, $z = -3.3$, $p = 9.73 \times 10^{-4}$), explaining 5.2% of the variance (Table S16). These findings suggest that SFC and DSFC play crucial roles in mediating genetic and age-related influences on cognitive outcomes, highlighting their potential as biomarkers for understanding the mechanisms of cognitive aging.

Robustness and reproducibility analyses

The spatial organization of SFC and DSFC was highly reproducible across different methodological settings (Supplementary Figures S1-S3, Table S17&18).

Replacing streamline-based structural connectivity with FA-based connectivity yielded highly consistent SFC and DSFC patterns at both individual and population levels. Specifically, mean individual-level parcel-wise Spearman's ρ values exceeded 0.82, network-level correlations across individuals were Pearson's r values consistently exceeded 0.90, and group-level spatial patterns showed strong correspondence after correcting for spatial autocorrelation using spin tests (Spearman's $\rho > 0.79$, spin-test $P < 0.0001$; Supplementary Figure S1).

Similarly, repeating the analyses using the Schaefer 200-area atlas showed highly similar SFC and DSFC organization to that observed with the Glasser 360-area parcellation, with strong network-level reproducibility (Pearson's $r > 0.74$) and robust correspondence between group-averaged spatial maps after accounting for spatial autocorrelation (Spearman's $\rho > 0.80$, spin-test $P < 0.0001$; Supplementary Figure S2).

Finally, varying the dynamic sliding window length from 30 TRs to 40 or 50 TRs resulted in highly similar DSFC patterns. Individual-level parcel-wise Spearman's ρ values were consistently above 0.99, network-level correlations exceeded Pearson's $r = 0.90$, and group-level spatial correspondence remained significant after spin-test correction (Spearman's $\rho > 0.98$, spin-test $P < 0.0001$; Supplementary Figure S3).

Together, these analyses demonstrate that the observed SFC and DSFC organization was robust to variations in structural connectivity estimation, cortical parcellation, and dynamic parameter selection.

Discussion

In this study, leveraging an extensive neuroimaging dataset from 34,067 participants, we characterized the complementary roles of static and dynamic structure-function coupling (SFC and DSFC) in aging and cognitive resilience. Our findings revealed that both SFC in sensorimotor systems and DSFC in higher-order networks declined significantly with age. Crucially, we demonstrated that while SFC and DSFC in higher-order networks supported cognitive performance, their disruptions—specifically within sensory-motor SFC and higher-order DSFC—linked to heightened mental and physical health burden. By integrating genetic and environmental evidence, we showed that aging and Alzheimer's disease-related risk factors were associated with altered coupling patterns and cognitive performance. We propose a conceptual framework where SFC reflects the stability of the brain's core architecture, while DSFC may capture temporal variability in coupling states, which could reflect aspects of functional adaptability. These two mechanisms likely serve as synergistic pillars of higher-order cognition. Consequently, Maintaining both network stability (SFC) and dynamic adaptability (DSFC) may be important for mitigating age-related cognitive decline and maintaining brain health in older adults.

Complementary Roles of Static and Dynamic Structure-Function Coupling in Cognitive Function and Health

We found that both SFC and DSFC in higher-order cognitive networks are positively correlated with cognitive performance, including fluid intelligence, problem-solving ability, and working memory. This aligns with prior research showing that SFC predicts various cognitive aspects, such as working memory (Baum et al., 2020), cognitive flexibility (Medaglia et al., 2018), fluid intelligence (Griffa et al., 2022) and composite cognitive scores (Gu et al., 2021). Griffa et al. reported that the SFC of higher-order networks is sensitive enough to distinguish between individuals and is more accurate than sensorimotor SFC in predicting cognitive performance, consistent with our results (Griffa et al., 2022). Our study extends this understanding by revealing that dynamic structure-function coupling, particularly DSFC, has a stronger association with cognitive performance than static SFC, suggesting that temporal variability in structure-function coupling is associated with cognitive abilities (Braun et al., 2015; Ju & Bassett, 2020; Shine, 2019). The association between DSFC in the temporal cortex and cognitive performance is especially pronounced (Fig. 3B). The temporal cortex is crucial for conceptual categorization, semantic processing, language function, and associative memory (Braunsdorf et al., 2021; Jackson, Bajada, Rice, Cloutman, & Lambon Ralph, 2018). A decline in its ability to decouple from structural constraints may impair integration with other networks, hindering the transfer of semantic information and memory to working memory, thus impacting cognition. Overall, our findings highlight the complementary roles of both SFC and DSFC in supporting cognitive function, with structural and functional coherence, alongside flexibility, being key to human intelligence.

In the context of health, we observed distinct spatial patterns in the effects of mental and physical health burden on SFC and DSFC: poorer health is associated with lower SFC in sensorimotor regions and higher DSFC in higher-order cognitive networks. Sensory and motor networks exhibit the highest levels of SFC across the brain (Dong et al., 2024; Fotiadis et al., 2023; Gu et al., 2021), with the highest cortical

myelination (M. F. Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014), and their functional activity is strongly constrained by white matter connectivity, supporting the high precision and robustness required for sensory-motor functions. Physical and mental health problems (such as depression and anxiety) and associated chronic stress activate immune responses, triggering neuroinflammation that impairs oligodendrocyte function, leading to myelin abnormalities, which might further reducing SFC (Antontseva, Bondar, Reshetnikov, & Merkulova, 2020; Gorlova et al., 2023; Knowles, Batra, Xu, & Monje, 2022; Murayama, Cai, Nakamura, & Hashimoto, 2025). Additionally, poor health may impair long-range white matter connectivity (de Lange et al., 2019; Marebwa et al., 2018; Meijer, Steenwijk, Douw, Schoonheim, & Geurts, 2020), compromising the brain's ability to integrate across brain modules (Betzel & Bassett, 2018), preventing higher cognitive networks from effectively decoupling from structural constraints, and ultimately reducing cognitive flexibility.

Aging, Cognitive Decline, and Static and Dynamic Structure-Function Coupling

Our results show that SFC and DSFC follow distinct aging trajectories, with SFC in sensorimotor regions and DSFC in higher-order cognitive networks decreasing with age. Consistent with previous evidence of age-related declines in global and sensorimotor SFC (Zamani Esfahlani et al., 2022), our findings extend this work by directly linking this reduction to physical and mental health decline in older adults.

Specifically, reduced sensorimotor SFC was significantly associated with poorer overall health, higher stress, and concrete physical symptoms—such as a history of falls over the past year and leg pain while walking (Fig. 3). These results suggest that sensorimotor SFC decline is not just a general reflection of aging itself, but is directly tied to the subsequent functional decline and physical and mental health issues in older adults.

Furthermore, our study extends this line of research to dynamic metrics, showing that aging also alters the flexibility of higher-order cognitive networks. We found that the temporal variability of structure-function coupling within these networks decreases with age. Our mediation analyses further demonstrate that aging influences fluid intelligence performance by modulating the level of DSFC, which further strengthens the chain of relationships between aging, the decline in the dynamic switching capability between coupling and uncoupling in higher-order networks, and cognitive decline. Given that these higher-order regions act as critical integration hubs—exhibiting high participation coefficients and occupying the top of the global brain functional gradient (Huntenburg, Bazin, & Margulies, 2018; Pedersen, Omidvarnia, Shine, Jackson, & Zalesky, 2020)—their dynamic flexibility reflects the brain's capacity to decouple from structural constraints and recruit global resources for complex tasks. Therefore, a decline in this dynamic coupling variability is associated with poorer cognitive performance in older adults, although causal mechanisms require further investigation.

We observed that the dynamic characteristics of later-developing higher-order cognitive networks appear to enter a decline phase earlier, supporting the classic "last-in, first-out" hypothesis in developmental neuroscience (Whalley, 2015). Early SFC development studies have shown an opposite trend, with SFC in

primary sensory systems declining throughout life, while SFC in higher-order cognitive networks increases during childhood and adolescence, stabilizing in early adulthood (Baum et al., 2020; Zamani Esfahlani et al., 2022; Z. Zhang et al., 2025). Our study adds a dynamic perspective to this framework, highlighting the significance of dynamic decoupling and coupling strength in assessing different aspects of the structure-function relationship and its development during the lifespan.

Biological Mechanisms and Environmental Influence Factors of Static and Dynamic Coupling

We found that APOE $\epsilon 4$ dosage negatively associated with SFC in VN and DSFC in SMN and higher-order cognitive networks (such as FPN and VAN). This pattern is similar to the SFC/DSFC aging pattern exhibited by normal aging. APOE, a key protein involved in lipid transport and the clearance of abnormal proteins in the brain, is primarily synthesized by astrocytes and microglia. APOE $\epsilon 4$ impairs the brain's ability to clear low-density lipoprotein cholesterol (LDL-C), increasing the risk of cardiovascular disease and Alzheimer's disease (AD). Previous studies have shown that APOE $\epsilon 4$ carriers exhibit reduced network efficiency (V. Heise, Filippini, Ebmeier, & Mackay, 2011) and lower white matter integrity (Verena Heise et al., 2024). These changes are also associated with a significant decrease in the efficiency of the medial temporal lobe functional networks in cognitively normal elderly individuals (Chen et al., 2015). We hypothesize that APOE $\epsilon 4$ may affect SFC by reducing white matter efficiency, weakening visual network robustness, and impairing higher cognitive regions' communication. Our GWAS analysis did not reveal significant genetic associations, which contrasts with twin studies showing higher heritability of SFC in visual, subcortical, cerebellar, and brainstem regions (Valk et al., 2022). This discrepancy may stem from differences in methodology, as GWAS typically reports lower heritability than twin studies (Owen & Williams, 2021). Additionally, our sample had a higher mean age compared to the HCP sample used in previous studies (by around 30 years), which may have reduced the observed genetic effects. While GWAS generally detects smaller effects from individual SNPs, our polygenic risk score (PRS) analysis identified significant associations between AD and schizophrenia PRS and SFC/DSFC (Fig. 5A, D), which suggests a cumulative genetic influence on SFC/DSFC.

We also identified the impact of environmental factors such as smoking habits, birth weight, and household income on SFC and DSFC. Smoking induces oxidative stress, increases inflammation, and may thus affect the white matter quality in higher-order brain regions (Brody et al., 2017; Gray et al., 2020; Yu et al., 2015). Previous studies have confirmed the effects of smoking on higher-order brain areas. Low birth weight, which indicates developmental or nutritional deficiencies, may affect the white matter development in sensorimotor networks, leading to abnormalities in white matter microstructure and reduced integrity (Alex et al., 2024; Eikenes et al., 2012; Neumane et al., 2022). Low household income is associated with chronic stress, which has been shown to accelerate brain aging and disrupt dynamic integration in higher-order brain regions (Blair & Raver, 2016; Farah, 2018; Krueger et al., 2025). Our findings provide insights into how environmental factors shape the structure-function relationships of the brain, offering a basis for interventions targeting environmental changes and lifestyle modifications to enhance cognitive function and health.

In addition to its role in aging, our findings have significant implications for understanding cognitive decline in the context of neurodegenerative diseases. Previous studies on SFC changes in AD have yielded inconsistent results, showing both increases and decreases (Cao et al., 2020; Dai et al., 2019; Sun et al., 2014), likely due to small sample sizes (the total sample size of all three studies was less than 100). Our research provides empirical evidence that clarifies the association between AD genetic risk and SFC and DSFC using an exceptionally large sample. Future longitudinal studies are needed to determine whether static and dynamic coupling alterations can serve as predictive markers of aging-related cognitive decline or neurodegenerative disease.

Conclusion

In conclusion, our results emphasize the importance of dynamic structure-function coupling as a potential correlate of cognitive resilience during aging. While static SFC supports network stability, dynamic SFC enables the brain to adapt to changing demands, facilitating the flexibility necessary for cognitive performance. Alterations in static and dynamic coupling are associated with cognitive decline, health burden, and neurodegenerative disease risk. Further research into the molecular and neurobiological mechanisms underlying these processes will be crucial for developing strategies to protect cognitive function in aging and disease.

Limitations

Several limitations should be noted. First, this study is an association analysis rather than causal analysis, which limits our ability to infer causal relationships or track individual changes in SFC. Additionally, our GWAS analysis did not reveal significant genetic associations, likely because both SFC and DSFC are influenced by the cumulative effects of multiple SNPs. Such weak associations also make it impossible to perform Mendelian randomization using genetic variants as instrumental variables to investigate causal effects. Third, DSFC was estimated from fMRI signals, which are indirect measures of neural activity. Future research should combine neural electrophysiological activity to more directly measure functional networks. Moreover, although mediation models provide evidence of statistical associations among age, APOE ϵ 4 dosage, coupling measures, and cognition, they cannot establish temporal precedence or causal mechanisms. Finally, the main participants in this study were of British descent, which may limit the generalizability of the findings. Further studies are needed to validate and extend these results in more diverse cohorts.

Methods

Samples and participants

The UK Biobank (UKB) is a prospective cohort study involving ~ 500,000 UK participants aged 40 to 69 years (Sudlow et al., 2015). Participant data encompass genomic and imaging data, electronic health record linkages, biomarkers, as well as physical and anthropometric measurements. Detailed

information can be found at <https://biobank.ndph.ox.ac.uk/showcase/>. The UKB includes four instances (Instance 0 to 3). About 40,000 individuals (aged 44 to 82 years) underwent MRI scanning at Instance 2, which was collected during a follow-up visit approximately 5 to 9 years after baseline (Instance 0). Ethical approval for the UK Biobank study was granted by the Human Biology Research Ethics Committee at the University of Cambridge, and informed consent was obtained from all participants. This study utilized data from the UK Biobank under project number 19542.

MRI data acquisition and Preprocessing

All UKB brain imaging data (connectome of Glasser parcellation, ID 31022; functional time series of Glasser parcellation, ID 31016) were acquired using 3T Siemens Skyra scanners with a standard 32-channel head coil. Details about data and preprocessing are available in the online documentation: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367> and <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977> (Alfaro-Almagro et al., 2018; Miller et al., 2016) and prior publications (Mansour L, Di Biase, Smith, Zalesky, & Seguin, 2023). The T1-weighted structural brain images were acquired using a 3D MPAGE acquisition at 1 mm isotropic resolution with a 256 mm superior-inferior field of view.

All imaging data were obtained from the UK Biobank imaging assessment. Resting-state fMRI time series were obtained from the Glasser parcellation data field (UKB field 31016), and structural connectomes were obtained from the Glasser (Matthew F. Glasser et al., 2016) and Tian subcortical connectome data field (UKB field 31022). The UKB connectome resource provides structural connectivity matrices, tractography endpoint coordinates, and tractography quality metrics derived from whole-brain diffusion MRI tractography. The derivation of these connectomes has been described previously.

Resting-state BOLD fMRI was acquired on 3-T Siemens Skyra scanners using a multiband gradient-echo EPI sequence (6-min acquisition; 490 volumes; voxel size, 2.4 mm isotropic; TE/TR, 39/735 ms; multiband factor, 8; flip angle, 52°). UKB preprocessing included EPI susceptibility-distortion correction, gradient-distortion correction, motion correction, grand-mean intensity normalization, high-pass temporal filtering, and ICA + FIX denoising (Alfaro-Almagro et al., 2018). Global signal regression was not performed to avoid introducing artificial negative connections (Murphy & Fox, 2017). Participants with mean framewise displacement > 0.20 mm were excluded.

Diffusion MRI was acquired using a multiband spin-echo EPI sequence with 100 diffusion-weighted directions distributed across $b = 1,000$ and $2,000$ s/mm² shells, together with $b = 0$ images. Structural connectomes were derived from whole-brain tractography of diffusion MRI data using the UKB connectome processing pipeline. Whole-brain probabilistic tractography was estimated using MRtrix3 (Tournier et al., 2019), constructing a 360×360 structural connectome. Edges were characterized by the number of streamlines and mean fractional anisotropy (FA). For the present analyses, streamline-count connectivity matrices were used as the structural connectivity measure. No additional streamline weighting or filtering was applied.

The structural connectivity matrices were used without distance correction or removal of zero-valued edges. Resting-state functional connectivity was calculated as the Pearson correlation between the BOLD time series of each pair of regions. Negative functional connectivity values were retained, and no Fisher r-to-z transformation was applied before SFC estimation.

We initially identified 39,836 participants with available structural connectome data and 40,334 participants with available resting-state fMRI time series. Their intersection comprised 38,853 participants with both structural and functional imaging data. Participants with excessive head motion during resting-state fMRI, defined as mean framewise displacement > 0.20 mm, were excluded. We further excluded participants with missing values in any imaging measure required for SFC or DSFC estimation; because SFC was calculated from matched structural and functional connectivity profiles, missingness in either modality resulted in exclusion of the entire participant. The final imaging sample included 34,067 participants.

Static and dynamic structure-function coupling

Dynamic structure-function coupling (DSFC) was estimated using a sliding-window approach. Resting-state fMRI data were divided into windows of 30 TRs (22.05 s), an appropriate size for dynamic functional connectivity analysis as demonstrated in previous studies (Shakil, Lee, & Keilholz, 2016), with a step size of 5 TRs. Each window therefore contained 30 valid fMRI volumes. No additional treatment of window boundaries was applied.

For each time window, a functional connectivity matrix was calculated using Pearson correlations between the BOLD time series of all cortical regions. For each brain region, regional SFC was calculated as the Spearman rank correlation between its structural connectivity profile and its functional connectivity profile. Specifically, for a given region i , the input vectors consisted of the structural and functional connections between region i and all other regions, excluding the self-connection of region i . Structural connectivity was represented by the corresponding streamline-count values, and functional connectivity was represented by the corresponding Pearson correlation coefficients. Zero-valued structural connections and negative functional connectivity values were retained. No Fisher r-to-z transformation, distance correction, streamline weighting, or additional edge filtering was applied before calculating the Spearman correlation.

For each participant and region, static SFC was defined as the mean regional SFC across all windows. DSFC was defined as the standard deviation of regional SFC across windows. Regional values were subsequently averaged within the seven canonical Yeo functional networks for network-level analyses.

To ensure our findings were robust to methodology, we re-evaluated SFC and DSFC across several parameter variations. These included employing different structural connectome measures (streamline count vs. fractional anisotropy), alternative parcellations (Glasser 360 vs. Schaefer 200), and varying sliding-window lengths (30, 40, and 50 TRs). The consistency of these measures was assessed by

calculating the similarity of SFC and DSFC at the average spatial, individual, and network levels. All validation tests demonstrated high robustness across different analytical frameworks (see Supplementary Methods).

Age effect analysis

We performed aging effect analyses of SFC and DSFC using linear mixed models (LMMs) (*fitlme* function in MATLAB R2018b) based on data from Instance 2. The fixed effects included age at the time of brain scan (UK Biobank Field ID 21003, Instance 2), the square of age (age²), sex (ID 31), race (ID 21000), body mass index (BMI, ID 21001), head movement (ID 25741), and total intracranial volume (TIV, ID 26521). Assessment centre (ID 54) was modeled as a random effect to estimate the random intercept. Statistical inference for each fixed effect was performed using the one-sample Student's t-test provided by the LMM framework, from which the t-statistic and corresponding p-value were derived and reported as the primary inferential metrics. Bonferroni correction was used to control Type I error. For regional nodal degree, multiple comparisons were corrected across 360 brain regions. At the network level, averaged SFC and DSFC were assessed across 7 network modules of Yeo 7 networks (Yeo et al., 2011). Generalized Additive Models (GAMs) were performed using the *gamm* function from the *mgcv* package in R (version 4.0), which were used to characterize age-related changes in the network-level SFC and DSFC. Participant inclusion criteria, missing-data handling procedures, analytic sample sizes for each model, and detailed fixed- and random-effect specifications are provided in Supplementary Methods.

To characterize the potential non-linear trajectories of network-level information profiles across the lifespan for visualization (in Fig. 2), Generalized Additive Models (GAMs) were additionally implemented using the *gamm* function from the *mgcv* package in R (version 4.0), with sex, head motion and site controlled.

Association study

We used LMMs to examine associations between network-averaged SFC/DSFC and three phenotype categories: cognitive function (Category 100026), mental health (Category 100060), and self-reported medical conditions (Category 1003). These analyses were restricted to Instance 2 cross-sectional data to maximize the statistical test power and ensure phenotype consist to brain imaging, adjusting for age and age², sex, race, BMI, head motion, SNR, and TIV as fix effect, while center as a random effect. Multiple comparisons were controlled using Family-Wise Error (FWE) correction. We first performed network-level association analyses (7×75 tests). Phenotypes showing significant network-level associations were further analyzed at the regional level (360 regions) to map their spatial distributions.

Effect sizes were calculated based on the statistics provided by the linear mixed models (LMM). All continuous predictors were standardized (Z-scored) prior to regression, whereas binary predictors

retained their original scale (0 or 1). Consequently, the resulting standardized regression coefficient (standardized β) derived from the LMM estimates serves as a scale-free metric of effect size. For continuous predictors, β represents a fully standardized coefficient, quantifying the change in the dependent variable (in standard deviation units) per one-standard-deviation change in the predictor. For binary predictors, β functions as a semi-standardized coefficient, indicating the statistical shift in the dependent variable (in standard deviation units) between the two categorical groups. This standardized framework ensures that effect magnitudes are directly comparable across both continuous and categorical analyses.

We further associated SFC/DSFC with 56 environmental and lifestyle measures at Instance 2. These factors spanned domains including socioeconomic status (SES), physical activity, social support, sleep, diet, substance use (alcohol/smoking), and traumatic experiences. Statistical modeling and FWE correction followed the same procedure as the phenotype analyses, starting at the network level (7×56 tests) and progressing to the regional level (360 regions) for significant factors.

Detailed variable IDs and descriptions are provided in Table S1.

Genetic analysis

Genotype data were available for all 502,409 participants in the UK Biobank cohort. Detailed genotyping and quality-control procedures for the UK Biobank are available in a previous publication (Bycroft et al., 2018) and online documentation: <https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=263>. We excluded single-nucleotide polymorphisms (SNPs) with call rates < 95%, minor allele frequency < 0.1% or deviation from the Hardy-Weinberg equilibrium with $P < 1e-5$ (Hayes, 2013). After the quality-control procedures, we obtained a total of 8,608,580 SNPs. We conducted genome-wide association analysis (GWAS) to investigate the relationship between genotype and 7 network-level SFC/DSFC. The GWAS was performed using PLINK 2.0 (Chang et al., 2015), adjusting for sex, age, BMI, head motion, SNR, TIV, centre, and the top 10 ancestry principal components (ID 22009).

Polygenic Risk Scores (PRSs)

We utilized the UK Biobank curated PRS dataset (Category 2405, Version 2, released May 2024), developed by Genomics PLC (Thompson et al., 2022, 2024). This dataset includes 90 Standard and Enhanced PRSs covering a broad spectrum of complex traits and diseases, ranging from neuropsychiatric disorders (e.g., Alzheimer's disease and schizophrenia) to metabolic markers (e.g., BMI, type 2 diabetes, and HbA1c). PRS values were z-scored across participants. Associations between SFC/DSFC and PRSs were tested using LMMs, adjusting for age, age², sex, BMI, head motion, SNR, TIV, genotype batch (ID 22000), and the first 10 genetic principal components. Multiple comparisons were controlled via FWE correction at both network (7×90 tests) and regional (360 regions) levels. Primary genetic analyses were defined a priori as associations between PRS measures and coupling phenotypes.

All tested PRSs, effect estimates, confidence intervals, and corresponding multiple-comparison correction procedures are reported in Supplementary Tables.

APOE Genotyping

To determine APOE genotypes for all participants, APOE ϵ 4 dosage (0, 1, or 2) was determined using PLINK 2.0 (build 20241124) based on two defining SNPs: rs429358 (Chr19:45411941, GRCh37; reference allele = T, alternate allele = C) and rs7412 (Chr19:45412079, GRCh37; reference allele = C, alternate allele = T) (Field IDs 23115). These two SNPs jointly encode the ϵ 2/ ϵ 3/ ϵ 4 alleles of the APOE gene, which are determined by the amino acid substitutions at positions 112 and 158 of the apolipoprotein E protein. Individuals were assigned APOE ϵ 4 dosage according to the dosage of the alternate alleles at the two SNPs, following the canonical haplotype definition: ϵ 2: rs429358 = T, rs7412 = T; ϵ 3: rs429358 = T, rs7412 = C; ϵ 4: rs429358 = C, rs7412 = C. Following canonical haplotype definitions, the count of the rs429358-C allele was used to represent ϵ 4 carrier status, a standard approach in UKB studies (Fernández-de-Las-Peñas et al., 2023; Lumsden, Mulugeta, Zhou, & Hyppönen, 2020). Associations between SFC/DSFC and PRSs were tested using linear mixed-effects models controlling for age, age², sex, BMI, head motion, SNR, TIV, genotype measurement batch, and the first 10 genetic principal components. For region-level analyses, 360 comparisons were performed (FWE correction). Kruskal-Wallis Rank Sum Test (using *kruskal.test* function in R package *stats*) was employed to assess differences between the APOE ϵ 4 dosage groups.

Mediation Effect Analysis

Mediation analyses and parallel mediation model were both conducted using the *lavaan* package in R v4.0. We used genetic factors (APOE ϵ 4 dosage) and age as independent variables, and cognitive outcomes (fluid intelligence) as dependent variables. SFC/DSFC in brain regions both significantly associated with age, ϵ 4 allele dosage, and cognitive performance (intersection regions) was averaged as mediators in the model. Before performing the mediation analysis, fixed effects for sex, ethnicity, BMI, head motion, SNR and TIV, as well as the random effect of center, were removed using a linear mixed model (LMM). The residuals were then retained for input into the mediation model. For the mediation analysis of smoking-SFC-intelligence, we also included age as an additional covariate. Because the study design is cross-sectional, mediation analyses were interpreted as statistical indirect-effect analyses rather than evidence of causal mediation.

Declarations

Data availability

The data used in the present study are available from UK Biobank with restrictions applied. Data were used under licence and are thus not publicly available. Researchers can apply for access to the UK

Biobank data via the Access Management System (<https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>). European ancestry reference data from the 1000 Genomes Project can be found via <https://github.com/getian107/PRScsx?tab=readme-ov-file>.

Code availability

For the analyses conducted in MATLAB 2025a and R (version 4.2.3). PLINK 2.0 was used to perform GWAS. The primary code used in this study has been made publicly accessible through the GitHub repository (https://github.com/XinRanWu/UKB_DynamicSFC).

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Contributions

X.W., J.Z. conceived and designed the experiment. X.W. did the analyses with support from Z.L. and J.Z. X.W. drafted the paper with contributions from P.F. and Z.L. and comments from all other authors. X.W. and P.F. contributed to the visualization of data. X.W., S.P., Z.L. and J.Z. contributed to the interpretation of results. J.Z. and J.F. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final paper.

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Competing interests

The authors declare no competing interests.

References

1. Alex, A. M., Aguade, F., Botteron, K., Buss, C., Chong, Y.-S., Dager, S. R., . . . the, E. O. g. (2024). A global multicohort study to map subcortical brain development and cognition in infancy and early childhood. *Nature Neuroscience*, 27(1), 176-186. doi:10.1038/s41593-023-01501-6

2. Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., . . . Smith, S. M. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage*, 166, 400-424. doi:10.1016/j.neuroimage.2017.10.034
3. Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T., & Calhoun, V. D. (2012). Tracking Whole-Brain Connectivity Dynamics in the Resting State. *Cereb Cortex*, 24(3), 663-676. doi:10.1093/cercor/bhs352
4. Andrews, S. J., Renton, A. E., Fulton-Howard, B., Podlesny-Drabiniok, A., Marcora, E., & Goate, A. M. (2023). The complex genetic architecture of Alzheimer's disease: novel insights and future directions. *EBioMedicine*, 90.
5. Antontseva, E., Bondar, N., Reshetnikov, V., & Merkulova, T. (2020). The Effects of Chronic Stress on Brain Myelination in Humans and in Various Rodent Models. *Neuroscience*, 10:441(1873-7544 (Electronic)), 226-238. doi:10.1016/j.neuroscience.2020.06.013
6. Baum, G. L., Cui, Z., Roalf, D. R., Ciric, R., Betzel, R. F., Larsen, B., . . . Moore, T. M. (2020). Development of structure-function coupling in human brain networks during youth. *Proceedings of the National Academy of Sciences*, 117(1), 771-778.
7. Betzel, R. F., & Bassett, D. S. (2018). Specificity and robustness of long-distance connections in weighted, interareal connectomes. *Proceedings of the National Academy of Sciences*, 115(21), E4880-E4889.
8. Blair, C., & Raver, C. C. (2016). Poverty, stress, and brain development: New directions for prevention and intervention. *Academic pediatrics*, 16(3), S30-S36.
9. Braun, U., Schäfer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., . . . Tost, H. (2015). Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proceedings of the National Academy of Sciences*, 112(37), 11678-11683.
10. Braunsdorf, M., Blazquez Freches, G., Roumazeilles, L., Eichert, N., Schurz, M., Uithol, S., . . . Mars, R. B. (2021). Does the temporal cortex make us human? A review of structural and functional diversity of the primate temporal lobe. *Neuroscience & Biobehavioral Reviews*, 131, 400-410. doi:https://doi.org/10.1016/j.neubiorev.2021.08.032
11. Brody, A. L., Hubert, R., Enoki, R., Garcia, L. Y., Mamoun, M. S., Okita, K., . . . Mandelkern, M. A. (2017). Effect of Cigarette Smoking on a Marker for Neuroinflammation: A [11C]DAA1106 Positron Emission Tomography Study. *Neuropsychopharmacology*, 42(8), 1630-1639. doi:10.1038/npp.2017.48
12. Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L. T., Sharp, K., . . . O'Connell, J. (2018). The UK Biobank resource with deep phenotyping and genomic data. *Nature*, 562(7726), 203-209.
13. Cao, R., Wang, X., Gao, Y., Li, T., Zhang, H., Hussain, W., . . . Xiang, J. (2020). Abnormal anatomical Rich-Club organization and structural-functional coupling in mild cognitive impairment and Alzheimer's disease. *Front Neurol*, 11, 53.
14. Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*, 4(1), s13742-13015-10047-13748.

15. Chen, Y., Chen, K., Zhang, J., Li, X., Shu, N., Wang, J., . . . Reiman, E. M. (2015). Disrupted functional and structural networks in cognitively normal elderly subjects with the APOE ϵ 4 allele. *Neuropsychopharmacology*, 40(5), 1181-1191.
16. Dai, Z., Lin, Q., Li, T., Wang, X., Yuan, H., Yu, X., . . . Wang, H. (2019). Disrupted structural and functional brain networks in Alzheimer's disease. *Neurobiol Aging*, 75, 71-82.
17. de Lange, S. C., Scholtens, L. H., van den Berg, L. H., Boks, M. P., Bozzali, M., Cahn, W., . . . van Haren, N. E. (2019). Shared vulnerability for connectome alterations across psychiatric and neurological brain disorders. *Nat Hum Behav*, 3(9), 988-998.
18. Deery, H. A., Di Paolo, R., Moran, C., Egan, G. F., & Jamadar, S. D. (2023). The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging. *Psychophysiology*, 60(1), e14159.
19. Dong, X., Li, Q., Wang, X., He, Y., Zeng, D., Chu, L., . . . Li, S. (2024). How brain structure-function decoupling supports individual cognition and its molecular mechanism. *Human Brain Mapping*, 45(2), e26575.
20. Eikenes, L., Martinussen, M. P., Lund, L. K., Løhaugen, G. C., Indredavik, M. S., Jacobsen, G. W., . . . Håberg, A. K. (2012). Being born small for gestational age reduces white matter integrity in adulthood: a prospective cohort study. *Pediatric Research*, 72(6), 649-654. doi:10.1038/pr.2012.129
21. Farah, M. J. (2018). Socioeconomic status and the brain: prospects for neuroscience-informed policy. *Nature Reviews Neuroscience*, 19(7), 428-438. doi:10.1038/s41583-018-0023-2
22. Fernández-de-Las-Peñas, C., Arendt-Nielsen, L., Díaz-Gil, G., Gómez-Esquer, F., Gil-Crujera, A., Gómez-Sánchez, S. M., . . . Giordano, R. (2023). Apolipoprotein E (ApoE) ϵ 4 genotype (ApoE rs429358–ApoE rs7412 polymorphisms) is not associated with long COVID symptoms in previously hospitalized COVID-19 survivors. *genes*, 14(7), 1420.
23. Fotiadis, P., Cieslak, M., He, X., Caciagli, L., Ouellet, M., Satterthwaite, T. D., . . . Bassett, D. S. (2023). Myelination and excitation-inhibition balance synergistically shape structure-function coupling across the human cortex. *Nat Commun*, 14(1), 6115.
24. Fotiadis, P., Parkes, L., Davis, K. A., Satterthwaite, T. D., Shinohara, R. T., & Bassett, D. S. (2024). Structure-function coupling in macroscale human brain networks. *Nature Reviews Neuroscience*, 25(10), 688-704.
25. Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., . . . Jenkinson, M. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, 536, 171-178. doi:10.1038/nature18933
26. Glasser, M. F., Goyal, M. S., Preuss, T. M., Raichle, M. E., & Van Essen, D. C. (2014). Trends and properties of human cerebral cortex: correlations with cortical myelin content. *Neuroimage*, 93 Pt 2, 165-175. doi:10.1016/j.neuroimage.2013.03.060
27. Gorlova, A., Svirin, E., Pavlov, D., Cespuglio, R., Proshin, A., Schroeter, C. A., . . . Strekalova, T. (2023). Understanding the role of oxidative stress, neuroinflammation and abnormal myelination in

- excessive aggression associated with depression: recent input from mechanistic studies. *International Journal of Molecular Sciences*, 24(2), 915.
28. Gray, J. A.-O. X., Thompson, M., Bachman, C., Owens, M. M., Murphy, M. A.-O., & Palmer, R. (2020). Associations of cigarette smoking with gray and white matter in the UK Biobank. *Neuropsychopharmacology*, 7;45(7)(1740-634X (Electronic)), 1215-1222. doi:10.1038/s41386-020-0630-2
 29. Griffa, A., Amico, E., Liégeois, R., Van De Ville, D., & Preti, M. G. (2022). Brain structure-function coupling provides signatures for task decoding and individual fingerprinting. *Neuroimage*, 250, 118970.
 30. Gu, Z., Jamison, K. W., Sabuncu, M. R., & Kuceyeski, A. (2021). Heritability and interindividual variability of regional structure-function coupling. *Nat Commun*, 12(1), 4894.
 31. Hayes, B. (2013). Overview of statistical methods for genome-wide association studies (GWAS). *Genome-wide association studies and genomic prediction*, 149-169.
 32. Heise, V., Filippini, N., Ebmeier, K. P., & Mackay, C. E. (2011). The APOE ε4 allele modulates brain white matter integrity in healthy adults. *Mol Psychiatry*, 16(9), 908-916.
 33. Heise, V., Offer, A., Whiteley, W., Mackay, C. E., Armitage, J. M., & Parish, S. (2024). A comprehensive analysis of APOE genotype effects on human brain structure in the UK Biobank. *Translational Psychiatry*, 14(1), 143.
 34. Honey, C. J., Thivierge, J.-P., & Sporns, O. (2010). Can structure predict function in the human brain? *Neuroimage*, 52(3), 766-776.
 35. Huntenburg, J. M., Bazin, P.-L., & Margulies, D. S. (2018). Large-Scale Gradients in Human Cortical Organization. *Trends in cognitive sciences*, 22(1), 21-31. doi:10.1016/j.tics.2017.11.002
 36. Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., . . . Gonzalez-Castillo, J. (2013). Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage*, 80, 360-378.
 37. Jackson, R. L., Bajada, C. J., Rice, G. E., Cloutman, L. L., & Lambon Ralph, M. A. (2018). An emergent functional parcellation of the temporal cortex. *Neuroimage*, 170, 385-399. doi:https://doi.org/10.1016/j.neuroimage.2017.04.024
 38. Jannot, A.-S., Ehret, G., & Perneger, T. (2015). $P < 5 \times 10^{-8}$ has emerged as a standard of statistical significance for genome-wide association studies. *Journal of clinical epidemiology*, 68(4), 460-465.
 39. Ju, H., & Bassett, D. S. (2020). Dynamic representations in networked neural systems. *Nature Neuroscience*, 23(8), 908-917.
 40. Knowles, J. K., Batra, A., Xu, H., & Monje, M. (2022). Adaptive and maladaptive myelination in health and disease. *Nature Reviews Neurology*, 18(12), 735-746.
 41. Krueger, K. R., Desai, P., Beck, T., Barnes, L. L., Bond, J., DeCarli, C., . . . Rajan, K. B. (2025). Lifetime Socioeconomic Status, Cognitive Decline, and Brain Characteristics. *JAMA Netw Open*, 8(2), e2461208-e2461208. doi:10.1001/jamanetworkopen.2024.61208

42. Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology*, 9(2), 106-118.
43. Liu, Z.-Q., Vazquez-Rodriguez, B., Spreng, R. N., Bernhardt, B. C., Betzel, R. F., & Misic, B. (2022). Time-resolved structure-function coupling in brain networks. *Communications Biology*, 5(1), 532.
44. Lumsden, A. L., Mulugeta, A., Zhou, A., & Hyppönen, E. (2020). Apolipoprotein E (APOE) genotype-associated disease risks: a phenome-wide, registry-based, case-control study utilising the UK Biobank. *EBioMedicine*, 59, 102954. doi:<https://doi.org/10.1016/j.ebiom.2020.102954>
45. Mansour L, S., Di Biase, M. A., Smith, R. E., Zalesky, A., & Seguin, C. (2023). Connectomes for 40,000 UK Biobank participants: A multi-modal, multi-scale brain network resource. *Neuroimage*, 283, 120407. doi:<https://doi.org/10.1016/j.neuroimage.2023.120407>
46. Marebwa, B. K., Adams, R. J., Magwood, G. S., Basilakos, A., Mueller, M., Rorden, C., . . . Bonilha, L. (2018). Cardiovascular risk factors and brain health: impact on long-range cortical connections and cognitive performance. *Journal of the American Heart Association*, 7(23), e010054.
47. Medaglia, J. D., Huang, W., Karuza, E. A., Kelkar, A., Thompson-Schill, S. L., Ribeiro, A., & Bassett, D. S. (2018). Functional alignment with anatomical networks is associated with cognitive flexibility. *Nat Hum Behav*, 2(2), 156-164.
48. Meijer, K. A., Steenwijk, M. D., Douw, L., Schoonheim, M. M., & Geurts, J. J. G. (2020). Long-range connections are more severely damaged and relevant for cognition in multiple sclerosis. *Brain*, 143(1), 150-160.
49. Miller, K. L., Alfaro-Almagro, F., Bangerter, N. K., Thomas, D. L., Yacoub, E., Xu, J., . . . Smith, S. M. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci*, 19(11), 1523-1536. doi:10.1038/nn.4393
50. Murayama, R., Cai, Y., Nakamura, H., & Hashimoto, K. (2025). Demyelination in psychiatric and neurological disorders: Mechanisms, clinical impact, and novel therapeutic strategies. *Neuroscience & Biobehavioral Reviews*, 174, 106209. doi:<https://doi.org/10.1016/j.neubiorev.2025.106209>
51. Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage*, 154, 169-173.
52. Neumane, S., Gondova, A., Leprince, Y., Hertz-Pannier, L., Arichi, T., & Dubois, J. (2022). Early structural connectivity within the sensorimotor network: Deviations related to prematurity and association to neurodevelopmental outcome. *Front Neurosci*, 25;16(1662-4548 (Print)). doi:10.3389/fnins.2022.932386
53. Owen, M. J., & Williams, N. M. (2021). Explaining the missing heritability of psychiatric disorders. *World Psychiatry*, 18;20(2)(1723-8617 (Print)), 294-295. doi:10.1002/wps.20870
54. Park, H.-J., & Friston, K. (2013). Structural and functional brain networks: from connections to cognition. *Science*, 342(6158), 1238411.
55. Pedersen, M., Omidvarnia, A., Shine, J. M., Jackson, G. D., & Zalesky, A. (2020). Reducing the influence of intramodular connectivity in participation coefficient. *Network Neuroscience*, 4(2), 416-431.

56. Perez, D. C., Hernandez, J. J., Wulfekuhle, G., & Gratton, C. (2024). Variation in brain aging: A review and perspective on the utility of individualized approaches to the study of functional networks in aging. *Neurobiol Aging*.
57. Preti, M. G., Bolton, T. A., & Van De Ville, D. (2016). The dynamic functional connectome: State-of-the-art and perspectives. *Neuroimage*, S1053811916307881.
58. Preti, M. G., & Van De Ville, D. (2019). Decoupling of brain function from structure reveals regional behavioral specialization in humans. *Nat Commun*, 10(1), 4747.
59. Preti, M. G., & Van De Ville, D. (2024). *Temporal Fluctuations of Brain Structure-Function Coupling as a Potential Marker of Drowsiness During Resting State*. Paper presented at the 2024 IEEE International Symposium on Biomedical Imaging (ISBI).
60. Shakil, S., Lee, C.-H., & Keilholz, S. D. (2016). Evaluation of sliding window correlation performance for characterizing dynamic functional connectivity and brain states. *Neuroimage*, 133, 111-128.
61. Shine, J. M. (2019). Neuromodulatory influences on integration and segregation in the brain. *Trends in cognitive sciences*.
62. Suárez, L. E., Markello, R. D., Betzel, R. F., & Misic, B. (2020). Linking structure and function in macroscale brain networks. *Trends in cognitive sciences*, 24(4), 302-315.
63. Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., . . . Landray, M. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS medicine*, 12(3), e1001779.
64. Sun, Y., Yin, Q., Fang, R., Yan, X., Wang, Y., Bezerianos, A., . . . Sun, J. (2014). Disrupted functional brain connectivity and its association to structural connectivity in amnesic mild cognitive impairment and Alzheimer's disease. *Plos One*, 9(5), e96505.
65. Thompson, D. J., Wells, D., Selzam, S., Peneva, I., Moore, R., Sharp, K., . . . Giner-Delgado, C. (2022). UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. *MedRxiv*, 2022-2006.
66. Thompson, D. J., Wells, D., Selzam, S., Peneva, I., Moore, R., Sharp, K., . . . Giner-Delgado, C. (2024). A systematic evaluation of the performance and properties of the UK Biobank Polygenic Risk Score (PRS) Release. *Plos One*, 19(9), e0307270.
67. Tooley, U. A., Kenley, J. K., Camacho, M. C., Latham, A., Alexopoulos, D., Nielsen, A. N., . . . Smyser, C. D. (2025). Structure-function coupling in the first month of life: Associations with age and attention. *Proceedings of the National Academy of Sciences*, 122(23), e2412729122. doi:10.1073/pnas.2412729122
68. Tournier, J.-D., Smith, R., Raffelt, D., Tabbara, R., Dhollander, T., Pietsch, M., . . . Connelly, A. (2019). MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage*, 116137.
69. Uddin, L. Q. (2013). Complex relationships between structural and functional brain connectivity. *Trends in cognitive sciences*, 17(12), 600-602.

70. Valk, S. L., Xu, T., Paquola, C., Park, B.-y., Bethlehem, R. A. I., Vos de Wael, R., . . . Kochunov, P. (2022). Genetic and phylogenetic uncoupling of structure and function in human transmodal cortex. *Nat Commun*, 13(1), 2341.
71. Vandewouw, M. M., Hunt, B. A. E., Ziolkowski, J., & Taylor, M. J. (2021). The developing relations between networks of cortical myelin and neurophysiological connectivity. *Neuroimage*, 237, 118142.
72. Whalley, K. (2015). Brain ageing: Last in, first out? *Nature Reviews Neuroscience*, 16(1).
73. Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., . . . Polimeni, J. R. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*.
74. Yu, R., Deochand, C., Krotow, A., Leão, R., Tong, M., Agarwal, A. R., . . . de la Monte, S. M. (2015). Tobacco Smoke-Induced Brain White Matter Myelin Dysfunction: Potential Co-Factor Role of Smoking in Neurodegeneration. *Journal of Alzheimer's Disease*, 50(1), 133-148. doi:10.3233/JAD-150751
75. Zamani Esfahlani, F., Faskowitz, J., Slack, J., Mišić, B., & Betzel, R. F. (2022). Local structure-function relationships in human brain networks across the lifespan. *Nat Commun*, 13(1), 2053.
76. Zarkali, A., McColgan, P., Leyland, L.-A., Lees, A. J., Rees, G., & Weil, R. S. (2021). Organisational and neuromodulatory underpinnings of structural-functional connectivity decoupling in patients with Parkinson's disease. *Communications Biology*, 4(1), 86.
77. Zhang, J., Zhang, Y., Wang, L., Sang, L., Yang, J., Yan, R., . . . Qiu, M. (2017). Disrupted structural and functional connectivity networks in ischemic stroke patients. *Neuroscience*, 364, 212-225.
78. Zhang, Z., Wei, W., Wang, S., Li, M., Li, X., Li, X., . . . Guo, W. (2024). Dynamic structure-function coupling across three major psychiatric disorders. *Psychological Medicine*, 54(8), 1629-1640.
79. Zhang, Z., Zhang, C., Zhang, X., Xu, Y., Dou, W., Li, M., . . . Li, B. (2025). Dynamic structure-function coupling in macroscale neonatal brain networks. *Communications Biology*.

Figures

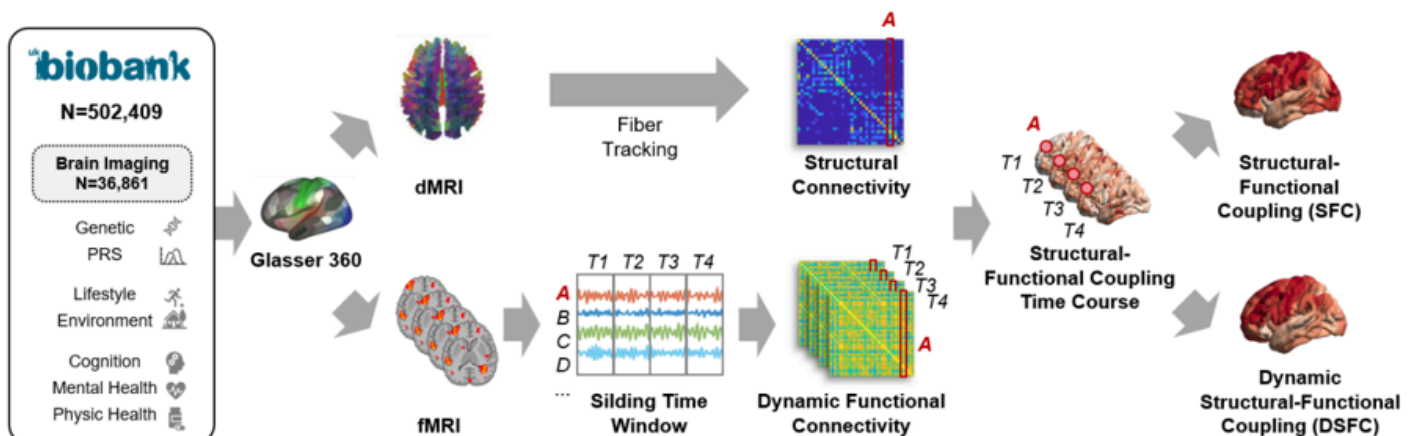


Figure 1

Study workflow for SFC and DSFC. Multimodal data integration and coupling analysis. Data from the UK Biobank ($N=502,409$; brain imaging after quality control, $N=34,067$) included genetics, lifestyle, and health phenotypes. Structural connectivity was derived from dMRI via tractography (Glasser 360 parcellation). Dynamic functional connectivity was estimated using a sliding-window approach (length: 30 TRs; step: 5 TRs), enabling calculation of dynamic structure–function coupling (DSFC). For each window ($T_1, T_2, T_3, T_4, \dots$) and region (in figure, region A), structure–function coupling was defined as the Spearman correlation between its structural and functional connectivity profiles. Static structure–function coupling (SFC) represents the temporal mean of coupling across windows, while dynamic structure–function coupling (DSFC) denotes the temporal standard deviation (SD).

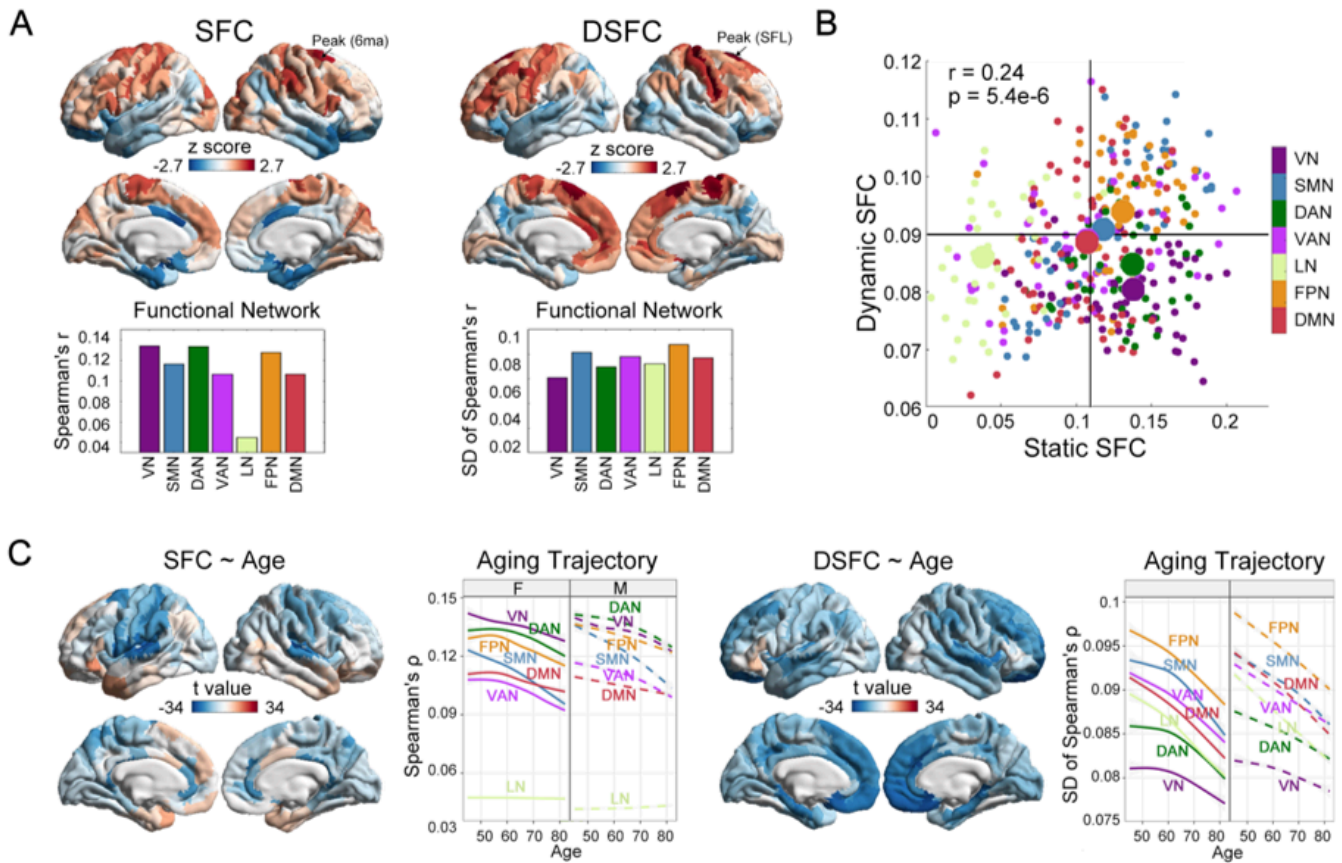


Figure 2

Spatial patterns and aging effects of SFC and DSFC. (A-B) Averaged patterns. Surface maps and network-level bar graphs (Yeo et al., 2011) show mean SFC and DSFC. Scatter plots illustrate regional values ($N=360$), with colors indicating functional network affiliation. (C) Aging trajectories. Brain maps display regional age effects (t-statistics from LMMs), thresholded at $p_{FWE} < 0.05/360$. Trajectory plots show network-specific aging for females (F, solid lines) and males (M, dashed lines), modeled via GAMMs. Left:

SFC shows significant declines primarily in sensorimotor systems. Right: DSFC highlights marked reductions in associative networks (e.g., DMN, FPN). Network abbreviations: VN, visual; SMN, sensorimotor; DAN, dorsal attention; VAN, ventral attention; LN, limbic; FPN, frontoparietal; DMN, default mode.

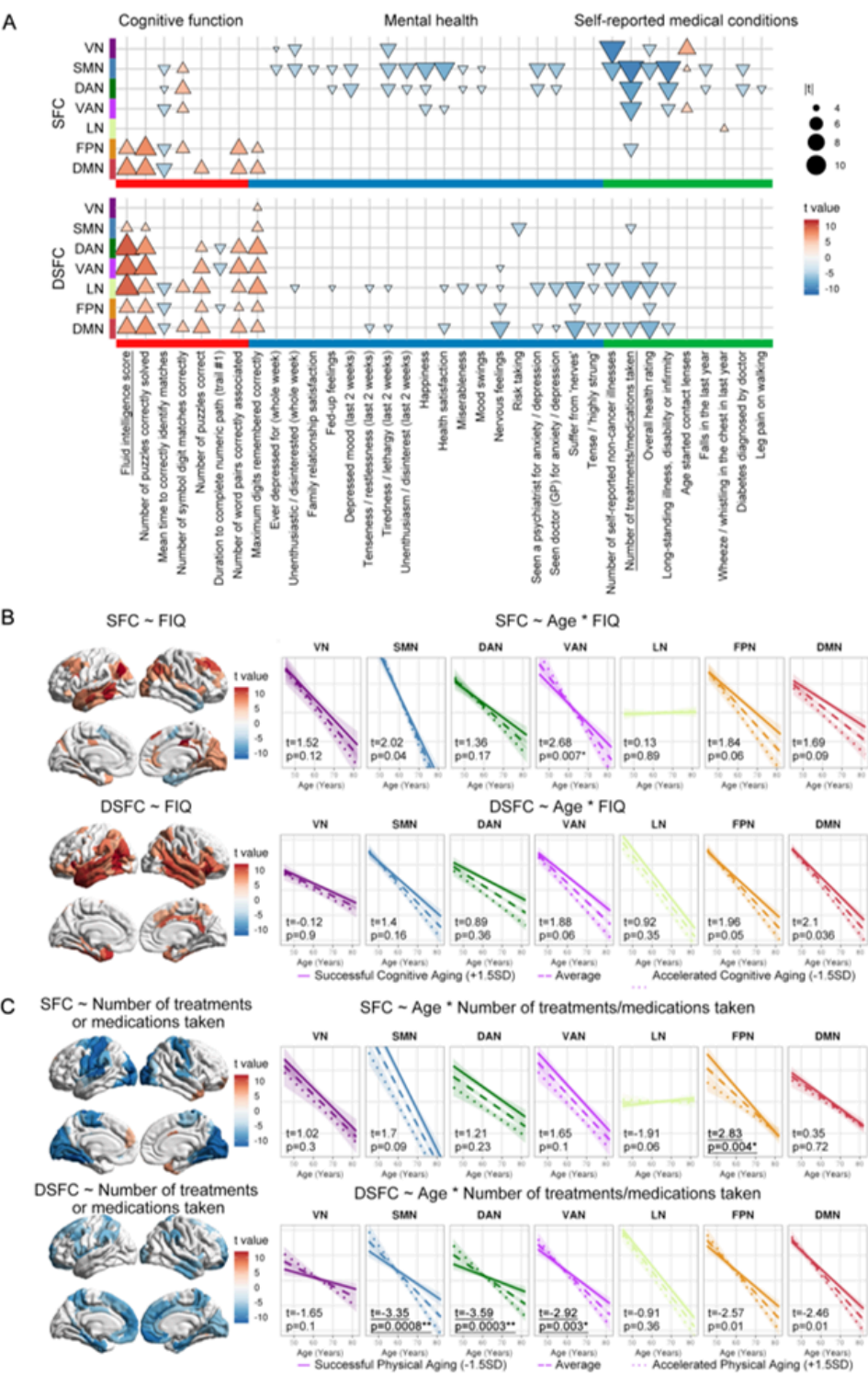


Figure 3

Associations of SFC and DSFC with cognitive and health phenotypes. (A) Heatmap of associations (t -values) between SFC (top) and DSFC (bottom) across cognitive (green), mental health (red), and physical health (blue) categories. Significant associations surviving FWE correction ($p_{FWE} < 0.05/(7 \times 75)$) are shown. (B-C) Spatial and interaction effects. Left: Surface maps of t -statistics for SFC/DSFC associations with fluid intelligence quotient (FIQ) and medication load (thresholded at $p_{FWE} < 0.05/360$ regions). Red-yellow/blue-light blue indicate positive/negative t -values. Right: Interaction between age and successful aging (SA) groups across functional networks. SA groups were defined based on higher fluid intelligence scores and lower medication load, reflecting better cognitive performance and lower health burden. Lines represent SA (solid; high intelligence/low medication), Intermediate (dashed), and Non-SA (dotted) groups. Subplots display t -statistics and p -values for interaction effects (LMMs). Underlines indicate interactions surviving FWE correction ($p_{FWE} < 0.05/7$ networks). Significance levels: * $p_{FWE} < 0.05/7$; ** $p_{FWE} < 0.01/7$.

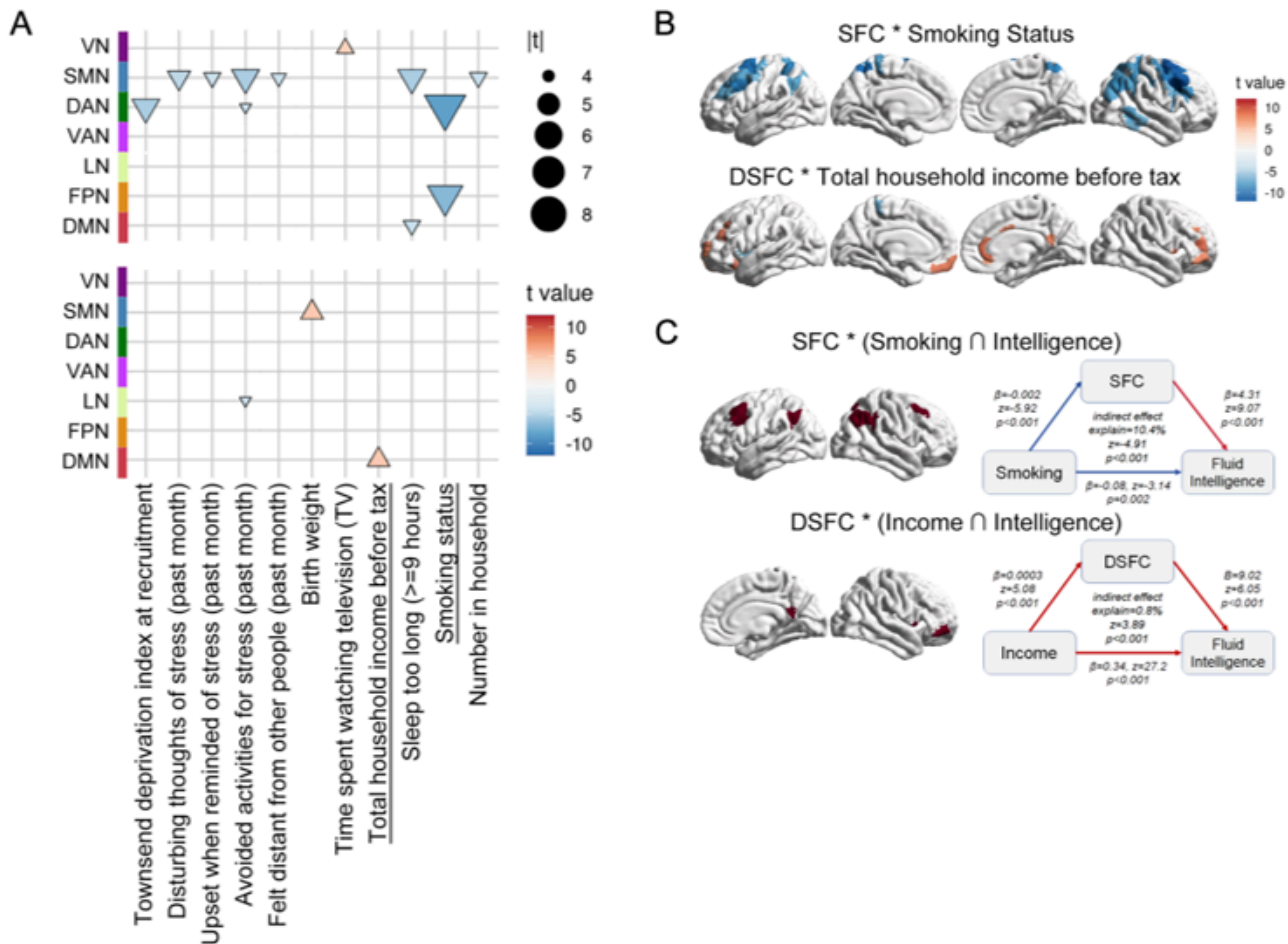


Figure 4

Environmental/lifestyle influences and mediation pathways. (A) Associations with environmental/lifestyle factors. Circle size and color in the matrix plot indicate the magnitude and direction of t -statistics, respectively. (B) Brain maps show the t -statistics, highlighting the significant effects of smoking on SFC and household income on DSFC ($p_{FWE} < 0.05$, corrected for 7 networks $\times$ 56 factors and 360 region). (C) Mediation

pathways. Models depict SFC/DSFC as mediators between environmental factors (smoking, income) and fluid intelligence. Path coefficients (β) represent standardized effect sizes. Indirect effects and their significance (p -values) were estimated using bootstrapping (10,000 iterations).

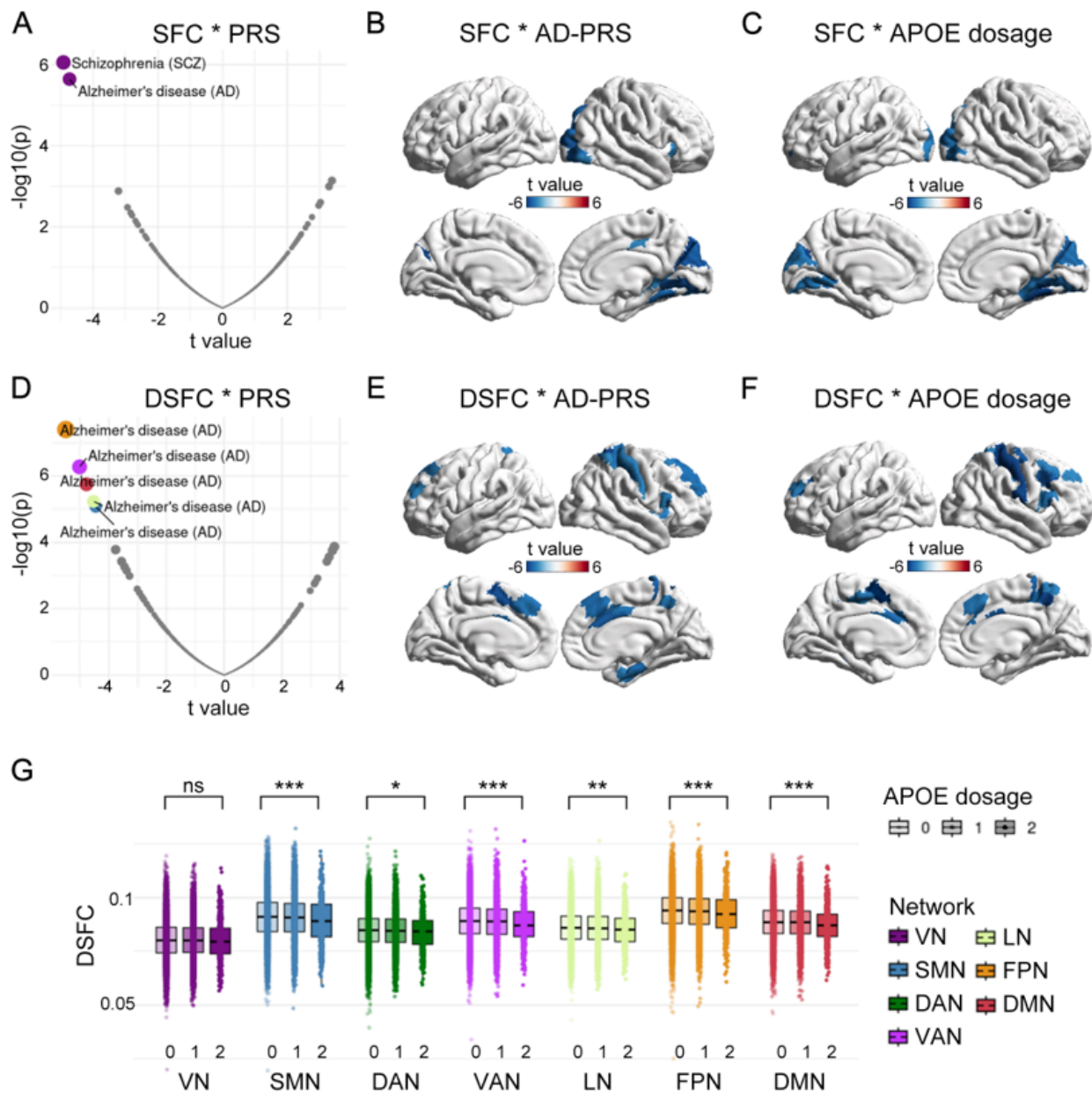


Figure 5

Associations of SFC and DSFC with polygenic risk scores and APOE $\epsilon 4$ dosage. (A, D) Volcano plots (or Manhattan-style plots) showing the association between network-level (A) SFC and (D) DSFC with 87 polygenic risk scores (PRSs). The y-axis represents $-\log_{10}(p)$ -values and the x-axis represents t-statistics. (B, E) Cortical surface maps illustrating the spatial distribution of associations (t-values) between (B) SFC

and (E) DSFC with the PRS for Alzheimer's disease (AD-PRS). (C, F) Brain maps showing the regional associations of (C) SFC and (F) DSFC with APOE $\epsilon 4$ allele dosage (0, 1, or 2). Results are thresholded at $p_{FWE} < 0.05$, with the number of comparisons defined as 7 networks $\times$ 87 PRSs for network-level analyses, and 360 regions for region-level analyses. (G) Network-specific effects of APOE $\epsilon 4$ dosage. Box plots illustrate the distribution of coupling strength across $\epsilon 4$ dosage groups for each functional network. Inter-group differences were assessed using the Kruskal-Wallis test, with significance levels denoted as: *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

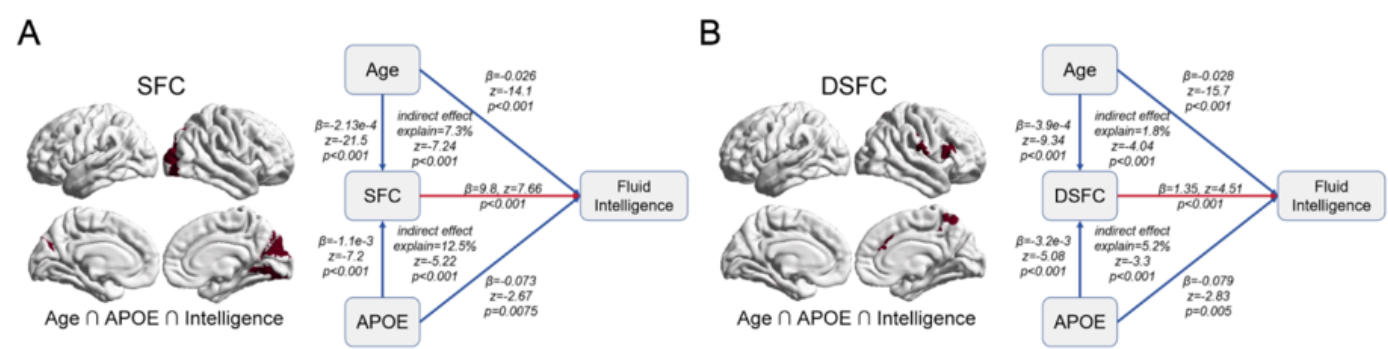


Figure 6

Mediation pathways linking aging and genetic risk to cognitive decline. (A) Static SFC mediation: parallel multiple predictor mediation illustrating the mediating role of SFC (specifically within occipital visual cortex) in the relationship between age, APOE $\epsilon 4$ dosage, and fluid intelligence. (B) Dynamic SFC mediation: Parallel mediation model for DSFC (specifically within the ventral attention/higher-order networks). In both models, standardized path coefficients (β) and their significance levels are provided for direct and indirect effects. Intersection brain regions used for calculating mediator values are highlighted in red on the surface maps. All indirect effects were tested using bootstrapping with 5,000 iterations.

Supplementary Files

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