Concept Paper

Provisional Paper Title: Does a common functional brain network explain why people with high cognitive ability also have better motor function and auditory processing?

Proposing Author: Ethan T. Whitman

P.I. Sponsor: Terrie Moffitt, Ahmad Hariri
(if the proposing author is a student or colleague of an original PI)

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

Objective of the study:

An aging global population has accelerated the need to understand the psychology and biology of aging. Crucially, not everyone ages at the same rate. Previous work in the Dunedin Study has shown that people of the same chronological age vary in behaviors such as gait speed, auditory discrimination, and cognitive ability (Elliott et al., 2021). In addition, variation in these behaviors may be linked, as measures of gait, audition, and cognitive ability tend to be correlated within an individual (Rasmussen et al., 2019). However, the extent to which these various behaviors are associated with common functional brain networks is unclear. Brain activity can be estimated by measuring blood flow using functional magnetic resonance imaging (fMRI). Human brain function is 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. Crucially, although these functional networks have coordinated activity, the brain areas that make up a single functional network may be located at distant parts of the brain. With this project, we want to test whether there is overlap between the functional networks most associated with gait speed, auditory processing, and cognitive ability.

This project will test two hypotheses. First, it is possible that the same few functional networks are associated with gait speed, auditory discrimination, and cognitive ability (Poole et al., 2019). This would suggest that we see correlations in these behaviors because they rely on the same set of functional brain networks. Second, it is possible that three or more different functional networks are each independently associated with gait speed, auditory discrimination, and cognitive ability. If this is the case, the correlation between these behaviors might not reflect a single shared network in the brain, but rather the health of many different functional networks across the brain. Distinguishing between these hypotheses can help tell us why people with greater cognitive ability also tend to have better motor and auditory functioning.

To test these hypotheses, we will use a novel approach to analyzing brain function called *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). The proposed analyses will use brain imaging data from the Dunedin cohort to produce the first population-representative estimates of functional topography. We will then conduct exploratory analyses to test whether gait speed, auditory discrimination, and cognitive ability are linked by a common functional brain network. This will help explain the brain mechanisms that link motor function, auditory processing, and cognition.

Question 1:

Is functional topography related to gait speed, auditory discrimination, and cognitive ability?

We will generate individual-specific functional topography maps of the cerebral cortex of each Dunedin study member 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 topography (Kong et al., 2019).

We will then use ridge regression models to predict each Study Member's cognitive ability, gait speed, and auditory discrimination from their unique functional topography. Ridge regression models show high efficacy at predicting behavior using functional topography data (Cui et al., 2020, Kong et al., 2019). These models will indicate how much individual differences in functional topography are correlated with individual differences in gait speed, auditory discrimination, and cognitive ability. As these behavioral association analyses are exploratory, we will use a split-half design to more rigorously tests any associations we observe. Specifically, we will use half of the Study Members' data to develop our regression models and then test these models' ability to predict the remaining Study Members' behaviors according to their functional topography data. We will also conduct cross-validation procedures to test the robustness of our findings to sample variation.

Question 2:

Which functional networks are most associated with gait speed, auditory discrimination, and cognitive ability?

Next, we will investigate which brain regions' functional topography is most correlated with these behaviors. Prior work has found the greatest correlation between functional topography and cognitive ability in frontal, parietal, and temporal brain regions (Kong et al., 2019). Networks comprised of these regions are considered "high-order," meaning that they are associated with complex behaviors such as cognitive ability, executive function, and decision making. These "high-order" networks are also comprised of many brain areas that are physically distant from each other. To our knowledge, associations between functional topography, motor function, and auditory discrimination have not been investigated. If we find associations between motor function and gait speed in the same brain regions that we find associations with cognitive ability, this suggests that a handful of "high-order" brain networks influences individual differences across a range of behaviors. On the other hand, finding that each different behavior is associated with its own unique brain region would suggest that these behaviors are somewhat "localized" to their respective brain area.

Question 3:
How do the functional networks associated with gait speed, auditory discrimination, and cognitive ability relate to other brain phenotypes?

After determining which brain regions' functional topography is most associated with gait speed, auditory discrimination, and cognitive ability, we will then test whether these regions spatially overlap with other measures of brain anatomy, brain function, and gene expression. Using recently developed tools, we will test whether the pattern of functional networks observed in Dunedin study members shows similarity to previously published patterns of related brain phenotypes such as myelination or evolutionary expansion (Alexander-Bloch et al., 2018; Markello et al., 2022). We will also test whether the pattern of functional networks most associated with behavior shows similarity to measures of cortical thickness and surface area derived from structural MRIs in our Study members.

Variables needed at which ages:
Adult IQ at age 45
Gait Rite at age 45
Auditory discrimination at age 45
Full fMRI scans (task and rest) at age 45
Total and regional cortical thickness at age 45
Total and regional surface area at age 45

Significance of the study:

This study will help explain why people with better motor function and better hearing tend to have higher cognitive ability. In doing so, we will help answer whether relatively simple behaviors such as gait and auditory processing are "localized" to specific regions of the brain or whether they also engage the "high-order" functional networks that are located across the brain and have been previously associated with cognitive ability.

References:

Alexander-Bloch, A. F., Shou, H., Liu, S., Satterthwaite, T. D., Glahn, D. C., Shinohara, R. T., Vandekar, S. N., & Raznahan, A. (2018). On testing for spatial correspondence between maps of human brain structure and function. *NeuroImage, 178,* 540–551. https://doi.org/10.1016/j.neuroimage.2018.05.070

Cui, Z., Li, H., Xia, C. H., Larsen, B., Adebimpe, A., Baum, G. L., Cieslak, M., Gur, R. E., Gur, R. C., Moore, T. M., Oathes, D. J., Alexander-Bloch, A. F., Raznahan, A., Roalf, D. R., Shinohara, R. T., Wolf, D. H., Davatzikos, C., Bassett, D. S., Fair, D. A., … Satterthwaite, T. D. (2020). Individual Variation in Functional Topography of Association Networks in Youth. *Neuron, 106*(2), 340–353.e8. https://doi.org/10.1016/j.neuron.2020.01.029

Elliott, M. L., Caspi, A., Houts, R. M., Ambler, A., Broadbent, J. M., Hancox, R. J., Harrington, H., Hogan, S., Keenan, R., Knodt, A., Leung, J. H., Melzer, T. R., Purdy, S. C., Ramrakha, S., Richmond-Rakerd, L. S., Righarts, A., Sugden, K., Thomson, W. M., Thorne, P. R., … Moffitt, T. E. (2021). Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. *Nature Aging, 1*(3), 295–308. https://doi.org/10.1038/s43587-021-00044-4

Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., Ortega, M., Hoyt-Drazen, C., Gratton, C., Sun, H., Hampton, J. M., Coalson, R. S., Nguyen, A. L., McDermott, K. B., Shimony, J. S., Snyder, A. Z., Schlaggar, B. L., Petersen, S. E., Nelson, S. M., & Dosenbach, N. U. F. (2017). Precision Functional Mapping of Individual Human Brains. *Neuron*, *95*(4), 791–807.e7. https://doi.org/10.1016/j.neuron.2017.07.011

Kong, R., Li, J., Orban, C., Sabuncu, M. R., Liu, H., Schaefer, A., Sun, N., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2019). Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion. *Cerebral Cortex* , *29*(6), 2533–2551. https://doi.org/10.1093/cercor/bhy123

Markello, R. D., Hansen, J. Y., Liu, Z.-Q., Bazinet, V., Shafiei, G., Suárez, L. E., Blostein, N., Seidlitz, J., Baillet, S., Satterthwaite, T. D., Mallar Chakravarty, M., Raznahan, A., & Misic, B. (2022). neuromaps: structural and functional interpretation of brain maps. In *bioRxiv* (p. 2022.01.06.475081). https://doi.org/10.1101/2022.01.06.475081

Poole, V. N., Lo, O.-Y., Wooten, T., Iloputaife, I., Lipsitz, L. A., & Esterman, M. (2019). Motor-Cognitive Neural Network Communication Underlies Walking Speed in Community-Dwelling Older Adults. *Frontiers in Aging Neuroscience*, *11*, 159. https://doi.org/10.3389/fnagi.2019.00159

Rasmussen, L. J. H., Caspi, A., Ambler, A., Broadbent, J. M., Cohen, H. J., d'Arbeloff, T., Elliott, M., Hancox, R. J., Harrington, H., Hogan, S., Houts, R., Ireland, D., Knodt, A. R., Meredith-Jones, K., Morey, M. C., Morrison, L., Poulton, R., Ramrakha, S., Richmond-Rakerd, L., … Moffitt, T. E. (2019). Association of Neurocognitive and Physical Function With Gait Speed in Midlife. *JAMA Network Open*, *2*(10), e1913123. https://doi.org/10.1001/jamanetworkopen.2019.13123

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011