Concept Paper

Provisional Paper Title: Associations of chronological age and pace of biological aging with individualized features of brain function

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Today's Date: 1/16/23

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The human brain changes substantially during aging. Beginning during early adulthood, accumulated damage leads to degeneration of the brain over decades and faster degradation is associated with many age-related diseases, most notably dementia. While the effects of aging on brain structure are increasingly well-characterized, the effects of aging on brain function are less clear. Better understanding changes in brain functional organization is important as brain function is a dynamic aspect of brain homeostasis that is sensitive to aging and is especially related to behavior (Marek et al, 2022). Brain function can be estimated by measuring blood flow using functional magnetic resonance imaging (fMRI) and can be organized into approximately 17 different *functional networks* (Yeo et al., 2011). Functional networks are sets of brain areas that have coordinated neural firing over time. While these functional networks have coordinated activity, the brain areas that make up one functional network may be located at distant parts of the brain. With this project, we seek to describe aging associations between the **size, shape, spatial location,** and **strength** of functional brain networks. As our measures of aging, we will use (i) the pace of biological aging during midlife using data from Phase 45 of the Dunedin Study (Elliott et al., 2021), and (ii) chronological age using data from the Human Connectome Project in Aging (HCP-A; Bookheimer et al., 2019).

The first measure of brain function we will use in this analysis is *functional topography. Functional* because this measure is derived from brain function from fMRI data, and *topography* because it estimates the spatial pattern of brain function. Traditional studies of functional networks in the brain assume that the brain areas involved in each functional network are identical from person to person. However, people have some variation in the brain areas that make up their functional networks (Gordon et al., 2017). Functional topography estimates which specific areas of the brain make up an individual person's functional networks. Individual differences in functional topography are related to individual differences in personality, emotion, and cognition (Kong et al., 2019). We will use previously generated estimates of functional topography generated in the Dunedin cohort (Whitman et al., 2023), and create analogous estimates in the HCP-A dataset. This will allow us to test how the **size, shape,** and **spatial location** of functional networks are associated both with the pace of biological aging and chronological age.

The second measure of brain function we will use in this analysis is *functional connectivity*. *Functional* because this measure is also derived from brain function from fMRI data, and *connectivity* because it estimates the strength of coordinated activity from different brain regions. To measure this, we will divide the brain into 400 regions and test how strongly brain activity is correlated between all pairs of brain regions. This is also referred to as a *connectome.* As described above, traditional studies have relied on group averages to define this set of brain regions. However, recent advances have made it possible to create individualized estimates of these 400 brain regions, thus making it possible to create individualized connectomes. These individualized connectomes are also more closely related to behavior than traditional connectomes (Kong et al., 2021). We will produce an individualized connectome for each Dunedin Study member and HCP-A participant. We will then test how pace of biological aging and chronological age are each associated with the strength of connections in that individual's connectome. This will allow us to test how the **strength** of functional networks are associated with pace of biological aging and with chronological age.

We hypothesize that associations with pace of biological aging and chronological age will both be most pronounced in "higher-order" functional networks such as the default mode, frontoparietal, and attention networks. Specifically, we predict that these higher-order networks will be smaller, weaker, and show greater variation in their shape and spatial location among older individuals in HCP-A and among those aging more quickly in the Dunedin Study.

Question 1:
How are the size, shape, spatial location, and strength of functional networks associated with pace of biological aging at midlife?

We use previously generated individualized functional topography maps of the cerebral cortex of 769 Dunedin Study members using Multi-Session Hierarchical Bayesian Modeling (MS-HBM) (Kong et al., 2019). MS-HBM is a well-validated, reliable, open-source algorithm. This method creates a group average of functional topography for the whole cohort and then identifies an individual study member's deviation from this group average to estimate that individual's unique functional network topography (Kong et al., 2019). We will also use MS-HBM to generate individualized areal parcellations of each Study member's brain (Kong et al., 2021). Using these individualized parcellations, we will then generate individualized connectomes.

We will then use ridge regression models to predict each Study Member's pace of biological aging from their unique functional topography and connectivity. Our first ridge regression model will be trained using network size, shape, and spatial location, while our second ridge regression model will be trained using network strength. Both models will predict the pace of biological aging using a split-half approach. Ridge regression models show high efficacy at predicting behavior using functional topography data (Kong et al., 2019; Whitman et al., 2023). These models will indicate how much individual differences in network **size**, **shape**, **spatial location**, and **strength** are correlated with individual differences in midlife pace of biological aging.

Question 2:
How are the size, shape, spatial location, and strength of functional networks associated with chronological age?

Next, we will repeat the above steps using the HCP-A dataset with chronological age as our outcome measure. We will use MS-HBM to generate both estimates of individualized

functional network topography as well as individualized connectomes of 711 HCP-A (ages 36-100 years, mean age = 60.3 years) participants. We will again train one ridge regression model on network size, shape, and spatial location. Next, we will train a second ridge regression model using network strength. We will again test these models' prediction ability using a split-half approach. These models will indicate how much individual differences in network **size**, **shape**, **spatial location,** and **strength** are correlated with chronological age during midlife and aging.

Question 3:
Are the same functional networks associated with pace of biological aging and with chronological age?

Next, we will explicitly compare the associations with pace of biological aging and chronological aging to test whether they converge on higher-order brain networks. To compare associations with network size, shape, and spatial location, we will repeat our ridge regression models using functional topography information from only certain regions of the brain. We can then empirically test whether network **size**, **shape**, and **spatial location** from similar brain regions are able to predict both pace of biological aging and chronological age.

We will then use a method known as a Haufe-transformation to identify which connections in participants' connectomes are most important for prediction (Chen et al., 2022). We will then test whether a similar set of connections most important for predicting pace of biological aging and chronological age. This will allow us to discern whether a similar pattern of network connectivity **strength** predicts pace of biological aging and chronological age.

Question 4:
How do these features of brain function relate to age-related behavioral outcomes?

Finally, based on prior work in the Dunedin Study (Whitman et al., 2023), we will attempt to expand and replicate functional network associations with cognitive ability, gait speed, and sensorimotor ability using data from the HCP-A study. Following the approach of Whitman et al., we will attempt to predict IQ, gait speed, and various sensorimotor abilities using ridge regression models trained on network **size**, **shape**, **spatial location**, and **strength** in both the Dunedin and the HCP-A study. We predict that functional topography associations with these behavioral measures will be strongest in higher-order functional networks, such as the default mode network.

Variables needed at which ages:

Dunedin:
Full fMRI scans (task and rest) at age 45
Pace of biological aging at age 45
Gait speed at age 45

HCP-A:
Full fMRI scans (task and rest)
Chronological age
Full-scale IQ
Gait speed
Words in noise task score

Visual acuity
Contrast sensitivity

Significance of the study:

This study will leverage two large datasets to provide first description of age- and aging-related associations with individualized features of brain function. In doing so, we will help answer whether chronological age and aging show similar patterns of associations with brain function. Second, we will answer whether these associations are most pronounced in higher-order brain networks that are thought to show the earliest and most pronounced changes during aging. Finally, we will attempt to validate these associations with common behavioral measures thought to index aging.

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