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Concept Paper Form

Provisional Paper Title: Can individual differences in the macroscale organization of cortex be reliably measured and mapped onto cognition and aging?
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Today's Date: 5/18/2021

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

Objective of the study:

The human brain supports many distinct sensory and cognitive processes, which to some degree reflect the specialized activity of discrete regions. One major goal of neuroscience is to understand how different brain regions work collectively to integrate concrete sensory information with abstract cognition to generate complex adaptive behaviors (Goldman-Rakic, 1988; Mesulam, 1998). For example, for an outfielder to catch a fly ball, the brain must first process and filter a rich field of visual information to detect subtle distinctions between the clouds and a baseball flying through the air. Then the outfielder must integrate this visual information over time to calculate an expected trajectory of the baseball. Then this expected trajectory must be refined as visual information is integrated with auditory information from the sound of the bat with motor and tactile information indicating the speed of the wind, to generate motor action towards the expected landing place of the baseball. This motor action is motivated and informed by abstract rules of the game of baseball that the outfielder has learned over time (e.g., an out is generated by catching the fly ball in the air), as well as information in working memory regarding the state of the current baseball game (e.g., there is one out with a runner on third-base) and self-awareness about the outfielder's location, in related to spatial awareness of the location of other players (i.e., I am the center fielder and therefore I must catch this ball because the right fielder is too far away).

This process of abstracting and integrating incoming sensory information has been suggested as a fundamental, low-dimensional, organizing principle of cortical specialization and function (Mesulam, 1998). A growing literature has recently identified and begun to describe a single macroscale gradient across the cortex that may

represent the anatomical basis of this organization. At one end of this macroscale gradient are regions specialized to perform low-level processing of sensory and motoric information (e.g., visual and motor cortex) (Mesulam, 1998). At the opposite end of this gradient are the so-called association cortices, which reach their apex in the default mode network – best known for its role in abstract cognitive faculties including episodic memory, semantic cognition, theory of mind, and reasoning about the future (Buckner & DiNicola, 2019).

The position of any specific anatomical cortical region along this macroscale gradient of sensory abstraction can be described by several features. Unimodal cortical regions lower in the hierarchy (e.g., visual and motor cortex) tend to be one or two synapses away from direct and specific sensory inputs (e.g., retinal ganglion cell and cochlear neurons), whereas multimodal cortical regions at the apex of the hierarchy (e.g., posterior cingulate cortex and dorsolateral prefrontal cortex), have very few direct synaptic connections to sensory neurons but, instead, are often 4 or more synapses removed (Buckner & Margulies, 2019; Mesulam, 1998). In addition, several other features differentiate multimodal association from unimodal sensory cortex in a graded, continuous fashion. Moving along the gradient from sensory to association cortex, the cortex becomes increasingly less myelinated, has more dendritic spines, more inhibitory interneurons, maintains information over longer timescales, and has more diverse connectivity to the rest of the brain (Burt et al., 2018; Demirtaş et al., 2019; Nakai & Nishimoto, 2020; Schultz et al., 2021; Wang, 2020). Together these features suggest a hierarchy of sensory abstraction with an ever-increasing capacity to flexibly gate a greater and greater number of inputs, along with fewer structural constraints, decreasing responsiveness to external stimulation, and an increasing ability to maintain information over time (Buckner & DiNicola, 2019; Fox et al., 2020; Huntenburg et al., 2018; Wang, 2020). In addition, multimodal association regions at the apex of this gradient are the most expanded in hominid evolution and take the longest to mature during development, suggesting that this macroscale gradient may be one mechanism through which human-specific cognitive abilities of abstract cognition, self-awareness, language, deliberation, and social cognition may have arisen (Buckner & Krienen, 2013; Hill et al., 2010). These observations form the basis of the “tethering hypothesis” of cortical differentiation, which states that the regions of the brain at the apex of this macroscale gradient (e.g., the default mode network) allow for uniquely human cognitive abilities because they have become relatively “untethered from sensory signaling hierarchies” allowing for the specialization of association cortex for abstract, internally generated cognitive abilities (Buckner & Krienen, 2013). This hypothesis suggests that the increasing physical and functional “distance” between sensory and association regions of the cortex over evolutionary time has allowed for more abstract, uniquely human cognitive abilities.

While many of the early studies of this macroscale functional gradient were limited to invasive tract tracing studies in rodents and non-human primates, new methods allow for the macroscale gradient to be measured non-invasively in humans using fMRI (Margulies et al., 2016; Vos de Wael et al., 2020). Using fMRI data, the macroscale gradient can be estimated by applying dimensionality reduction techniques (typically

diffusion map embedding) to a functional connectivity (FC) matrix comprised of correlations between 1000s of voxels across the cortex (i.e., edges). When dimensionality reduction is performed, the macroscale sensory-association gradient typically emerges as the first gradient, explaining the most variance in the FC matrix (Margulies et al., 2016). Furthermore, on a group level, this principal FC gradient is strongly associated with MRI measures of myelination, fMRI estimates of functional timescales, and post-mortem patterns of gene expression (Burt et al., 2018; Demirtaş et al., 2019; Ito et al., 2020), revealing close conceptual alignment with invasive findings from non-human primates and mouse models (Fulcher et al., 2019; Murray et al., 2014; Wang, 2020).

While mounting evidence suggests that FC can be used to measure the macroscale gradient at a group level, it is still unclear to what extent individual differences in the macroscale gradient can be reliably measured and to what extent any resulting variability may be associated with individual differences in normal and pathological cognition. In this project, we will investigate individual differences in the fMRI-derived macroscale gradient with two primary aims.

Aim 1 - We will estimate the test-retest reliability of individual differences in the principal gradient derived from FC data. We will perform these test-retest studies using 2 samples: The Dunedin Study and the HCP-Young adult sample. In this aim we will ask 4 primary questions:

1) Can individual differences in the macroscale gradient be reliably measured?
   - We hypothesize that individual differences in the gradient can be reliably measured (ICC > 0.6) when enough data is used to generate estimates.

2) Are these individual differences more reliable than the measures of edgewise FC from which the gradient is derived?
   - We hypothesize that measures of the gradient will be more reliable, on average, than edgewise measures of FC because dimensionality reduction will tend to remove noise by extracting correlated dimensions of stable variation.

3) Are individual differences in the macroscale gradient more reliable when estimated from more fMRI data (as is the case with FC)?
   - We hypothesize that longer fMRI scans will produce more reliable measures of individual differences in the macroscale gradient than short fMRI scans.

4) Can individual differences in the macroscale gradient be reliably measured by combining short-resting scans with task-fMRI scans (as is the case with FC)?
   - We hypothesize that individual differences in the gradient will be measurable with rest alone, as well as by combining task-fMRI with resting-state data.

Aim 2 - If we can reliably measure individual differences in the macroscale gradient, our second aim is to test their behavioral and disease relevance. We will perform this aim in

3 samples: The Dunedin Study, the HCP-Young adult sample, and the HCP-Aging sample. First, given that evolutionarily expanded brain regions at the apex of the macroscale gradient are thought to support uniquely human cognitive abilities (Buckner & Krienen, 2013; Hill et al., 2010; Reardon et al., 2018), we will test whether individual differences in the macroscale gradient are associated with individual differences in cognitive abilities measured with cognitive tests. Second, we will investigate associations between individual differences in the macroscale gradient and aging because multiple theories of brain aging jointly implicate the macroscale gradient. Namely, the “last-in-first-out” and the “frontal” theories of brain aging, both suggest that association cortex (brain areas thought to support human-specific cognitive abilities that also have protracted development in humans and are disproportionately expanded during human development and evolution) are especially sensitive and susceptible to age-related degeneration (Fjell et al., 2014). In support of this theory, amyloid-beta and tau depositions, characteristic of Alzheimer's disease and related dementias (ADRD), are disproportionately found in association cortex, especially within the default mode network (Jagust, 2018). Furthermore, changes in functional connectivity in the default mode network have been found to predict cognitive decline and amyloid deposition, further highlighting the potential benefits of refining neurobiologically grounded FC biomarkers for understanding aging and ADRD-risk (Buckley et al., 2017; Elman et al., 2016; Jagust, 2018). Therefore, we will test whether individual differences in the macroscale gradient are associated with both chronological age and the pace of biological aging.

Given that little is known about individual differences in the FC-derived macroscale gradient, we will begin by testing whole-brain data-driven associations between the gradient, cognitive ability, and aging. However, within these data-driven investigations, we have hypotheses about the pattern of the results that we will further interrogate with follow-up hypothesis-driven analyses. First, because the tethering hypothesis proposes that human cognitive abilities emerged, in part, because association cortex became increasingly untethered and thus more functionally distinct from sensory input, we hypothesize that higher cognitive ability will be associated with a “larger gradient” in which the apex of the gradient (the default mode network) is further away from, and thus more functionally distinct, from primary sensory regions (e.g., visual and motor cortex). Second, because theories of brain aging suggest that the latest to develop and most evolutionary expanded brain regions (i.e., the default mode network) are the most affected by age-related decline, we hypothesize that advancing age will be associated with a “smaller gradient” in which the apex of the gradient (the default mode network) is closer to and therefore less functionally distinct from primary sensory regions (e.g., visual and motor cortex). It is worth noting that these aging and cognition hypotheses make complementary and opposing predictions that are consistent with the downward trajectory of many cognitive abilities across the lifespan.

Data analysis methods:

Samples: Human Connectome Project, Dunedin, and HCP-Aging samples will be investigated.

We will measure the sensory-association macroscale gradient from functional connectivity data with the BrainSpace toolbox (Vos de Wael et al., 2020). To generate gradients, we will use established parameters (e.g., diffusion map embedding, 10% sparsity, etc). Reliability will be assessed using test-retest reliability in the HCP and Dunedin datasets.

General cognitive ability will be assessed using the Raven's progressive matrices in the HCP dataset, the composite "total cognition" score in HCP-Aging, and WAIS full-scale IQ in Dunedin. Age associations will be assessed using chronological age in HCP and HCP-aging. The validity of these associations will be further explored by testing associations with biological aging, using the Pace of Aging measure in the Dunedin study.

First, whole-brain data-driven associations with gradient scores will be investigated in each region of the “Glasser 360” parcellation. Sex-adjusted OLS regression will be used to test for linear associations separately between each parcel’s gradient value, age, and cognition. FDR correction will be used to correct for multiple comparisons across all 360 regions.

Second, the "size of the gradient" will be quantified by calculating the distance between gradient values in sensory and association cortex. Gradient values in sensory and association regions will be separately averaged together. Then the difference between mean gradient values for sensory and association cortex will be calculated for each person to operationalize the gradient “size” or “untethering” of association cortex from sensory cortex.

Variables needed at which ages:

- WAIS IQ
- Pace of Aging
- sex

fMRI

- FC matrices

Significance of the Study (for theory, research methods, or clinical practice):

By measuring the reliability and behavioral relevance of the FC-derived macroscale gradient, this project has the potential to provide researchers with an FC-derived measure that is more reliable with less data than traditional FC measures. Moreover, associations with cognition and aging would help establish the gradient as a translational biomarker of interest with established neurobiological relevance.

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Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
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☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

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