Decreased segregation of brain systems across the healthy adult lifespan Micaela

* healthy adult lifespan sample (n = 210; 20–89 y)
* Increasing age is accompanied by decreasing segregation of brain systems

Young adults’ brain systems exhibit a balance of within- and between-system correlations that is characteristic of segregated and specialized organization. Increasing age is accompanied by decreasing segregation of brain systems

Healthy adult aging is characterized by a progressive degradation of brain structure and function associated with gradual changes in cognition (see

reduction in the specificity with which distinct neural structures mediate particular processing roles [i.e., a reduction in functional specialization, or “dedifferentiation”

Despite the compelling evidence for age-accompanied reductions in functional specialization across numerous brain areas, the relationship between neural specialization and cognition generally is weak. This likely is related to the fact that broad cognitive domains such as “long-term memory” and “executive control” are mediated by distributed and interacting brain systems, each consisting of multiple interacting brain areas. Thus, relating functional specialization in a single brain area to general measures of cognition likely will be unsuccessful. Such

cognitive decline evident even in healthy older adults may be related to decreased functional integrity at a systems level of organization.

relate systems-related functional specialization to age-accompanied differences in cognition

systems of brain areas typically mediate processing roles that span multiple stimulus and task demands. This

An alternative formal and complementary approach to defining a brain system involves understanding how brain areas relate to one another via their patterns of shared functional or anatomical relationships in the context of a large-scale network

When a brain network graph represents the interaction of areas, one prominent feature is the presence of subsets of areas that are highly interactive with one another and less interactive with other subsets of areas. T

Just like social networks, brain networks contain subnetworks or systems of highly related or interacting nodes (in the case of brains, nodes may represent neurons or brain areas). Using functional MRI to measure functional correlations between brain areas during periods of rest, we describe differences in brain network organization in a large group of individuals sampled across the healthy adult lifespan (20–89 y). We characterize a measure of system segregation, reflecting the degree to which the systems share connections among one another. Increasing age is accompanied by decreasing segregation of brain systems. Importantly, system segregation is predictive of measures of long-term memory function, independent of age.

Modular brain networks are characterized by a fine balance of dense within-system relationships among brain areas (nodes) that have highly related processing roles, as well as sparser (but not necessarily absent) relationships between areas in systems with divergent processing roles. This

As such, any deviation in the patterns of within- and between-system connectivity may be considered evidence for a change in the system’s specialization. Furthermore, if aging is associated with changes in functional specialization at the level of brain systems, this may be revealed by examining the differences in patterns of within- and between- system areal connectivity across age.

In the present study, the age-accompanied differences in the functional specialization of brain systems are revealed by examining patterns of within- and between-system areal RSFCs in a large healthy adult lifespan sample (n = 210; age range, 20–89 y)

references in general measures of cognitive ability. To foreshadow the results that follow, we report that aging is associated with differences in patterns of connectivity within and between brain systems, that these differences are not uniform across all systems, and that the segregation of brain systems has a direct relation- ship to measures of cognitive ability independent of age

a recently published RSFC-based area parcellation map. This parcellation map identified cortical locations where patterns of RSFCs exhibited abrupt transitions in a large group of subjects [i.e., putative area borders; Fig. 1A (37)]. Fixed- radius disks (3-mm radius) were built around putative area centers, defined in relation to the transitions, along the cortical surface (Fig. 1B). A total of 441 nonoverlapping disks were created across the

cortical surface of the two hemispheres; each of these disks served as a node in the construction of a graph representing an individual’s brain network. E

Each node was labeled according to a published functional system map, defined by consensus of system assignments using community detection of RSFCs across multiple thresholds (Fig. 1C) (19). The final system labels of each node are depicted in Fig. 1D, and SI Appendix, Table S6 lists the node count for each functional system. Using independent datasets to define nodes and assign system labels to these nodes allowed interrogation of connectivity within and between systems in an unbiased fashion. Brain graphs were constructed for each participant as a 441 × 441-node graph, labeled by RSFC-defined functional system. Edge weights were calculated as the Fisher z-transformed correlation (Pearson’s r) between each pair of nodes, and negatively weighted edges were removed from each correlation matrix to eliminate potential misinterpretation of negative edge weights (see

first were characterized according to whether they connected areas within a functional system or between distinct functional systems. Fig.

suggest that aging is accompanied by decreased independence of brain systems (by way of exhibiting weaker connectivity among areas within systems and greater connectivity between areas of distinct systems)

As a way of summarizing and quantifying the pattern of differences in the within-system correlations in relation to the between- system correlations, we created a measure of system segregation. This measure was calculated as the difference between the mean magnitudes of between-system correlations from the within-system correlations as a proportion of mean within-system correlation

Accordingly, values greater than 0 reflect relatively lower between-system correlations in relation to within-system correlations (i.e., stronger segregation of systems), and values less than 0 reflect higher between-system correlations relative to within-system correlations (i.e., diminished segregation of systems).

cross age, segregation values are greater than 0, demonstrating that mean within-system correlations are stronger than mean between-system correlations, regardless of age

Despite this commonality, older age is associated with decreasing system segregation (r = −0.53, P < 0.001). Moreover, this pattern was observed in 8 of the 10 systems of interest when interrogated individually (SI Appendix, Fig. S3B and Table S7).

Our measure of segregation is intimately related to the graph- theoretic concept of participation coefficient. A node’s partici- pation coefficient is a measure of the extent to which a given node connects to nodes in systems (communities) other than its own. Higher values indicate that the node is connected to many nodes in other systems, whereas lower values indicate that the node’s interactions are limited largely to its own system. Based on our findings of decreased segregation with age, we predicted that participation coefficients would increase with increasing age. The mean participation coefficient across all nodes increases with increasing age (r = 0.46, P < 0.001; Fig. 2D;alsosee SI

changes in segregation. For example, it appears that areas in the frontal–parietal control system exhibit greater con- nectivity to areas in several other systems, including the ventral attention and cingulo-opercular control systems, in OA compared with YA (Fig. 2B). One broad yet useful distinction that char- acterizes functional systems and their constituent areas is whether they are involved primarily in sensory-motor processing or in more associative processes (

s in association systems exhibit widespread and diverse anatomical projections with distributed brain systems (e.g., refs. 38, 40) and have been demonstrated to exhibit greater RSFC with areas in other systems compared with areas in sensory- motor systems (19)

Overall, the results show that aging is associated with decreasing

segregation of both association and sensory-motor systems; how- ever, their patterns of age-related changes in segregation differ

sensory-motor system segregation, we found that the age function for these systems was fit significantly only by a linear mode

n contrast, association system segregation was fit significantly by both a linear (t nd a quadratic model [

quadratic model having a higher adjusted R2 than the linear model (0.28 vs. 0.26, respectively)

The different patterns of age-related changes in system segregation as a function of system type can be appreciated by viewing spring-embedded layouts of each cohort’s areal network graph (Fig. 3C). Association systems exhibit less within-system connectivity and greater between-system connec- tivity, particularly in the oldest age cohort.

Segregation

After we controlled for age, segregation of association systems was significantly related to episodic memory (r = 0.18, P = 0.007): individuals with greater association system segregation exhibited higher episodic memory scores (Fig.

We have suggested that the functional specialization of a system may be characterized by the balance of connections between areas within the system and limited interaction with areas in other systems. In

Importantly, we believe our measure of segregation is more sensitive to age-related differences in network organization than modularity (SI Appendix, Fig. S6) and allows clearer insight re- garding the underlying changes contributing to the measure. We hypothesize that age-associated decreases in system segregation may indicate decreased functional specificity of system-based processing roles. Brain areas in distinct systems exhibit greater interaction with continual aging, as reflected in patterns of RSFC. Although this may be an adaptive response to ongoing anatomical and biochemical alterations (1, 2), it does not appear that the increasing interaction between areas in distinct systems confers a benefit to the individual; rather, the increased “blur- ring” across systems and decreased communication within sys- tems may reflect a fundamental age-related mechanism that negatively affects cognitive function. We return to this point in the

Systems involved in “associative” oper- ations exhibited greater age-accompanied decreases in seg- regation compared with systems involved in processing sensory input and motor output

decreasing association system segregation was fit better by a quadratic than a linear function, distinguished by a sharper rate of decline from age 50 onward (Fig. 3). This distinction between association and sensory-motor systems may reflect different trajectories in the patterns of decreasing functional specialization.

execution of task set, allocation of attention, controlled mne- monic retrieval, and executive control, likely are performed by multiple brain systems and require substantial interaction be- tween areas in these systems (39, 51, 52). The decreasing exec- utive ability that characterizes older age (42, 53, 54) may be a consequence of reduced functional specialization of systems that mediate these abilities, as indexed by decreasing association system segregation.

Based on our present findings, we speculate that the underlying substrate of the observations leading to the common-cause hypothesis may be the degree of between-system interactions occurring in the adult brain. Specifically, we suggest that the tighter link be- tween sensory and cognitive function in older age is intimately related to the decreasing RSFC-defined system segregation observed here.

System segregation was predictive of a summary measure of memory. The age-invariant relationship between association system segregation and long-term memory scores suggests that our measurements of network properties exhibit a much broader relationship to behavior than that which simply char- acterizes differences present across adult aging.

In the present study, exam- ining the relationship between GE and age also reveals that increasing age is accompanied by increasing GE. Critically, this observation is trivial and logical when one recognizes that the introduction/strengthening of connections (edges) between systems (clusters) quickly decreases average path length (58). Given the negative relationship between age and system seg- regation, it is not surprising that GE increases with age. Im- portantly, accounting for system segregation eliminates the significant age–GE relationship (SI Appendix,Fig.S7). Obser- vations related to differences in other summary measures, such as “small-worldness” (e.g., ref. 33), may be similarly sensitive to these forms of basic underlying properties.

Among the age-accompanied functional changes, one prominent obser- vation is a reduction in the specificity with which distinct neural structures mediate particular processing roles