

# Reconfiguration and dedifferentiation of functional networks during cognitive control across the adult lifespan

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## ABSTRACT

Healthy aging is accompanied by reduced cognitive control and widespread alterations in the underlying brain networks; but the extent to which large-scale functional networks in older age show reduced specificity across different domains of cognitive control is unclear. Here we use cov-STATIS (a multi-table multivariate technique) to examine similarity of functional connectivity during different domains of cognitive control—inhibition, initiation, shifting, and working memory—across the adult lifespan. We report two major findings: (1) Functional connectivity patterns during initiation, inhibition, and shifting were more similar in older ages, particularly for control and default networks, a pattern consistent with dedifferentiation of the neural correlates associated with cognitive control; and (2) Networks exhibited age-related reconfiguration such that frontal, default, and dorsal attention networks were more integrated whereas sub-networks of somato-motor system were more segregated in older age. Together these findings offer new evidence for dedifferentiation and reconfiguration of functional connectivity underlying different aspects of cognitive control in normal aging.

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## 1. Introduction

Normal aging is characterized by reductions in cognitive control processes that coordinate and oversee the flexible allocation of mental resources during goal-directed behavior (Baltes and Lindenberger, 1997; Park et al., 2002; Salthouse et al., 2003). Cognitive control is generally conceptualized as a superordinate process comprised of correlated, yet distinct, sub-domains (Miyake et al., 2000; Miyake and Friedman, 2012) including: inhibition, initiation (or response selection), shifting (or flexibility), and working memory (or updating; Lenartowicz et al., 2010; Sabb et al., 2008). Functional neuroimaging studies confirm the behavioral evidence for multiple sub-domains of cognitive control and reveal a robust fronto-parietal network that subserves many different tasks of cognitive control (Niendam et al., 2012). Further work examining the functional specificity of different cognitive control domains within the same participant reports unique and separate functional activity patterns associated with the different sub-domains of inhibition, shifting, and working memory (Derrfuss et al., 2004;

Lemire-Rodger et al., 2019; McNab et al., 2008; Rieck et al., 2021; Sylvester et al., 2003). Researchers have proposed that age-related reductions in cognition might be accounted for by alterations in underlying brain function including a loss of specialized cognitive processing (termed dedifferentiation; Grady, 2012; Park and Reuter-Lorenz, 2009). However, the extent to which dedifferentiation extends to cognitive control and its individual sub-domains is still unclear.

Dedifferentiation in aging has been examined at both the behavioral (Baltes et al., 1980) and brain levels (Koen and Rugg, 2019). Behavioral dedifferentiation is characterized by greater shared variance in task performance across different cognitive domains, although a recent meta-analysis indicates that previously reported age effects of behavioral dedifferentiation may not be reliable when examined in a cross-sectional framework (termed "static dedifferentiation"; Tucker-Drob et al., 2019). Indeed, prior work examining the factor structure of cognitive control sub-domains in older adults reveals mixed findings. For example, Hedden and Yoon (2006) reported that the domains of shifting and working memory were not distinct from one another, whereas Hull and colleagues (2008) found robust shifting and working memory factors but failed to find a separate inhibition domain. Although Tucker-Drob and colleagues (2019) did not find

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meta-analytic support for “static dedifferentiation”, they did find evidence for increased coupling of cognitive domains when examining longitudinal cognitive changes within an individual (i.e., “dynamic dedifferentiation”). Similarly, one longitudinal assessment of cognitive control sub-domains found that cognitively-elite older adults’ performance fit a multi-factor model (with inhibition, shifting, and working memory having unique contributions) whereas cognitively-impaired older adults’ performance fit a one-factor general model of cognitive control, a pattern of results providing evidence that dynamic behavioral dedifferentiation of cognitive control domains (i.e., shifting from multi- to uni-dimensional representations) is linked to cognitive decline (de Frias et al., 2009). Given the evidence that behavioral dedifferentiation may be best examined within a longitudinal framework, we therefore chose to focus on brain dedifferentiation (which has considerable support; Koen and Rugg, 2019) within our cross-sectional study.

At the brain level, age-related dedifferentiation can manifest as neural representations showing more similar patterns of activation (Carp et al., 2011) or connectivity (Chan et al., 2014), such that functional signals are less dissociable for different task states (see Koen and Rugg, 2019 for a review). In particular, large-scale brain networks show widespread alterations in normal aging (Ferreira and Busatto, 2013; Sala-Llanch et al., 2015). One consistent finding is that older age is associated with reductions in the specialization and specificity of network connectivity (an effect reflecting a form of brain dedifferentiation; Goh, 2011) that is characterized by decreased connectivity of regions within the same network, often coupled with increased connectivity between regions of different networks (Betzel et al., 2014; Chan et al., 2014; Grady et al., 2016). During rest, age-related decreases in network specificity are apparent for both default mode networks that are typically engaged in resting state (Andrews-Hanna et al., 2007; Geerligs et al., 2015; Onoda et al., 2012; Tomasi and Volkow, 2012; Zhang et al., 2014) and for association systems involved in higher-order cognition, including the salience network (Onoda et al., 2012; Zhang et al., 2014), dorsal attention network (Tomasi and Volkow, 2012; Zhang et al., 2014), and fronto-parietal executive (i.e., cognitive control) network (Campbell et al., 2012; Geerligs et al., 2015).

Although the majority of studies examining functional connectivity in normal aging have focused on functional network characteristics during the resting state, more recent work has started to explore how aging affects network connectivity when participants are engaged in effortful cognitive processing, including tasks that encompass sub-domains of cognitive control. Researchers generally find that older adults exhibit weaker functional connectivity within regions of the fronto-parietal control network during task fMRI including: target detection with interference (Geerligs et al., 2014), inhibiting a prepotent response (Tsvetanov et al., 2018), local task switching (Madden et al., 2010), and n-back working memory tasks (Burianová et al., 2015; Nagel et al., 2010; Sambataro et al., 2010). Older adults also exhibit weaker connectivity within the default mode network during fixation trials of attentional and delayed match-to-sample working memory tasks (Grady et al., 2010). In addition to decreased connectivity within the fronto-parietal and default networks, there is evidence for increased connectivity between prefrontal and default regions during working memory tasks (Sambataro et al., 2010), between prefrontal and motor regions during inhibitory processing (Geerligs et al., 2014), and between dorsal attention and fronto-parietal control networks during a working memory task with interference (Grady et al., 2016). Together these task-based connectivity findings of decreased within-network connectivity and increased between-network connectivity mirror resting state data (Chan et al., 2014), an effect suggesting that network connectivity, particularly for fronto-parietal and de-

**Table 1**  
Sample demographics

Age Range	N (N Female)	Mean Age	Years Education	MMSE
20-31	39 (22)	25.74 (3.85)	16.85 (2.81)	29.13(0.98)
32-48	34 (20)	40.00 (4.44)	17.12 (2.36)	29.32(0.84)
49-65	38 (25)	58.03 (4.64)	17.24 (3.78)	28.87(0.91)
66-86	33 (20)	74.03 (5.56)	16.11 (2.58)	28.67(0.99)

Note. Mean (standard deviation); Data were analyzed with age as a continuous variable; however, participants were split into age groups (via a quartile split) for visualization of some results;

Key: MMSE, Mini Mental Status Exam.

fault networks, might become less specialized and dedifferentiated during tasks of cognitive control.

The goal of the current study was to extend prior work by examining functional connectivity profiles associated with multiple domains of cognitive control across the adult lifespan and to specifically test if large-scale brain connectivity associated with different sub-domains of cognitive control was less specialized in older age. We utilized a new application of a multi-table multivariate technique called cov-STATIS (Abdi et al., 2012) which can quantify the similarity (and dissimilarity) of functional connectivity across multiple cognitive control task conditions for each participant. In line with prior behavioral work (Miyake et al., 2000), we anticipated that younger adults would show distinct functional connectivity patterns associated with each domain of cognitive control, particularly for the three core domains of inhibition, shifting, and working memory. We hypothesized that increasing age would be accompanied by a decrease in the multi-dimensional representations of each domain, such that functional connectivity across different control conditions would become more similar in older age, possibly due to differences in within- and between-network connectivity for the primary networks involved in cognitive control, such as the fronto-parietal, dorsal attention, salience, and default networks.

## 2. Methods

### 2.1. Participants

A total of 158 adults, ages 20 to 86, were recruited from the greater Toronto area. Fourteen participants were excluded from all analyses due to poor (i.e., below chance) performance on the fMRI tasks, resulting in a final sample of 144 for the current study. Specifically, the numbers excluded for each task were as follows: 4 go/no-go, 1 task switch, 8 n-back, 1 n-back and task switch. Participants were screened to be healthy (i.e., free from any major psychiatric, or neurological conditions; no history of head trauma), cognitively normal (MMSE > 26), right-handed, fluent English speakers, with normal or corrected-to-normal vision (at least 20/30) and if necessary, vision was corrected using MRI-compatible lenses during scanning. Sample demographics (broken down by a quartile split) can be found in Table 1. Participants’ informed consent was obtained in accordance with protocol approved by the Research Ethics Board at Baycrest Health Sciences Centre.

### 2.2. Cognitive Session

Participants completed two sessions (cognitive testing and MRI testing) that were scheduled approximately one week apart. The cognitive testing session (1.5–2 hours) included the Cognitive Battery of the NIH Toolbox (Weintraub et al., 2013) in addition to measures of physical activities and emotional state. For the current study, the primary measures of interest were derived from tasks tapping into cognitive control. In the NIH Toolbox Cogni-

tive Battery, inhibition was measured with an arrow flanker task. Shifting was measured with a card sorting task in which participants matched images based on either color or shape. Working memory was measured with a list sorting task in which participants had to remember lists of animals and foods and re-order the items by size. There was no equivalent NIH toolbox task available for the domain of initiation. For all tasks, we used unadjusted scores that were normalized and scaled to a population sample (see Weintraub et al., 2013 for more details on the NIH tasks and how the normed scores were computed).

### 2.3. MRI Session and Acquisition

All participants were scanned on the same Siemens Trio 3T magnet at Baycrest Health Sciences Centre. The MRI session (2 hours total) began with a 30-minute mock-scanning session in which participants practiced each of the three fMRI tasks in a simulator (i.e., a demagnetized MRI gantry). Afterwards, participants underwent a 1.5-hour MRI scan that included: (1) T2-weighted FLAIR, (2) 10-minute blood-oxygen-level-dependent (BOLD) resting state, (3) T1-weighted anatomical imaging, (4) three BOLD fMRI tasks (details below), (5) diffusion weighted imaging, and (6) if time permitted, arterial spin labeling. Each of the three BOLD fMRI tasks measured a different domain of cognitive control and therefore were of primary interest for the current study. The order of the three tasks was randomized across participants.

High resolution anatomical scans (used for co-registration with functional images and warping to a standardized space) were acquired with a T1-weighted MP-RAGE sequence in which 160 axial slices were collected with the following parameters: TR = 2000ms, TE = 2.63ms, FOV = 256mm;  $192 \times 256 \times 160$  acquisition matrix;  $1 \text{ mm}^3$  isotropic voxel. BOLD fMRI data were collected using an echo-planar imaging sequence with 40 axial slices acquired parallel to the anterior-posterior commissure with the following parameters: TR = 2000ms, TE = 27ms, Flip Angle =  $70^\circ$ ; FOV = 192mm,  $64 \times 64 \times 40$  acquisition matrix;  $3 \text{ mm}^3$  isotropic voxels (with .5 mm gap). A total of 216 volumes were collected for the go/no-go task; 223 volumes collected for task switching; and 266 volumes collected for the n-back task.

### 2.4. fMRI Cognitive Control Task Design

In-scanner, participants completed one run each of three tasks designed to look at different domains of cognitive control. For all tasks, stimuli were letters presented in the middle of a dark gray background, and participants made their responses on an MR-compatible button box using the index and middle fingers of their right hand (corresponding finger response was randomized and counterbalanced across participants).

#### 2.4.1. Go/No-Go

To measure inhibition, a go/no-go paradigm was used in which participants were presented with a series of letters and told to respond (i.e., “go”) when they saw the letter “X” and not respond (i.e., “no-go”) for all other letters (Supplemental Figure 1A). Letters were presented for 400 ms with a mean interstimulus interval of 1200 ms (jittered between 900 and 1500 ms) during which a fixation cross was presented. The task was separated into an “inhibition” block in which there were more go trials than no-go trials (120 go, 40 no-go) and a shorter “initiation” block in which there were more no-go trials than go trials (20 go, 60 no-go). The order of these two blocks was randomized across participants. In total, the go/no-go task lasted 6 minutes 26 seconds. The primary behavioral measure from this task was a measure of speed-accuracy trade-off (referred to as the “skill index;” see Seli, 2016) computed

as accuracy of no-go responses divided by the median response time to go responses.

#### 2.4.2. Task Switch

To measure shifting, a local-switching paradigm was used in which participants saw a letter in the center of the screen and one of two cues above the letter to categorize the letter as either uppercase/lowercase or consonant/vowel (Supplemental Figure 1B). The cues and letters were also presented in two different colors (e.g., blue and green) to differentiate between the two kinds of judgments and facilitate performance. There were 60 total trials (50% uppercase/lowercase judgments; 50% vowel/consonant judgments) organized such that half the trials involved switching between judgments (i.e., vowel/consonant then uppercase/lowercase) and half of trials repeated the same judgment (i.e., vowel/consonant then vowel/consonant). Letters were presented for 2000 ms with a mean interstimulus interval of 4500 ms (jittered between 1500–7500 ms) during which a fixation cross was presented. In total, task switch lasted 7 minutes 26 seconds. The primary behavioral measure from this task was the response time switch cost, which was computed as the difference in response time for trials that required switching versus trials that repeated the same letter judgement (with a smaller switch cost reflecting better task performance).

#### 2.4.3. N-Back

To measure working memory, an n-back paradigm was utilized with 0-, 1-, and 2-back loads in which participants saw a series of letters and had to respond if the letter was a “target” or “non-target” (Supplemental Figure 1C). For 0-back, the targets were “X,” making the 0-back condition similar to the initiation task (except in the 0-back, participants responded to every trial). For 1-back, the targets were letters that matched the previously presented letter. For 2-back, the targets were letters that matched the letter presented two positions back. The task was organized into three blocks (one for each load level), the order of which were randomized across participants, and each block had 90 total trials (30 target and 60 non-target). Letters were presented for 500ms with a mean interstimulus interval of 1200ms (jittered between 900 and 1500ms) during which a fixation cross was presented. The total time for the n-back task was 8 minutes 52 seconds. The primary behavioral measure of interest on the n-back task was accuracy for each working memory load level.

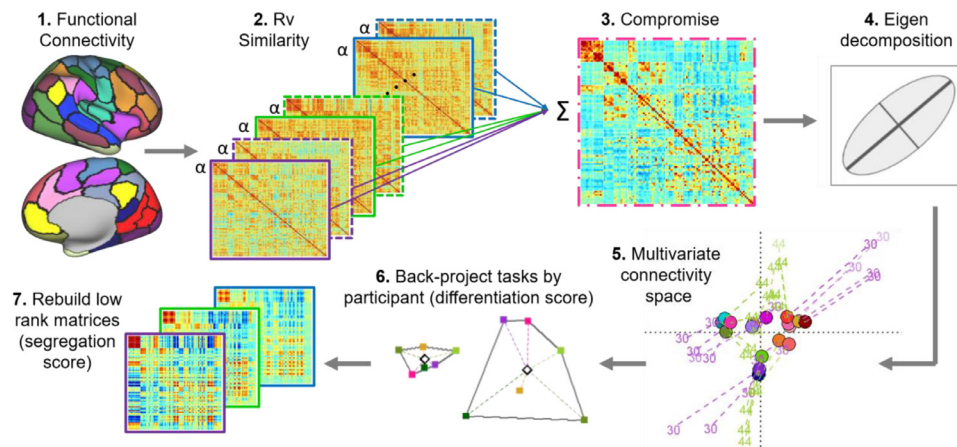
### 2.5. fMRI Preprocessing

Functional data for each task were preprocessed with a mix of AFNI functions as well as Octave and MatLab scripts using the Optimizing of Preprocessing Pipelines for Neuroimaging software package (an overview and more details of the preprocessing pipeline can be found in Churchill et al., 2017). For the current study, the following steps were conducted: (1) rigid-body alignment of the time series to correct for movement via *3dvolreg* in AFNI; (2) removal and interpolation of outlier volumes using Octave scripts (see Campbell et al., 2013); (3) correction for physiological noise via *3dretroicor* in AFNI; (4) slice timing correction via *3dTshift* in AFNI; (5) spatial smoothing with a 6mm smoothing kernel via *3dmerge* in AFNI; (6) temporal detrending (see Churchill et al., 2017); (7) motion parameter regression (see Churchill et al., 2017); (8) regression of signal in tissue of no interest (white matter, vessels and cerebrospinal fluid); and finally (9) warping to MNI space and resampling to  $4 \text{ mm}^3$  isotropic voxel.

### 2.6. Functional Connectivity

Functional connectivity was computed for each of the three fMRI tasks using the CONN toolbox (Whitfield-Gabrieli and Nieto-





**Fig. 1.** Cov-STATIS steps. Step 1: Functional connectivity was computed for each task condition with the Schaefer 100 node, 17 network atlas. Step 2: The  $R_V$  similarity coefficient was used to weight individual functional connectivity matrices to create the compromise matrix (Step 3) which represents an optimum weighted average of all the individual matrices. Step 4: The compromise matrix was submitted to the eigen decomposition to generate the multivariate connectivity space (Step 5) which illustrates the strength of connectivity of network nodes. Step 5: Individual participants (Participant 30 [purple] and Participant 44 [green]) were back-projected onto the multivariate space to compute estimates of how much a participant deviates from the mean. Step 6: For each individual participant (diamond), connectivity during each task was back-projected (filled squares and connecting dashed lines) to see how similar connectivity patterns were across tasks. The farther points were from the participant center (diamond), the more distinct patterns of connectivity were for each task. The area of the convex hull (solid line) around each point was used to compute “differentiation scores.” The convex hull illustration on the left is a 71-year-old participant with a low differentiation score (small area), whereas the right is a 28-year-old participant with a high differentiation score (large area). Step 7: Low rank functional connectivity matrices were rebuilt from the multivariate space to compute additional network metrics such as segregation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Castanon, 2012) and applying an atlas with 100 parcels belonging to 17 networks (Schaefer et al., 2018; Thomas Yeo et al., 2011; Fig. 1, step 1; see Supplemental Figure 2 for a full visualization of this parcellation). Analyses were also repeated using two additional atlases: (1) an iteration of the network coordinates provided by Power and colleagues (2011) that included 229 5mm spherical nodes associated with 10 functional networks and (2) the Schaefer et al., (2018) 200 parcel, 17 network atlas which is roughly equivalent to the 100 parcel atlas, but with smaller and more fine-grained parcels (see Rieck et al., submitted). Findings that did not replicate for the additional atlases have been indicated in Results, and those findings that did not replicate for either additional atlas are not illustrated in the relevant Figure.

In CONN, task design (i.e., trial information) was regressed out of the time series, and the BOLD signal in each voxel was converted to a percent signal change value by scaling the whole time series to the average time series value of that voxel. Percent signal change values were averaged across voxels within each of the 100 nodes, and the time courses associated with each task condition were correlated to create a  $100 \times 100$  correlation matrix for each of task condition. For go/no-go, time series correlations were computed separately for the “inhibition” (i.e., more “go”) and “initiation” (i.e., more “no-go”) blocks. For task switch, the entire time series was used to compute the correlation. For n-back, the connectivity correlations were computed separately for each working memory load block (0-, 1-, and 2-back). This resulted in six  $100 \times 100$  correlation matrices for each participant representing the functional connectivity during different aspects of cognitive control (inhibition, initiation, switching, 0-, 1-, and 2-back working memory).

## 2.7. Statistical Analyses

In order to examine the similarity of the functional network connectivity across task conditions (and how network connectivity differed by participant), we utilized a multivariate multi-table method of Procrustean analysis (Gower and Dijksterhuis, 2004) called cov-STATIS, a (French) acronym which loosely translates to

“structuring three-way statistical (in our case, correlation) tables” (Abdi et al., 2012, 2009, 2007; St-Laurent et al., 2011; DistatisR R package, see Beaton et al., 2019). Cov-STATIS comprises several steps (see Fig. 1). After computing functional connectivity (step 1), the similarity structure of all the data tables (i.e., our connectivity matrices; 780 total matrices, 6 per participant) was analyzed using the  $R_V$  similarity coefficient (Escoufier, 1973; step 2) in order to integrate the data into an optimum weighted average (called the “compromise” or “consensus;” step 3).  $R_V$  similarity scores underwent bootstrap resampling (1000 iterations) in order to determine differences in the overall similarity of functional connectivity by age group and task condition.

Next, the compromise connectivity map was submitted to principal components analysis to reveal the components or latent variables describing the common functional network structure for all our data (step 4). Points that are closer together represent regions with relatively stronger connectivity and points further apart indicate regions with weaker connectivity (step 5, colored circles). From there we projected each of the original data sets (i.e., each functional connectivity matrix per task condition per participant) onto the compromise space to determine commonalities or discrepancies in how individuals or task conditions were represented in reference to the common “compromise” space (step 5 illustrates two participants’ back projections to each network for one condition). Participants that projected far from a compromise would indicate a strong deviation from the overall group connectome, whereas participants that projected closer to the compromise point show connectivity patterns similar to the overall group structure.

### 2.7.1. Task differentiation Scores

The back-projections of the original connectivity matrices onto the factor space also allowed us to compute a “task differentiation score” for each functional network by taking into account the distance of each of the partial factor scores for each task condition to the network center for a particular participant (Fig. 1, step 6). Specifically, for each network, an individual participant’s factor score (across all task conditions) was computed for Components 1 and 2 which represented that participant’s average network con-

**Table 2**  
fMRI task performance correlations

	Initiation (GNG) Speed-Acc	Shifting (TSW) Switch Cost	Working Memory (NBK) Mean Acc
Inhibition (GNG)	0.80	-0.15	0.29
Initiation (GNG)		-0.16	0.24
Shifting (TSW)			-0.06

key: GNG, Go/No-Go; NBK, N-Back; TSW, Task Switching.

nectivity regardless of task condition (diamonds). Then, the six task conditions were back-projected for that participant (around their mean; filled squares), and a convex hull was generated to encompass these six points (solid line). The area of this convex hull was computed to represent the “task differentiation score” which described how similar a participant’s connectivity for a particular network was across all the six task-conditions—the greater the area (i.e., the greater the spread of the individual task conditions around the mean), the less similar or more differentiated the connectivity patterns. Conversely, a smaller area would indicate that connectivity patterns for a particular network did not differ across task conditions for that participant (i.e., task dedifferentiation). Fig. 1, step 6 illustrates the convex hulls for the default mode network for two representative participants—the participant on the left is a 71-year-old with a low differentiation score (small area), whereas the participant on the right is a 28-year-old with a high differentiation score (large area).

### 2.7.2. Segregation Scores

Through cov-STATIS we also rebuilt low rank functional connectivity matrices from the latent variables generated in the multivariate space (Fig. 1, step 7). From these rebuilt connectivity matrices, we computed “segregation scores” for each network which describes the relative strength of connectivity within a network versus between networks as (within – between-network connectivity) / within-network connectivity (see Chan et al., 2014). Segregation score calculations allowed us to examine network reconfiguration by identifying those networks that became more integrated (i.e., more interconnected with other networks) versus more segregated (i.e., less connected to other networks) during cognitive control.

Finally, in-line with prior work examining age-independent effects of network segregation on cognitive performance (Chan et al., 2014), we explored how network segregation predicted cognitive control behavioral measures from the NIH toolbox and fMRI in-scanner tasks. Specifically, for those networks in which we found significant age associations, we computed linear models with network segregation, age, and their interaction as predictors to one of the NIH toolbox or in-scanner task measures of cognitive control performance. If a significant interaction was found, it was further decomposed using Johnson-Neyman simple slopes analyses (Johnson and Fay, 1950; Preacher et al., 2006) to examine how age modulated the relationship between functional networks segregation and cognitive performance. This allowed us to determine when in the lifespan brain-behavior relationships were most prominent. Due to the exploratory and *post-hoc* nature of these brain-behavior analyses, we did not correct for multiple-comparisons.

## 3. Results

### 3.1. fMRI Task Behavioral Results

First, we computed the correlations among the performance variables derived from each fMRI task across all participants (Table 2) to examine whether performance from each domain was

relatively independent of that from the other domains, as prior studies have reported (Miyake et al., 2000). In general, the correlations across fMRI task performance were relatively low to moderate (i.e.,  $|r| \leq 0.3$ ), even after controlling for age or looking within age group. Inhibition and initiation were the exception, likely because these two measures were computed in a similar manner (i.e., a speed-accuracy trade-off measure) from different blocks of the go/no-go fMRI task.

Next, we examined the relationship between performance on the three fMRI tasks and age. For the go/no-go task, increasing age was associated with worse speed-accuracy during inhibition ( $r = -0.34$ ,  $p < 0.001$ ; Supplemental Figure 3A) and initiation ( $r = -0.18$ ,  $p = 0.033$ ; Supplemental Figure 3B). For task switching, there was no relationship between age and switch cost ( $r = 0.03$ ,  $p = 0.705$ ), however, the majority of participants showed a switch cost effect (values  $> 0$ ; Supplemental Figure 3C). Accuracy on n-back showed a main effect of age ( $F(1,128) = 6.88$ ,  $p < 0.001$ ), a main effect of working memory load ( $F(2, 256) = 106.35$ ,  $p < 0.001$ ), and an interaction between age and load, such that there were greater load-related declines in accuracy in older age ( $F(2,256) = 4.97$ ,  $p < 0.001$ ; Supplemental Figure 3D).

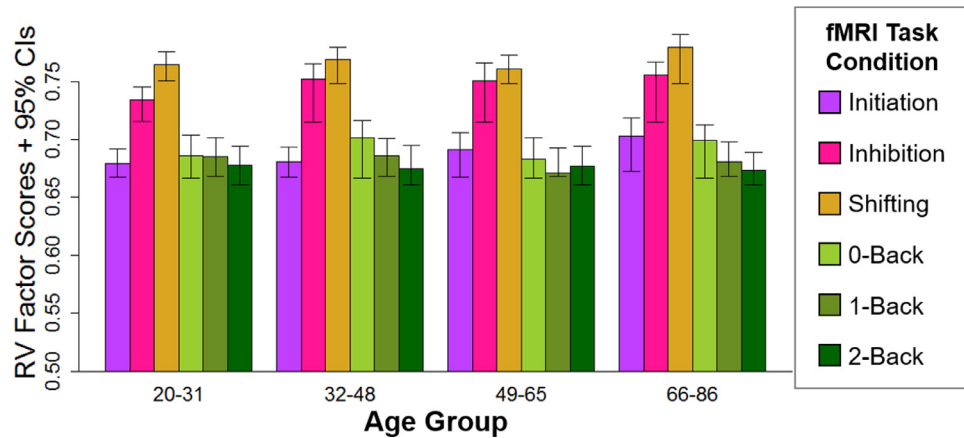
### 3.2. $R_V$ Similarity Results

As the first step in cov-STATIS, the  $R_V$  coefficient was used to assess similarity among all the functional connectivity matrices (6 task conditions per participant). Bootstrapping these values produced estimates of how similar overall functional connectivity patterns (regardless of network) were for each task condition across age groups (using a quartile split on age). We found that the youngest adults (ages 20 – 31) showed significantly distinct connectivity patterns for inhibition, initiation, shifting, and working memory as evidenced by non-overlapping 95% confidence intervals (CIs; Fig. 2). Initiation was also significantly different from inhibition and shifting but did not differ from working memory, as expected due to the similarity of the 0-back and initiation tasks. However, adults over the age of 32 did not show different connectivity patterns for inhibition and shifting (overlapping CIs) meaning that connectivity for these domains becomes more similar in later adulthood. Furthermore, initiation and inhibition no longer show distinct connectivity profiles after age 66. Together these results illustrate that functional connectivity associated with different domains of cognitive control become more similar at different points along the lifespan.

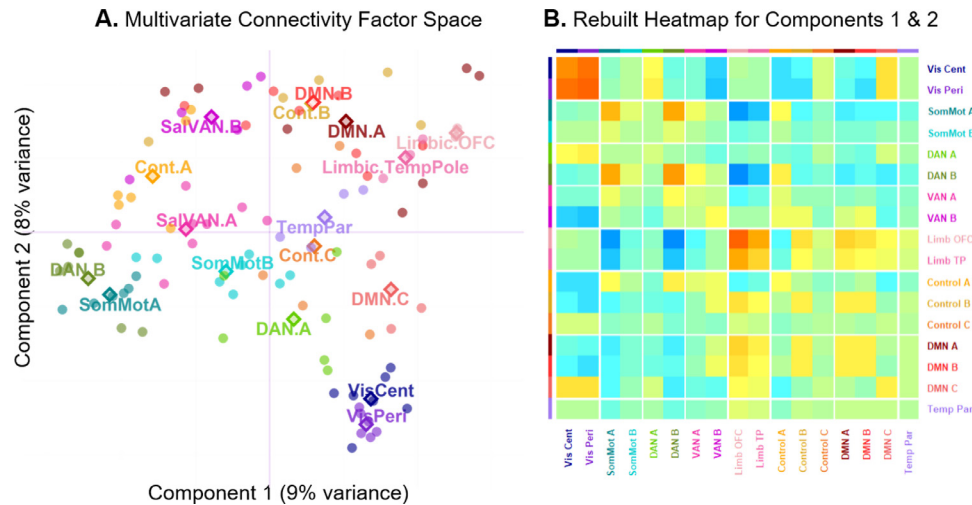
### 3.3. Compromise Space Results

The next step in cov-STATIS involves the eigen decomposition of the compromise matrix (i.e., an optimum weighted average of all the functional connectivity matrices) in order to identify the multivariate configuration of the functional networks. A broken-elbow test of the resulting scree plot (Supplemental Figure 4), identified the first seven components as contributing the most to the structure and together explained 38% of variance in the data. However, for the current study we focus on describing results from the first two components (9% and 8% variance explained respectively).

Illustrating Components 1 and 2 on a factor map shows the common network configuration across all participants and tasks (Fig. 3A). Component 1 was characterized by stronger connectivity in Dorsal Attention, Somato-Motor, and Ventral Attention networks (left side) compared to Limbic and Default networks (right side). Component 2 was characterized by greater connectivity in visual networks (bottom) versus mainly non-sensory networks such as Default and Control networks (top). The multivariate connectivity space can also be illustrated with a heatmap (Fig. 3B) of the com-



**Fig. 2.**  $R_V$  Similarity by Task Condition and Age Group.  $R_V$  factor scores represent the degree of similarity between functional connectivity matrices for a particular domain and age group. Error bars represent bootstrapped 95% confidence intervals. The youngest age group shows significantly different  $R_V$  coefficients for the domains of inhibition, shifting, and working memory. Inhibition and shifting were no longer significantly different in early middle age (ages 32–48), and initiation and inhibition were no longer different in late adulthood (ages 66–86).



**Fig. 3.** Group-Level Multivariate Connectivity Space. (A) Individual ROIs (dots) projected in the compromise space (and colored by network) show the common network configuration across all participants. The diamonds illustrate the network averages. Component 1 (9% variance) was characterized by dorsal attention, somato-motor and ventral attention regions vs. default and limbic regions. Component 2 (8% variance) was characterized by visual versus non-sensory networks. (B) A heatmap of the compromise space rebuilt from components 1 & 2 illustrates the networks with the strongest connectivity (hot colors). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

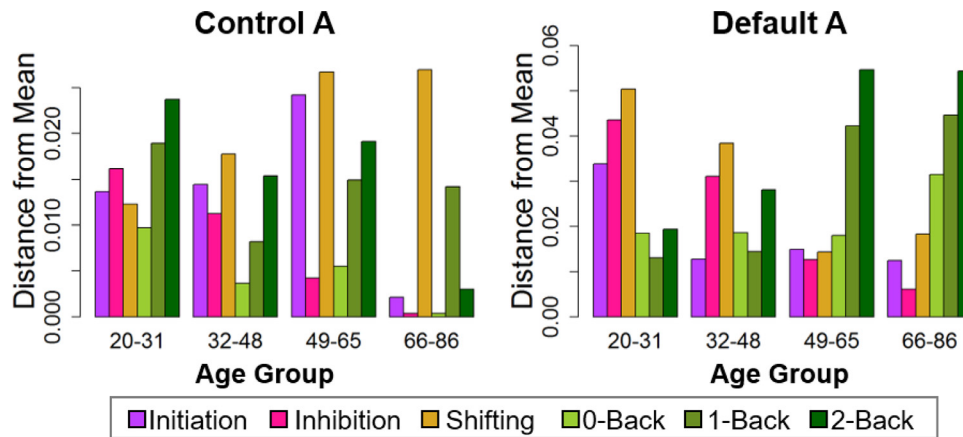
promise space rebuilt from Components 1 & 2. Complementary to the factor map (Fig. 3A), the heatmap shows stronger connectivity between Limbic and Default networks, between Somato-Motor and Dorsal Attention B, and between Visual subnetworks (Fig. 3B).

As illustrated in Step 5 of Fig. 1, individual participants and task conditions were projected onto this multivariate connectivity space (i.e., the compromise) in order to see similarities or discrepancies in how individuals or groups contributed to the space. First, we examined how much each age group deviated from the network mean in order to determine changes in how each age group utilized different networks across the task conditions—the greater the deviation from the network mean (i.e., distance in the component space), the greater the unique contribution (see Supplemental Figure 5 for an illustration of all networks in each of the four age groups). To note, because these distances are computed at group level, it is not possible to compute inferential statistics of these metrics; therefore, these findings serve as an additional descriptive illustration of the multivariate connectivity space when broken down by age group and task condition. As an example, Fig. 4 illustrates Control A and Default A networks that showed an age

by task condition interaction in how they were engaged. Specifically, compared to younger age groups, older adults showed a shift from utilizing prefrontal control to medial default regions during working memory, and this scaled with working memory load.

### 3.4. Network Task Differentiation Scores

As described above in *Statistical Analyses*, the individual participant by task back-projections into the compromise space allowed us to compute “task differentiation scores” which were computed as the area of a convex hull around the partial factor scores for each task condition to the network center for that participant: the greater the area of the convex hull, the more distinct (and less similar) the connectivity profile of that network. When predicting task differentiation scores from age, we found that patterns of connectivity across all the tasks became less differentiated (i.e., dedifferentiated) in older age for Control ( $\beta = -0.232$ ,  $t(142) = -2.82$ ,  $p = 0.005$ ), Default ( $\beta = -0.274$ ,  $t(142) = -3.40$ ,  $p < 0.001$ ), Salience/Ventral Attention A (insula, pars opercularis and medial frontal;  $\beta = -0.175$ ,  $t(142) = -2.12$ ,  $p = 0.036$ ), and



**Fig. 4.** Control and Default Network Contributions for Age Group by Task Conditions. The mean connectivity for each age group and task condition was back projected onto the multivariate space (Figure 2, Step 5) to examine how much each task by age group deviated from the mean of the entire sample. A larger distance from the mean would indicate that a particular age group or condition exhibited more unique engagement of a particular network. For working memory n-back conditions (green bars), younger adults showed increased involvement of Control A, whereas older adults showed increased involvement of Default A. Other networks are visualized in a factor map in Supplemental Figure 4.

Temporo-Parietal ( $\beta = -0.169$ ,  $t(142) = -2.04$ ,  $p = 0.043$ ) networks<sup>1</sup> (Fig. 5A). To note, age effects for each of the A, B, and C subnetworks of Control and Default networks were evident, therefore the differentiation scores were combined across subnetworks. Furthermore, a quadratic age-trajectory was evident for the Somato-Motor network ( $\beta = -1.59$ ,  $t(141) = -3.16$ ,  $p = 0.002$ ; Fig. 5B). To better understand the shape of this quadratic age effect, we identified the age of the inflection point from the regression model and then examined age-differentiation correlations for participants above and below this age-inflection point. The age trajectory of dedifferentiation in Somato-Motor networks was characterized by increased differentiation until age 52 (for ages 20–52,  $r = 0.27$ ) followed by increased dedifferentiation in older ages (for ages 53–86,  $r = -0.26$ ). No other networks showed an effect of age on task differentiation.

### 3.5. Network Segregation Scores

Finally, because cov-STATIS allowed us to build back individual heatmaps from the multivariate space, we computed a metric of segregation to assess differences in the strength of functional connectivity within and between networks (see Chan et al., 2014). Individual heatmaps were rebuilt from the multivariate space using the first seven components (accounting for 38% variance, assessed by the broken stick test)—in this way, the rebuilt matrices represent the most robust signal in the data, and eliminate potential noise in components (Fig. 1, Step 6).

With increasing age, several networks became less segregated (in line with prior work) including: Control (all subnetworks;  $\beta = -0.469$ ,  $t(142) = -6.34$ ,  $p < 0.001$ ), Default (all subnetworks;  $\beta = -0.488$ ,  $t(142) = -6.66$ ,  $p < 0.001$ ), Somato-Motor B ( $\beta = -3.22$ ,  $t(142) = -4.05$ ,  $p < 0.001$ ) and Salience/Ventral Attention A ( $\beta = -0.167$ ,  $t(142) = -2.02$ ,  $p = 0.046$ ; Fig. 6A)<sup>2</sup>. Dorsal Attention Network (both subnetworks) was characterized

by a quadratic decrease with age ( $\beta = -1.56$ ,  $t(141) = -3.20$ ,  $p = .002$ ), such that segregation slightly increased until age 42 ( $r = 0.18$ ) and showed steeper decreases from age 43 to 86 ( $r = -0.35$ ; Fig. 6B). As in the prior analyses, when all the individual subnetworks (e.g., Control A, B, C) evidenced similar age-trajectories, they were combined as one network. Examining the age-correlations for within- versus between-network connectivity estimates separately revealed that age-related decreases in segregation for Control, Default, and Somato-Motor B networks were largely driven by age-related reductions in within-network connectivity, whereas Dorsal Attention was driven by age-related increases in between-network connectivity (Supplemental Figure 6; Supplemental Table 1A). Salience/Ventral Attention A showed no age effect on within- or between-network connectivity estimates, suggesting that age differences in segregation of this network was not driven by a singular measure alone, rather the relationship between the two measures (Supplemental Figure 6; Supplemental Table 1A).

Two networks showed age-related increases in network segregation: Somato-Motor A (motor and precentral cortex;  $\beta = 0.583$ ,  $t(142) = 8.55$ ,  $p < 0.001$ ; Fig. 6C) and Salience/Ventral Attention B<sup>3</sup> (dorsal anterior cingulate and inferior parietal lobule;  $\beta = 0.170$ ,  $t(142) = 2.06$ ,  $p = 0.042$ ), which was driven by stronger age-related increases in within-network connectivity estimates, although between-network estimates also showed slight increases with age (Supplemental Figure 7; Supplemental Table 1B).

### 3.6. Brain-cognition associations

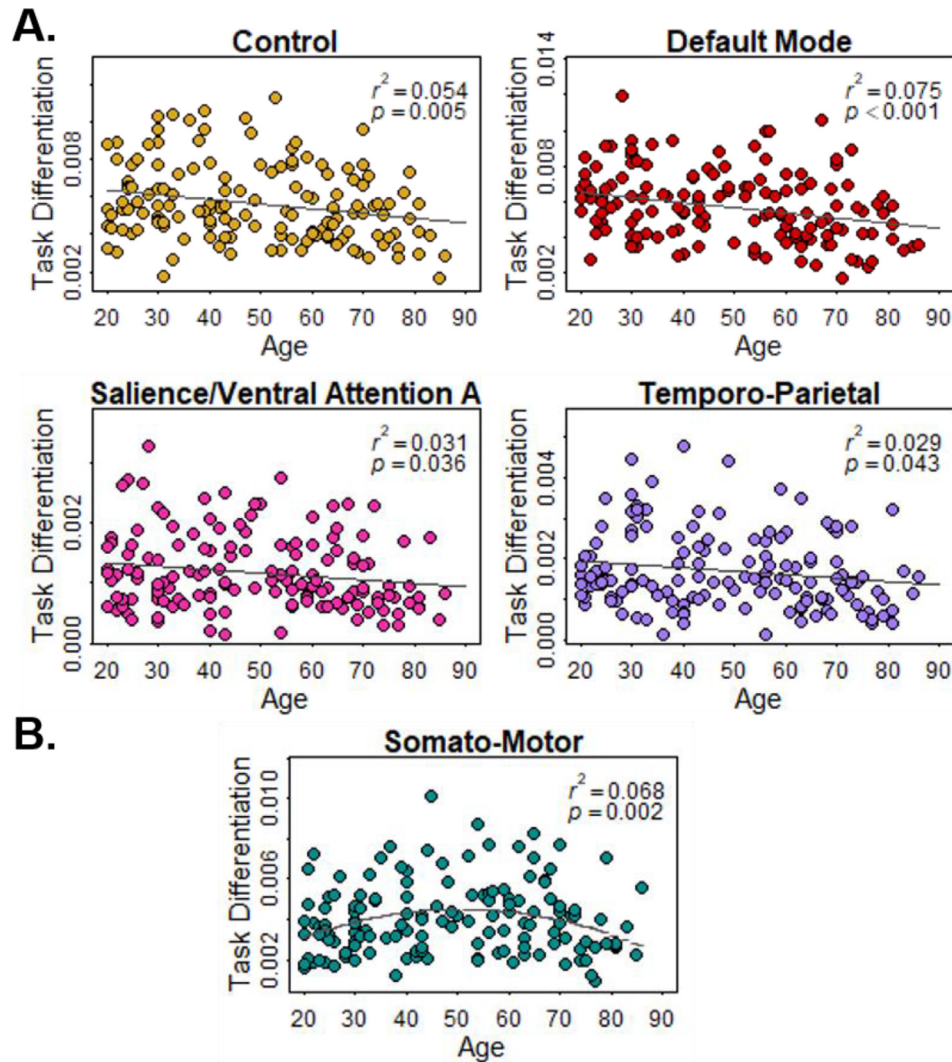
For those functional networks that showed significant differences in network segregation as a function of age, we also examined how network segregation and age interacted to predict behavioral performance on tasks of cognitive control both in and out of the scanner. This resulted in 49 models (7 networks with significant age effects with 7 behavioral measures), and given the exploratory nature of these analyses we did not correct for multiple comparisons, so findings should be considered preliminary. We found that greater Control network segregation predicted bet-

<sup>1</sup> With the Power atlas, all findings were replicated except for the age effects on default and somato-motor networks. Using the 200 parcel Schaefer atlas replicated all findings except for the age effect on temporo-parietal network (see Rieck et al., submitted).

<sup>2</sup> The negative age effects on segregation were replicated with the Power atlas except for somato-motor B, which was reduced to a trend effect ( $p < .1$ ). Likewise, the negative age effects were replicated with the Schaefer 200 parcel atlas except for the salience/ventral attention A network (see Rieck et al., submitted).

<sup>3</sup> The effect of age on increased segregation of the salience/ventral attention B network was not replicated with either the Power or Schaefer 200 atlases (see Rieck et al., submitted). Because this effect did not replicate in either additional analysis, this plot was excluded from Fig. 6 in the main manuscript.





**Fig. 5.** Task Differentiation Scores and Age. Task differentiation quantifies the degree similarity of connectivity patterns across different domains of cognitive control for a particular network. (A) Control, Default, Salience/Ventral Attention A, and Temporo-Parietal networks all showed decreased task differentiation in older age (i.e., dedifferentiation). (B) The Somato-Motor network showed a quadratic difference across age that peaked around age 52.

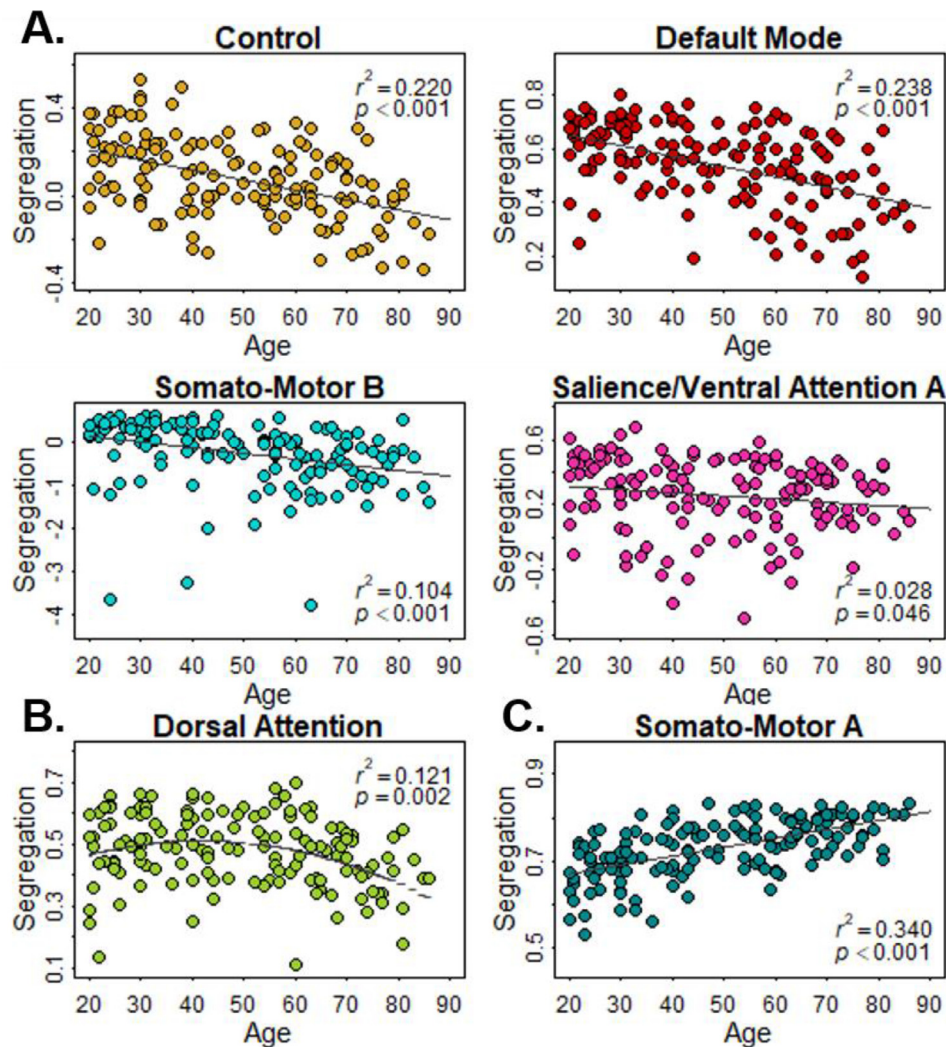
ter performance on the NIH list sorting working memory task ( $\beta = 0.183$ ,  $t(141) = 2.06$ ,  $p = 0.041$ ; Fig. 7A) after accounting for the effect of age. On the other hand, greater Dorsal Attention network integration predicted better performance on the NIH flanker inhibitory control task ( $\beta = -0.137$ ,  $t(141) = -2.28$ ,  $p = 0.024$ ; Fig. 7B).

There was also an interaction between Salience/Ventral Attention B and age on predicting switch cost (calculated as the difference in response time to switching vs. repeated trials on the fMRI shifting task;  $\beta = -19.87$ ,  $t(140) = -2.31$ ,  $p = 0.022$ ) that was driven by the oldest adults in the sample. A simple slopes analysis that estimated the slope of the brain-behavior relationship at each point in the lifespan revealed that there was no significant association between brain and behavior in younger and middle ages, as illustrated by 95% confidence intervals that overlapped with 0 on the Johnson-Neyman plot (Fig. 7C). But, after about age 58, greater segregation of Salience/Ventral Attention B was associated with lower switch cost (negative relationship), suggesting that connectivity of dorsal anterior cingulate and inferior parietal lobule supported performance on the in-scanner shifting task in these older participants.

#### 4. Discussion

The current study examined functional connectivity using a new multivariate technique during three different fMRI tasks of cognitive control in an adult lifespan sample. Our results offer new evidence for unique age differences in network connectivity profiles during the cognitive control domains of inhibition, response initiation, shifting, and working memory. We report two major findings: (1) an age-related brain dedifferentiation that is characterized by functional connectivity patterns during initiation, inhibition, and shifting becoming more similar in older age, particularly for control and default networks, and (2) multiple forms of age-related functional network reconfiguration such that frontal, default, and dorsal attention networks become more integrated (as previously reported; see Chan et al., 2014; Grady et al., 2016), whereas sub-networks of somato-motor and ventral attention networks are more segregated in older age. We also link measures of network segregation to cognitive control performance both in and out of the scanner and show that individual differences in network connectivity may support cognition. Each of these major findings are discussed in turn.





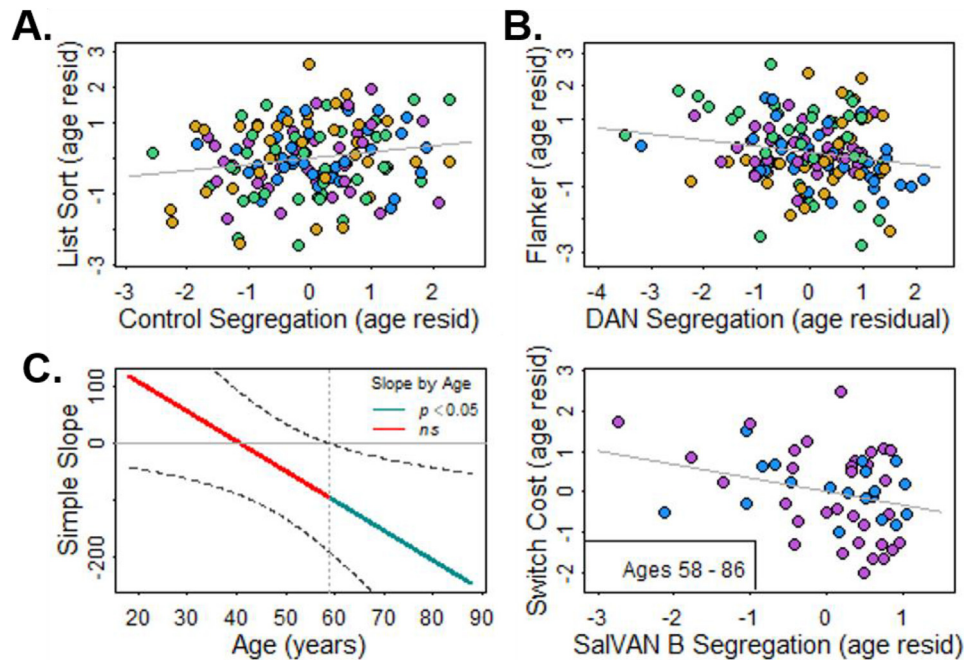
**Fig. 6.** Network Segregation and Age. Network segregation describes the degree of within network connectivity relative to between network connectivity for low-rank connectivity matrices rebuilt from the multivariate space. (A) Control, Default, Somato-Motor B (auditory) and Salience/Ventral Attention A (pars operculum and insula) networks showed linear decreases in network segregation with increasing age. (B) The Dorsal Attention network, exhibited a quadratic age trajectory, such that segregation increased until age 42 and decreased into late adulthood. (C) Somato-Motor A, which primarily includes motor regions, showed an increase in network segregation in older age.

#### 4.1. Functional dedifferentiation of cognitive control domains

Normal aging is characterized by the loss of specialization at both the cognitive and brain level, a phenomenon described as dedifferentiation (Grady, 2012; Park and Reuter-Lorenz, 2009). Cognitive dedifferentiation describes a behavioral shift from multi- to uni-dimensional representations such that different cognitive processes within an individual become more correlated as they age (Baltes et al., 1980; Tucker-Drob et al., 2019). Similarly, at the brain level, age-related dedifferentiation can manifest as neural representations showing more similar patterns of activation (Carp et al., 2011) or connectivity (Chan et al., 2014) such that functional signals are less dissociable for different task states (see Koen and Rugg, 2019 for a review). In the current study, we examined dedifferentiation of functional connectivity across large-scale brain networks for different sub-domains of cognitive control by utilizing a new application of cov-STATIS—a multivariate statistical method designed to examine similarity (and dissimilarity) of covariance matrices (in this case, functional connectivity correlation matrices for different task conditions). This approach allowed us to examine both domain-specific and network-specific age differences in the similarity of functional connectivity patterns.

##### 4.1.1. Domain-specific dedifferentiation

On a behavioral level, we found that the inter-subject correlations of performance across the domains were low to moderate (with the exception of inhibition and initiation), indicating that the tasks were relatively differentiated in terms of cognitive processing. This was the case even in the older adults, consistent with previous evidence that healthy older adults show the same separation of cognitive control components as seen in younger adults (de Frias et al., 2009). To assess differentiation of brain networks we used Cov-STATIS, which uses the  $R_V$  coefficient (a metric of similarity between correlation or covariance matrices) to quantify the degree of global similarity across our six task conditions (initiation, inhibition, shifting, 0-, 1- and 2-back working memory loads). From this, we report that whole-brain patterns of connectivity (that were not specific to any network) were significantly different for inhibition, shifting, and working memory in our youngest participants, a pattern of effects suggesting that on a global level, the functional representations of these cognitive control sub-domains are distinct in younger adults (a conclusion in line with prior behavioral evidence, Miyake et al., 2000). Functional neuroimaging studies in younger adults examining the amplitude of neural response across different domains of cognitive control generally find



**Fig. 7.** Brain-Behavior Associations. (A) After controlling for the effect of age, greater segregation of the control network predicted better working memory performance on a list sorting task. (B) Conversely, decreased segregation of the dorsal attention network (DAN) predicts better performance on a flanker inhibitory processing task. (C) There was a salience/ventral attention B (SalVAN B) segregation by age interaction that was driven by a negative relationship between switch cost and segregation for adults ages 58 and older, such that greater switch cost (i.e., worse performance) was associated with decreased segregation. The Johnson-Neyman plot illustrates the brain-behavior slope at each point of the lifespan with 95% confidence intervals (dashed lines). The vertical dotted line delineates significant slope values (dark cyan) from non-significant values (red). Note. points are color coded by age group based on a quartile split: green=ages 20-31; yellow=ages 32-52; blue=ages 53-65; purple = ages 66-86. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

that all sub-domains activate a common fronto-parietal control network with some additional evidence for domain-specific activity both within and outside fronto-parietal regions (Collette et al., 2005; Derrfuss et al., 2004; Lemire-Rodger et al., 2019; Rieck et al., 2021), suggesting that specialized and distinct patterns of brain function may subserve different control domains. However, these previous studies did not explicitly test the specificity of functional response, making it difficult to interpret their findings as additional support for functionally distinct cognitive control representations. Likewise, studies examining functional connectivity for different sub-domains of cognitive control in younger adults report domain-specific networks of connectivity during task fMRI for inhibition (Tsvetanov et al., 2018; Zheng et al., 2008), initiation (Hoffstaedter et al., 2014), shifting (Madden et al., 2010), and working memory (Burianová et al., 2015; Sambataro et al., 2010); however the regions identified in these domain-specific networks generally overlap with the canonical fronto-parietal control network. Because no other studies to our knowledge have directly compared connectivity patterns across domains, the current study is an important contribution to this literature on the functional representations underlying cognitive control sub-domains.

In addition to finding evidence for separable domains of cognitive control in younger adults, we report that after the early thirties, functional connectivity patterns during inhibition and shifting were no longer dissociable. This is in line with prior work finding that even within healthy, younger age ranges (i.e., ages 22–36), there are dissociable developmental trajectories, such that individual differences in inhibitory processing can predict differences in network connectivity (Petrican and Grady, 2017). Furthermore, we report that response initiation (which is recognized as a sub-domain of cognitive control [Lenartowicz et al., 2010; Sabb et al., 2008], but may not represent a completely independent cognitive process; Miyake et al., 2000) was no longer dissociable from in-

hibition after about age 66. Together, these results show neural evidence for multi-dimensional cognitive control representations in young adulthood that become more integrated at two different points in the lifespan, and emphasize the importance of including a full lifespan sample when studying normal aging. This complements behavioral findings showing that separate domains may merge into one factor in older age (Hedden and Yoon, 2006; Hull et al., 2008) and additional behavioral work that shows a shift to a uni-dimensional cognitive control domain which was associated with greater cognitive decline in aging (de Frias et al., 2009). However, it is important to note that these prior studies examined only older adult samples, thus the degree to which cognitive control domains become more integrated across the full adult lifespan in terms of behavioral measures, particularly in a longitudinal framework as suggested by Tucker-Drob and colleagues (2019), is still unclear.

To date, there are few functional neuroimaging studies examining multiple cognitive control domains in the context of normal aging. A recent meta-analysis of age-related differences in functional activity associated with inhibition, shifting, and working memory found a pattern of increased overlap in prefrontal brain regions associated with shifting and working memory tasks for older adults, which the authors interpreted as dedifferentiation of these domains at the brain level (Spreng et al., 2017). Although the current study did not find that functional connectivity patterns associated with shifting and working memory became more similar in older age, this could be because we examined functional representations across large-scale brain networks. Our recent work examining the effect of age on mean functional activity for this same study found that for all sub-domains of cognitive control, the effects of age on functional activity were evident in regions outside the common fronto-parietal regions engaged by each task, a result suggesting that aging might exert a stronger ef-

fect on other functional systems that interact with cognitive control (Rieck et al., 2021). This is consistent with findings from the current analysis of functional connectivity in this dataset in which age affects the global-representations of domain-specific connectivity across the entire brain, not just the fronto-parietal control network.

#### 4.1.2. Network-specific dedifferentiation

Within the multivariate connectivity space, cov-STATIS also computed partial factor scores for each participant which described the degree to which connectivity during each task condition deviated from that participant's mean pattern of connectivity for a particular network. This provided a network-specific metric of how similar connectivity within a given network was across all task conditions, with more similar connectivity profiles indicating functional dedifferentiation (i.e., less distinct representations) of the different domains. Specifically, we found that control, default, salience/ventral attention A, temporo-parietal, and somato-motor networks exhibited age-related dedifferentiation across all task conditions, such that older age was characterized by connectivity patterns in these networks that do not differ much as a function of task condition or cognitive control domain. This lack of task specificity of functional connectivity patterns may reflect reduced fidelity of neural activity (perhaps due to reduced neuronal signal-to-noise) which is thought to be one mechanism underlying functional dedifferentiation (see Koen and Rugg, 2019 for a review).

Our finding of increased similarity of connectivity patterns across tasks in older age is also consistent with work examining how the amplitude of functional activity during executive function is modulated in response to differing task demands or conditions. Prior work has reported that younger adults typically show large increases in fronto-parietal functional activity and large decreases in default mode activity in response to increasing cognitive demands or task difficulty within executive function paradigms (Persson et al., 2007; Schneider-Garces et al., 2010). In contrast, older adults show a reduced range of functional response when cognitive demands increase, such that fronto-parietal control (Cappell et al., 2010; Grady et al., 2020; Kennedy et al., 2015; Rieck et al., 2017; Schneider-Garces et al., 2010), salience/ventral attention (e.g., insula and medial frontal/dorsal anterior cingulate; Rieck et al., 2017; Kennedy et al., 2015), and motor regions (i.e., precentral gyrus; Qin and Basak, 2020; Saverino et al., 2016) are under-recruited, whereas activity in default (Kennedy et al., 2017; Persson et al., 2007; Rieck et al., 2017; Sambataro et al., 2010) and temporal cortex (Kennedy et al., 2017) is less dampened. Likewise, older adults show less modulation of BOLD signal variability during cognitive tasks compared to a baseline fixation state (Garrett et al., 2013). Across all these studies, reduced modulation in older adults was characterized by more similar functional response across different task conditions (resulting in a reduced range of activity), a pattern providing further support that the functional representations underlying different cognitive control conditions may be less differentiated in older age, particularly for regions of the fronto-parietal control, ventral attention, and default networks. Our results suggest that reduced specificity of functional connectivity across these functional networks could be related to prior findings of a reduced range and variability of functional response. A recent study reported that in addition to showing reduced modulation of fronto-parietal and dorsal attention regions as face-judgments became more difficult, older adults also show reduced modulation of whole-brain functional connectivity patterns (Grady et al., 2020), but more work is needed to directly test the link between patterns of functional connectivity and neural modulation during tasks of cognitive control.

#### 4.2. Age-related network reconfiguration during cognitive control

The next major finding from the current work was that large-scale functional networks showed age differences in how they interacted with each other during tasks of cognitive control. Fronto-parietal control, default, dorsal attention, somato-motor B (auditory cortex), and salience/ventral attention A (insula, pars opercularis and medial frontal) networks became less segregated with age, whereas somato-motor A (motor cortex) and salience/ventral attention B (dorsal anterior cingulate and inferior parietal lobule) became more segregated with age, providing evidence for multiple forms of network reconfiguration in normal aging.

##### 4.2.1. Age-related decreases in network segregation

Decreased network segregation in older age is generally characterized by weaker within-network connectivity and greater between-network connectivity, and this decrease has been consistently reported when examining large-scale functional networks during resting state (Betzel et al., 2014; Chan et al., 2014; Sala-Lluch et al., 2015). Fewer studies have assessed segregation of multiple large-scale brain networks during task-based fMRI, but prior work has examined the connectivity of specific regions within broader functional networks. Specifically, researchers report that older age is associated with weaker connectivity of fronto-parietal regions during inhibitory processing (Geerligs et al., 2014; Tsvetanov et al., 2018), shifting (Madden et al., 2010), and working memory (Burianová et al., 2015; Nagel et al., 2010; Sambataro et al., 2010) and weaker connectivity of default mode regions during working memory (Grady et al., 2010). This prior work supports our finding that age-related decreases in network segregation of fronto-parietal control and default regions are largely driven by weakened connectivity within each network, suggesting that functional representations within these networks might be compromised in older adults. We also report that normal aging was characterized by decreased segregation of the somato-motor B network (i.e., auditory regions) which may reflect increased distraction from task-irrelevant input from the noisy fMRI environment (Stevens et al., 2008).

In addition to age-related decreases in within-network connectivity, we found that decreased dorsal attention network segregation in older age is driven by age-related increases in between-network connectivity, suggesting that regions involved in top-down attentional processing become more integrated with other networks during cognitive control tasks. Prior work has also found that older adults show increased dorsal attention–fronto-parietal connectivity during a delayed match-to-sample working memory task (Grady et al., 2016) and increased dorsal attention–default connectivity during autobiographical planning (Spreng et al., 2016). This general pattern of age-related decrease provides further evidence that when cognitive control is reduced (as it is in normal aging), attentional systems may interact more heavily with other networks underlying cognitive control domains. Subsequently, more diffuse dorsal attention connectivity in normal aging could be a compensatory mechanism to account for reduced within-network connectivity of other networks (e.g., fronto-parietal control). The idea of compensation is supported by our additional finding that greater integration of dorsal attention regions predicts better inhibitory processing (this brain-behavior finding is discussed in further detail below).

##### 4.2.2. Age-related increases in network segregation

We also report a new finding of age-related increases in network segregation for two networks: somato-motor A (precentral/motor cortex) and salience/ventral attention B (dorsal anterior cingulate and inferior parietal lobule) that was largely driven



by stronger connectivity within each network in older ages. The finding of increased somato-motor segregation during task fMRI in older age is at odds with resting state work that has generally found that older adults show increased connectivity of motor regions to other networks (Chan et al., 2014; Geerligs et al., 2015) and decreased connectivity within motor regions (Wu et al., 2007). However, a task-based fMRI study in which younger and older adults completed finger movement sequences found that older adults showed reduced connectivity of cortical motor regions (e.g., precentral) to subcortical regions (e.g., basal ganglia, thalamus), but increased connectivity between cortical motor regions (Taniwaki et al., 2007), a result which was interpreted as a sign of reduced interhemispheric inhibition. The somato-motor A network used in the current study only included cortical regions, therefore our finding of increased functional connectivity characterizes connectivity between left and right precentral gyrus, in line with Taniwaki and colleagues. Together, these findings suggest that when participants are required to make motor responses (as in during task fMRI), greater segregation of the motor network in aging might reflect failed suppression of cross-hemispheric communication between relevant (in this case, left precentral gyrus because participants responded with their right hand) and non-relevant motor regions (e.g., right precentral gyrus).

We also report that salience/ventral attention B (i.e., medial prefrontal, dorsal anterior cingulate, and inferior parietal lobule) segregation increased in older age, largely due to age-related increases in connectivity within this network (although salience/ventral attention B also showed age-related increases in between-network connectivity). However, this particular age effect did not replicate when using two additional atlas parcellations (see Rieck et al., submitted), therefore our interpretation of this finding is preliminary. The dorsal anterior cingulate region of the salience/ventral attention network is thought to be involved in processing response conflict (Swainson et al., 2003) and response preparation (Schulz et al., 2011). Therefore, increased connectivity both within this network (and to a lesser extent with other networks), might indicate a greater reliance on attention resources during cognitive control tasks in older age. Furthermore, increased segregation of salience/ventral attention B network was found to be associated with better performance on the in-scanner shifting task selectively in older adults, suggesting that this reflects compensatory recruitment when cognitive control resources are compromised (brain-behavior findings are discussed in further detail below).

Our findings also highlight the importance of including finer-scaled regions when assessing functional connectivity, as the somato-motor and salience/ventral attention A and B sub-networks showed opposite segregation effects across the lifespan, suggesting that the broader network structure is less intact in older ages. Future work examining age effects on functional connectivity in *a-priori* defined networks should keep this in consideration when examining large-scale brain networks that might also have distinct sub-networks.

#### 4.2.3. Network segregation-cognitive performance associations

Finally, we examined how network segregation and age predicted individual differences in performance on tasks of cognitive control. Given that these brain-behavior analyses were *post-hoc* and did not take into account correcting for multiple comparisons, these findings should be regarded as preliminary and worth further exploration in future research. Furthermore, some brain-behavior associations we found are for performance on out-of-scanner tasks (i.e., list sorting, arrow flanker); therefore, these effects may represent trait-based relationships between cognitive control abilities, rather than a direct comparison of network mea-

sures generated during a task and subsequent performance on that task.

Prior work has linked resting state network connectivity to performance on different domains of cognitive control and found that connectivity within frontal-parietal regions during rest is associated with individual differences in general executive functioning (Reineberg et al., 2015), whereas connectivity within salience/ventral attention regions supported shifting-specific performance (Reineberg et al., 2015) and inhibition performance (Duchek et al., 2013). Work in younger adults also found that superior inhibition ability corresponded to greater segregation of ventral attention networks as cognitive control demands increased during task-based fMRI (Petrican and Grady, 2017). Similarly, in the current work, we found that greater segregation of fronto-parietal control regions was associated with better working memory on an out-of-scanner list sorting task (after controlling for the effect of age), an effect suggesting that individual differences in fronto-parietal connectivity may account for the higher levels of cognitive control. We further report that greater segregation of the salience/ventral attention B network was associated with decreased response time switch cost (i.e., better performance) on our local switching in-scanner task, but only in older adults (ages 58+). Given that older adults also showed greater segregation of salience/ventral attention B network compared to younger adults, this finding could indicate that more robust connectivity within bottom-up attention regions, specifically dorsal anterior cingulate and inferior parietal lobule, during cognitive control might serve as a compensatory mechanism in older adults that enables more efficient shifting between different cognitive judgements. Connectivity of the dorsal anterior cingulate in particular plays a role in error processing during task performance (Han et al., 2013), and this role further suggests that the older adults who perform best may also exhibit enhanced error detection and management when having to shift between judgment criteria.

We also report that, after controlling for age, greater dorsal attention network integration with other brain networks (i.e., less segregation) predicted better performance on an out-of-scanner arrow-flanker task of inhibitory processing. Reineberg and colleagues (2015) also report that the expansion of the dorsal attention network into other brain regions during resting state was associated with higher executive functioning, suggesting that increased connectivity of top-down attentional networks to other brain regions may support cognitive control abilities, such as inhibition. Greater connectivity between default and dorsal attention networks has also been linked to increased cognitive reserve in older adults with mild cognitive impairment (Franzmeier et al., 2017), providing additional evidence that increased connectivity of dorsal attention regions to broader functional networks may serve as a scaffold to maintaining cognition during aging.

#### 4.3. Limitations

Although this work provides a thorough examination of functional connectivity profiles across multiple domains of cognitive control in normal aging, there are several limitations. Due to the scale and complexity of the data being analyzed, we focused on providing summary metrics of network differentiation and segregation to quantify how functional patterns were expressed across the adult lifespan. Therefore, this limited us in detailing specific age  $\times$  domain  $\times$  network interactions that were observed in the multivariate connectivity space (but see Fig. 4 for an illustration in two networks and Supplemental Figure 5). We were also limited in examining specific network-network interactions (i.e., fronto-parietal to dorsal attention network connectivity) as previous work examining a much smaller set of networks has done. Furthermore,

the current brain-behavior results should be regarded as preliminary, due to the large number of statistical tests and exploratory nature of these findings. Finally, the current study was unable to examine dedifferentiation of cognitive control domains at the behavioral level, due to lack of multiple cognitive tests per domain and lack of longitudinal data, which provide more reliable estimates of behavioral dedifferentiation (Tucker-Drob et al., 2019). Examining the inter-subject correlations of performance on the fMRI tasks did reveal somewhat low similarity in performance across domains for the full sample (with the exception of the inhibition and initiation), suggesting relative process purity at a behavioral level. However, even though we provide evidence at the brain level that functional representations of these domains are less distinct with aging, this does not necessarily indicate behavioral dedifferentiation, which may even be a different manifestation of cognitive aging that is distinct from brain dedifferentiation. Our findings could indicate that brain dedifferentiation may even precede behavioral dedifferentiation, but this suggestion requires further investigation within the proper longitudinal framework. Nonetheless, we believe the current study offers a broad overview of the large-scale network connectivity profiles in normal aging and lays the groundwork for future researchers to test more network-specific or domain-specific hypotheses.

#### 4.4. Conclusions

This work offers a comprehensive evaluation of the functional connectivity profiles of large scale-brain networks during different domains of cognitive control across the adult lifespan. We used a new application of cov-STATIS—a multi-table multivariate method—to quantitatively assess the similarity of functional connectivity patterns across age and cognitive control task conditions. We found that patterns of functional connectivity associated with the domains of inhibition, shifting, and working memory were no longer dissociable in older age due to increased similarity in functional connectivity patterns of fronto-parietal control, default mode, salience/ventral attention, temporo-parietal and motor networks. These findings support evidence for functional dedifferentiation of neural representations underlying different domains of cognitive control. We also report that large-scale functional networks show age-related reconfiguration such that some networks become more integrated and diffuse in aging (i.e., fronto-parietal control, default, dorsal attention) whereas others show greater segregation (i.e., motor). Additional preliminary evidence suggests that cognitive control performance, both in and out of the scanner, may be predicted by individual differences in network connectivity: Specifically, greater segregation of control and salience/ventral attention B networks was associated with better performance, whereas greater integration of dorsal attention network with other brain networks predicted better inhibitory control. Taken together our results provide new evidence for dedifferentiation and reconfiguration of large-scale brain networks during different domains of cognitive control in normal aging and provide a template for using cov-STATIS to examine complex brain network interactions across different participant groups and task conditions.

#### Disclosure statement

The authors have no actual or potential conflicts of interest.

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#### Supplementary materials

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#### References

- Abdi, H., Dunlop, J.P., Williams, L.J., 2009. How to compute reliability estimates and display confidence and tolerance intervals for pattern classifiers using the Bootstrap and 3-way multidimensional scaling (DISTATIS). *NeuroImage* 45, 89–95. doi:[10.1016/j.neuroimage.2008.11.008](https://doi.org/10.1016/j.neuroimage.2008.11.008), Doi:.
- Abdi, H., Valentin, D., Chollet, S., Chrea, C., 2007. Analyzing assessors and products in sorting tasks: DISTATIS, theory and applications. *Food Qual. Prefer.* 18, 627–640. doi:[10.1016/j.foodqual.2006.09.003](https://doi.org/10.1016/j.foodqual.2006.09.003), Doi:.
- Abdi, H., Williams, L.J., Valentin, D., Bennani-Dosse, M., 2012. STATIS and DISTATIS: optimum multitable principal component analysis and three way metric multidimensional scaling. *WIREs Comput. Stat.* 4, 124–167. doi:[10.1002/wics.198](https://doi.org/10.1002/wics.198), Doi:.
- Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of large-scale brain systems in advanced aging. *Neuron* 56, 924–935. doi:[10.1016/j.neuron.2007.10.038](https://doi.org/10.1016/j.neuron.2007.10.038), Doi:.
- Baltes, P.B., Cornelius, S.W., Spiro, A., Nesselroade, J.R., Willis, S.L., 1980. Integration versus differentiation of fluid/crystallized intelligence in old age. *Dev. Psychol.* 16, 625–635. doi:[10.1037/0012-1649.16.6.625](https://doi.org/10.1037/0012-1649.16.6.625), Doi:.
- Baltes, P.B., Lindenberger, U., 1997. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol. Aging* 12, 12–21. doi:[10.1037/0882-7974.12.1.12](https://doi.org/10.1037/0882-7974.12.1.12), Doi:.
- Beaton, D., Fatt, C.C., Abdi, H., 2019. DistatisR: DiSTATIS Three Way Metric Multidimensional Scaling. R package version 1.0.1. <https://CRAN.R-project.org/package=DistatisR>.
- Betzel, R.F., Byrge, L., He, Y., Goñi, J., Zuo, X.-N., Sporns, O., 2014. Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage* 102, 345–357. doi:[10.1016/j.neuroimage.2014.07.067](https://doi.org/10.1016/j.neuroimage.2014.07.067), Doi:.
- Burianová, H., Marstaller, L., Choupan, J., Sepehrband, F., Ziaei, M., Reutens, D., 2015. The relation of structural integrity and task-related functional connectivity in the aging brain. *Neurobiol. Aging* 36, 2830–2837. doi:[10.1016/j.neurobiolaging.2015.07.006](https://doi.org/10.1016/j.neurobiolaging.2015.07.006), Doi:.
- Campbell, K.L., Grady, C.L., Ng, C., Hasher, L., 2012. Age differences in the frontoparietal cognitive control network: implications for distractibility. *Neuropsychologia* 50, 2212–2223. doi:[10.1016/j.neuropsychologia.2012.05.025](https://doi.org/10.1016/j.neuropsychologia.2012.05.025), Doi:.
- Campbell, K.L., Grigg, O., Saverino, C., Churchill, N., Grady, C.L., 2013. Age differences in the intrinsic functional connectivity of default network subsystems. *Front. Aging Neurosci.* 5, 73. doi:[10.3389/fnagi.2013.00073](https://doi.org/10.3389/fnagi.2013.00073), Doi:.
- Cappell, K.A., Gmeindl, L., Reuter-Lorenz, P.A., 2010. Age differences in prefrontal recruitment during verbal working memory maintenance depend on memory load. *Cortex J. Devoted Study Nerv. Syst. Behav.* 46, 462–473. doi:[10.1016/j.cortex.2009.11.009](https://doi.org/10.1016/j.cortex.2009.11.009), Doi:.
- Carp, J., Park, J., Polk, T.A., Park, D.C., 2011. Age differences in neural distinctiveness revealed by multi-voxel pattern analysis. *NeuroImage, Multivariate Decoding and Brain Reading* 56, 736–743. doi:[10.1016/j.neuroimage.2010.04.267](https://doi.org/10.1016/j.neuroimage.2010.04.267).
- Chan, M.Y., Park, D.C., Savalia, N.K., Petersen, S.E., Wig, G.S., 2014. Decreased segregation of brain systems across the healthy adult lifespan. *Proc. Natl. Acad. Sci.* 111, E4997–E5006. doi:[10.1073/pnas.1415122111](https://doi.org/10.1073/pnas.1415122111), Doi:.
- Churchill, N.W., Raamana, P., Spring, R., Strother, S.C., 2017. Optimizing fMRI preprocessing pipelines for block-design tasks as a function of age. *NeuroImage* 154, 240–254. doi:[10.1016/j.neuroimage.2017.02.028](https://doi.org/10.1016/j.neuroimage.2017.02.028), Doi:.
- Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., Salmon, E., 2005. Exploring the unity and diversity of the neural substrates of executive functioning. *Hum. Brain Mapp.* 25, 409–423. doi:[10.1002/hbm.20118](https://doi.org/10.1002/hbm.20118), Doi:.
- de Frias, C.M., Dixon, R.A., Strauss, E., 2009. Characterizing executive functioning in older special populations: from cognitively elite to cognitively impaired. *Neuropsychology* 23, 778–791. doi:[10.1037/a0016743](https://doi.org/10.1037/a0016743), Doi:.
- Derrfuss, J., Brass, M., von Cramon, D.Y., 2004. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. *NeuroImage* 23, 604–612. doi:[10.1016/j.neuroimage.2004.06.007](https://doi.org/10.1016/j.neuroimage.2004.06.007), Doi:.
- Duchek, J.M., Balota, D.A., Thomas, J.B., Snyder, A.Z., Rich, P., Benzinger, T.L., Fagan, A.M., Holtzman, D.M., Morris, J.C., Ances, B.M., 2013. Relationship between Stroop performance and resting state functional connectivity in cognitively normal older adults. *Neuropsychology* 27, 516–528. doi:[10.1037/a0033402](https://doi.org/10.1037/a0033402), Doi:.
- Escoufier, Y., 1973. Le Traitement des Variables Vectorielles. *Biometrics* 29, 751–760. doi:[10.2307/2529140](https://doi.org/10.2307/2529140), Doi:.
- Ferreira, L.K., Busatto, G.F., 2013. Resting-state functional connectivity in normal brain aging. *Neurosci. Biobehav. Rev.* 37, 384–400. doi:[10.1016/j.neubiorev.2013.01.017](https://doi.org/10.1016/j.neubiorev.2013.01.017), Doi:.

- Franzmeier, N., Göttinger, J., Grimmer, T., Drzezga, A., Áraque-Caballero, M.A., Simon-Vermot, L., Taylor, A.N.W., Bürger, K., Catak, C., Janowitz, D., Müller, C., Duerig, M., Sorg, C., Ewers, M., 2017. Resting-state connectivity of the left frontal cortex to the default mode and dorsal attention network supports reserve in mild cognitive impairment. *Front. Aging Neurosci.* 9. doi:[10.3389/fnagi.2017.00264](https://doi.org/10.3389/fnagi.2017.00264), Doi:.
- Garrett, D.D., Kovacevic, N., McIntosh, A.R., Grady, C.L., 2013. The Modulation of BOLD Variability between cognitive states varies by age and processing speed. *Cereb. Cortex* 23, 684–693. doi:[10.1093/cercor/bhs055](https://doi.org/10.1093/cercor/bhs055), Doi:.
- Geerligs, L., Maurits, N.M., Renken, R.J., Lorist, M.M., 2014. Reduced specificity of functional connectivity in the aging brain during task performance. *Hum. Brain Mapp.* 35, 319–330. doi:[10.1002/hbm.22175](https://doi.org/10.1002/hbm.22175), Doi:.
- Geerligs, L., Renken, R.J., Saliassi, E., Maurits, N.M., Lorist, M.M., 2015. A brain-wide study of age-related changes in functional connectivity. *Cereb. Cortex N. Y. N* 1991 25, 1987–1999. doi:[10.1093/cercor/bhu012](https://doi.org/10.1093/cercor/bhu012), Doi:.
- Goh, J.O.S., 2011. Functional dedifferentiation and altered connectivity in older adults: neural accounts of cognitive Aging. *Aging Dis* 2, 30–48.
- Gower, J.C., Dijkstra, G.B., 2004. *Procrustes Problems*. OUP, Oxford.
- Grady, C., 2012. The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi:[10.1038/nrn3256](https://doi.org/10.1038/nrn3256), Doi:.
- Grady, C., Sarraf, S., Saverino, C., Campbell, K., 2016. Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiol. Aging* 41, 159–172. doi:[10.1016/j.neurobiolaging.2016.02.020](https://doi.org/10.1016/j.neurobiolaging.2016.02.020), Doi:.
- Grady, C.L., Protzner, A.B., Kovacevic, N., Strother, S.C., Afshin-Pour, B., Wojtowicz, M., Anderson, J.A.E., Churchill, N., McIntosh, A.R., 2010. A multivariate analysis of age-related differences in default mode and task positive networks across multiple cognitive domains. *Cereb. Cortex N. Y. N* 1991 20, 1432–1447. doi:[10.1093/cercor/bhp207](https://doi.org/10.1093/cercor/bhp207), Doi:.
- Grady, C.L., Rieck, J.R., Nichol, D., Garrett, D.D., 2020. Functional connectivity within and beyond the face network is related to reduced discrimination of degraded faces in young and older adults. *Cereb. Cortex*. doi:[10.1093/cercor/bhaa179](https://doi.org/10.1093/cercor/bhaa179), Doi:.
- Hedden, T., Yoon, C., 2006. Individual differences in executive processing predict susceptibility to interference in verbal working memory. *Neuropsychology* 20, 511–528. doi:[10.1037/0894-4105.20.5.511](https://doi.org/10.1037/0894-4105.20.5.511), Doi:.
- Hoffstaedter, F., Grefkes, C., Roski, C., Caspers, S., Zilles, K., Eickhoff, S., 2014. Age-related decrease of functional connectivity additional to gray matter atrophy in a network for movement initiation. *Brain Struct. Funct.* 220, 999–1012. doi:[10.1007/s00429-013-0696-2](https://doi.org/10.1007/s00429-013-0696-2), Doi:.
- Hull, R., Martin, R.C., Beier, M.E., Lane, D., Hamilton, A.C., 2008. Executive function in older adults: a structural equation modeling approach. *Neuropsychology* 22, 508–522. doi:[10.1037/0894-4105.22.4.508](https://doi.org/10.1037/0894-4105.22.4.508), Doi:.
- Johnson, P.O., Fay, L.C., 1950. The Johnson-Neyman technique, its theory and application. *Psychometrika* 15, 349–367. doi:[10.1007/BF02288864](https://doi.org/10.1007/BF02288864), Doi:.
- Kennedy, K.M., Boylan, M.A., Rieck, J.R., Foster, C.M., Rodrigue, K.M., 2017. Dynamic range in BOLD modulation: lifespan aging trajectories and association with performance. *Neurobiol. Aging* 60, 153–163. doi:[10.1016/j.neurobiolaging.2017.08.027](https://doi.org/10.1016/j.neurobiolaging.2017.08.027), Doi:.
- Kennedy, K.M., Rodrigue, K.M., Bischof, G.N., Hebrank, A.C., Reuter-Lorenz, P.A., Park, D.C., 2015. Age trajectories of functional activation under conditions of low and high processing demands: an adult lifespan fMRI study of the aging brain. *NeuroImage* 104, 21–34. doi:[10.1016/j.neuroimage.2014.09.056](https://doi.org/10.1016/j.neuroimage.2014.09.056), Doi:.
- Koen, J.D., Rugg, M.D., 2019. Neural dedifferentiation in the Aging Brain. *Trends Cogn. Sci.* 23, 547–559. doi:[10.1016/j.tics.2019.04.012](https://doi.org/10.1016/j.tics.2019.04.012), Doi:.
- Lemire-Rodger, S., Lam, J., Viviano, J.D., Stevens, W.D., Spreng, R.N., Turner, G.R., 2019. Inhibit, switch, and update: a within-subject fMRI investigation of executive control. *Neuropsychologia* 132, 107134. doi:[10.1016/j.neuropsychologia.2019.107134](https://doi.org/10.1016/j.neuropsychologia.2019.107134), Doi:.
- Lenartowicz, A., Kalar, D.J., Congdon, E., Poldrack, R.A., 2010. Towards an ontology of cognitive control. *Top. Cogn. Sci.* 2, 678–692. doi:[10.1111/j.1756-8765.2010.01100.x](https://doi.org/10.1111/j.1756-8765.2010.01100.x), Doi:.
- Madden, D.J., Costello, M.C., Dennis, N.A., Davis, S.W., Shepler, A.M., Spaniol, J., Bucur, B., Cabeza, R., 2010. Adult age differences in functional connectivity during executive control. *NeuroImage* 52, 643–657. doi:[10.1016/j.neuroimage.2010.04.249](https://doi.org/10.1016/j.neuroimage.2010.04.249), Doi:.
- McNab, F., Leroux, G., Strand, F., Thorell, L., Bergman, S., Klingberg, T., 2008. Common and unique components of inhibition and working memory: an fMRI, within-subjects investigation. *Neuropsychologia* 46, 2668–2682. doi:[10.1016/j.neuropsychologia.2008.04.023](https://doi.org/10.1016/j.neuropsychologia.2008.04.023), Doi:.
- Miyake, A., Friedman, N.P., 2012. The nature and organization of individual differences in executive functions: four general conclusions. *Curr. Dir. Psychol. Sci.* 21, 8–14. doi:[10.1177/0963721411429458](https://doi.org/10.1177/0963721411429458), Doi:.
- Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cognit. Psychol.* 41, 49–100. doi:[10.1006/cogp.1999.0734](https://doi.org/10.1006/cogp.1999.0734), Doi:.
- Nagel, I.E., Preuschhof, C., Li, S.-C., Nyberg, L., Bäckman, L., Lindenberger, U., Heekeren, H.R., 2010. Load Modulation of BOLD Response and Connectivity Predicts Working Memory Performance in Younger and Older Adults. *J. Cogn. Neurosci.* 23, 2030–2045. doi:[10.1162/jocn.2010.21560](https://doi.org/10.1162/jocn.2010.21560), Doi:.
- Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci.* 12, 241–268. doi:[10.3758/s13415-011-0083-5](https://doi.org/10.3758/s13415-011-0083-5), Doi:.
- Onoda, K., Ishihara, M., Yamaguchi, S., 2012. Decreased functional connectivity by aging is associated with cognitive decline. *J. Cogn. Neurosci.* 24, 2186–2198. doi:[10.1162/jocn\\_a.00269](https://doi.org/10.1162/jocn_a.00269), Doi:.
- Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K., 2002. Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320. doi:[10.1037/0882-7974.17.2.299](https://doi.org/10.1037/0882-7974.17.2.299), Doi:.
- Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. *Annu. Rev. Psychol.* 60, 173–196. doi:[10.1146/annurev.psych.59.103006.093656](https://doi.org/10.1146/annurev.psych.59.103006.093656), Doi:.
- Persson, J., Lustig, C., Nelson, J.K., Reuter-Lorenz, P.A., 2007. Age differences in deactivation: a link to cognitive control? *J. Cogn. Neurosci.* 19, 1021–1032. doi:[10.1162/jocn.2007.19.6.1021](https://doi.org/10.1162/jocn.2007.19.6.1021), Doi:.
- Petrican, R., Grady, C.L., 2017. Contextual and developmental differences in the neural architecture of cognitive control. *J. Neurosci.* 37, 7711–7726. doi:[10.1523/JNEUROSCI.0667-17.2017](https://doi.org/10.1523/JNEUROSCI.0667-17.2017), Doi:.
- Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., Vogel, A.C., Laumann, T.O., Miezin, F.M., Schlaggar, B.L., Petersen, S.E., 2011. Functional network organization of the human brain. *Neuron* 72, 665–678. doi:[10.1016/j.neuron.2011.09.006](https://doi.org/10.1016/j.neuron.2011.09.006), Doi:.
- Preacher, K.J., Curran, P.J., Bauer, D.J., 2006. Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *J. Educ. Behav. Stat.* 31, 437–448. doi:[10.3102/10769986031004437](https://doi.org/10.3102/10769986031004437), Doi:.
- Qin, S., Basak, C., 2020. Age-related differences in brain activation during working memory updating: An fMRI study. *Neuropsychologia* 138, 107335. doi:[10.1016/j.neuropsychologia.2020.107335](https://doi.org/10.1016/j.neuropsychologia.2020.107335), Doi:.
- Reineberg, A.E., Andrews-Hanna, J.R., Depue, B.E., Friedman, N.P., Banich, M.T., 2015. Resting-state networks predict individual differences in common and specific aspects of executive function. *NeuroImage* 104, 69–78. doi:[10.1016/j.neuroimage.2014.09.045](https://doi.org/10.1016/j.neuroimage.2014.09.045), Doi:.
- Rieck, J.R., Baracchini, G., Grady, C.L., 2021. Contributions of brain function and structure to three different domains of cognitive control in normal aging. *J. Cogn. Neurosci.* 1–22. doi:[10.1162/jocn\\_a.01685](https://doi.org/10.1162/jocn_a.01685), Doi:.
- Rieck, J.R., Baracchini, G., Nichol, D., Abdi, H., Grady, C.L., submitted. Dataset of functional connectivity during cognitive control for an adult lifespan sample. Data Brief.
- Rieck, J.R., Rodrigue, K.M., Boylan, M.A., Kennedy, K.M., 2017. Age-related reduction of BOLD modulation to cognitive difficulty predicts poorer task accuracy and poorer fluid reasoning ability. *NeuroImage* 147, 262–271. doi:[10.1016/j.neuroimage.2016.12.022](https://doi.org/10.1016/j.neuroimage.2016.12.022), Doi:.
- Sabb, F.W., Bearden, C.E., Glahn, D.C., Parker, D.S., Freimer, N., Bilder, R.M., 2008. A collaborative knowledge base for cognitive phenomics. *Mol. Psychiatry* 13, 350–360. doi:[10.1038/sj.mp.4002124](https://doi.org/10.1038/sj.mp.4002124), Doi:.
- Sala-Lluch, R., Bartrés-Faz, D., Junqué, C., 2015. Reorganization of brain networks in aging: a review of functional connectivity studies. *Front. Psychol.* 6, 663. doi:[10.3389/fpsyg.2015.00663](https://doi.org/10.3389/fpsyg.2015.00663), Doi:.
- Salthouse, T.A., Atkinson, T.M., Berish, D.E., 2003. Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *J. Exp. Psychol. Gen.* 132, 566–594. doi:[10.1037/0096-3445.132.4.566](https://doi.org/10.1037/0096-3445.132.4.566), Doi:.
- Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H.-Y., Das, S., Weinberger, D.R., Mattay, V.S., 2010. Age-related alterations in default mode network: impact on working memory performance. *Neurobiol. Aging* 31, 839–852. doi:[10.1016/j.neurobiolaging.2008.05.022](https://doi.org/10.1016/j.neurobiolaging.2008.05.022), Doi:.
- Saverino, C., Fatima, Z., Sarraf, S., Oder, A., Strother, S.C., Grady, C.L., 2016. The associative memory deficit in aging is related to reduced selectivity of brain activity during encoding. *J. Cogn. Neurosci.* 28, 1331–1344. doi:[10.1162/jocn\\_a.00970](https://doi.org/10.1162/jocn_a.00970), Doi:.
- Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cereb. Cortex* 28, 3095–3114. doi:[10.1093/cercor/bhx179](https://doi.org/10.1093/cercor/bhx179), Doi:.
- Schneider-Garcés, N.J., Gordon, B.A., Brumback-Peltz, C.R., Shin, E., Lee, Y., Sutton, B.P., MacLain, E.L., Gratton, G., Fabiani, M., 2010. Span, CRUNCH, and beyond: working memory capacity and the aging brain. *J. Cogn. Neurosci.* 22, 655–669. doi:[10.1162/jocn.2009.21230](https://doi.org/10.1162/jocn.2009.21230), Doi:.
- Schulz, K.P., Bédard, A.-C.V., Czarnecki, R., Fan, J., 2011. Preparatory activity and connectivity in dorsal anterior cingulate cortex for cognitive control. *NeuroImage* 57, 242–250. doi:[10.1016/j.neuroimage.2011.04.023](https://doi.org/10.1016/j.neuroimage.2011.04.023), Doi:.
- Seli, P., 2016. The attention-lapse and motor decoupling accounts of SART performance are not mutually exclusive. *Conscious. Cogn.* 41, 189–198. doi:[10.1016/j.concog.2016.02.017](https://doi.org/10.1016/j.concog.2016.02.017), Doi:.
- Spreng, R.N., Shoemaker, L., Turner, G.R., 2017. Chapter 8 - executive functions and neurocognitive aging. In: Goldberg, E. (Ed.), *Executive Functions in Health and Disease*. Academic Press, San Diego, pp. 169–196. doi:[10.1016/B978-0-12-803676-1.00008-8](https://doi.org/10.1016/B978-0-12-803676-1.00008-8), Doi:.
- Spreng, R.N., Stevens, W.D., Viviano, J.D., Schacter, D.L., 2016. Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. *Neurobiol. Aging* 45, 149–160. doi:[10.1016/j.neurobiolaging.2016.05.020](https://doi.org/10.1016/j.neurobiolaging.2016.05.020), Doi:.
- Stevens, W.D., Hasher, L., Chiew, K.S., Grady, C.L., 2008. A neural mechanism underlying memory failure in older adults. *J. Neurosci.* 28, 12820–12824. doi:[10.1523/JNEUROSCI.2622-08.2008](https://doi.org/10.1523/JNEUROSCI.2622-08.2008), Doi:.
- St-Laurent, M., Abdi, H., Burianová, H., Grady, C.L., 2011. Influence of aging on the neural correlates of autobiographical, episodic, and semantic memory retrieval. *J. Cogn. Neurosci.* 23, 4150–4163. doi:[10.1162/jocn\\_a.00079](https://doi.org/10.1162/jocn_a.00079), Doi:.
- Swainson, R., Cunnington, R., Jackson, G.M., Rorden, C., Peters, A.M., Morris, P.G., Jackson, S.R., 2003. Cognitive control mechanisms revealed by ERP and fMRI:



- evidence from repeated task-switching. *J. Cogn. Neurosci.* 15, 785–799. doi:[10.1162/0899290322370717](https://doi.org/10.1162/0899290322370717), Doi:.
- Sylvester, C.-Y.C., Wager, T.D., Lacey, S.C., Hernandez, L., Nichols, T.E., Smith, E.E., Jonides, J., 2003. Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia. Functional Neuroimaging of Memory* 41, 357–370. doi:[10.1016/S0028-3932\(02\)00167-7](https://doi.org/10.1016/S0028-3932(02)00167-7), Doi:.
- Taniwaki, T., Okayama, A., Yoshiura, T., Togao, O., Nakamura, Y., Yamasaki, T., Ogata, K., Shigeto, H., Ohyagi, Y., Kira, J., Tobimatsu, S., 2007. Age-related alterations of the functional interactions within the basal ganglia and cerebellar motor loops in vivo. *NeuroImage* 36, 1263–1276. doi:[10.1016/j.neuroimage.2007.04.027](https://doi.org/10.1016/j.neuroimage.2007.04.027), Doi:.
- Thomas 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. *J. Neurophysiol.* 106, 1125–1165. doi:[10.1152/jn.00338.2011](https://doi.org/10.1152/jn.00338.2011), Doi:.
- Tomasi, D., Volkow, N.D., 2012. Aging and functional brain networks. *Mol. Psychiatry* 17, 549–558. doi:[10.1038/mp.2011.81](https://doi.org/10.1038/mp.2011.81), Doi:.
- Tsvetanov, K.A., Ye, Z., Hughes, L., Samu, D., Treder, M.S., Wolpe, N., Tyler, L.K., Rowe, J.B. for the Cambridge Centre for Ageing and Neuroscience, 2018. Activity and connectivity differences underlying inhibitory control across the adult life Span. *J. Neurosci.* 38, 7887–7900. doi:[10.1523/JNEUROSCI.2919-17.2018](https://doi.org/10.1523/JNEUROSCI.2919-17.2018), Doi:.
- Tucker-Drob, E.M., Brandmaier, A.M., Lindenberger, U., 2019. Coupled cognitive changes in adulthood: a meta-analysis. *Psychol. Bull.* 145, 273–301. doi:[10.1037/bul0000179](https://doi.org/10.1037/bul0000179), Doi:.
- Weintraub, S., Dikmen, S.S., Heaton, R.K., Tulsky, D.S., Zelazo, P.D., Bauer, P.J., Carlozzi, N.E., Slotkin, J., Blitz, D., Wallner-Allen, K., Fox, N.A., Beaumont, J.L., Mungas, D., Nowinski, C.J., Richler, J., Deocampo, J.A., Anderson, J.E., Manly, J.J., Borosh, B., Havlik, R., Conway, K., Edwards, E., Freund, L., King, J.W., Moy, C., Witt, E., Gershon, R.C., 2013. Cognition assessment using the NIH Toolbox. *Neurology* 80, S54–S64. doi:[10.1212/WNL.0b013e3182872ded](https://doi.org/10.1212/WNL.0b013e3182872ded), Doi:.
- Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* 2, 125–141. doi:[10.1089/brain.2012.0073](https://doi.org/10.1089/brain.2012.0073), Doi:.
- Wu, T., Zang, Y., Wang, L., Long, X., Hallett, M., Chen, Y., Li, K., Chan, P., 2007. Aging influence on functional connectivity of the motor network in the resting state. *Neurosci. Lett.* 422, 164–168. doi:[10.1016/j.neulet.2007.06.011](https://doi.org/10.1016/j.neulet.2007.06.011), Doi:.
- Zhang, H.-Y., Chen, W.-X., Jiao, Y., Xu, Y., Zhang, X.-R., Wu, J.-T., 2014. Selective vulnerability related to aging in large-scale resting brain networks. *PLoS ONE* 9. doi:[10.1371/journal.pone.0108807](https://doi.org/10.1371/journal.pone.0108807), Doi:.
- Zheng, D., Oka, T., Bokura, H., Yamaguchi, S., 2008. The key locus of common response inhibition network for no-go and stop signals. *J. Cogn. Neurosci.* 20, 1434–1442. doi:[10.1162/jocn.2008.20100](https://doi.org/10.1162/jocn.2008.20100), Doi:.