Connectome-based models predict attentional control in aging adults

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ABSTRACT

There are well-characterized age-related differences in behavioral and neural responses to tasks of attentional control. However, there is also increasing recognition of individual variability in the process of neurocognitive aging. Using connectome-based predictive modeling, a method for predicting individual-level behaviors from whole-brain functional connectivity, a sustained attention connectome-based prediction model (saCPM) has been derived in young adults. The saCPM consists of two large-scale functional networks: a high-attention network whose strength predicts better attention and a low-attention network whose strength predicts worse attention. Here we examined the generalizability of the saCPM for predicting inhibitory control in an aging sample. Forty-two healthy young adults (n = 21, ages 18–30) and older adults (n = 21, ages 60–80) performed a modified Stroop task, on which older adults exhibited poorer performance, indexed by higher reaction time cost between incongruent and congruent trials. The saCPM generalized to predict reaction time cost across age groups, but did not account for age-related differences in performance. Exploratory analyses were conducted to characterise the effects of age on functional connectivity and behavior. We identified subnetworks of the saCPM that exhibited age-related differences in strength. The strength of two low-attention subnetworks, consisting of frontoparietal, medial frontal, default mode, and motor nodes that were more strongly connected in older adults, mediated the effect of age group on performance. These results support the saCPM's ability to capture attention-related patterns reflected in each individual's functional connectivity signature across both task context and age. However, older and younger adults exhibit functional connectivity differences within components of the saCPM networks, and it is these connections that better account for age-related deficits in attentional control.

Healthy older adults exhibit deficits in the executive control of attention, which are characterized by slower reaction times and reduced task accuracy at the behavioral level, and increased recruitment of the frontoparietal network (FPN) and default-mode network (DMN) at the neural level (Lustig and Jantz, 2015). Early work posited that advancing age is associated with a primary deficit in inhibitory control, whereby increasing amounts of irrelevant information are allowed to enter the processing stream (Hasher and Zacks, 1988). This hypothesis has been corroborated by a more recent 14-year longitudinal study of cognitive change in older adults demonstrating that greater recruitment of frontal regions is associated with poorer performance on tasks of executive attention, including inhibitory control (Goh et al., 2012). Since the inception of brain imaging techniques, a central aim in the field of cognitive aging has been to relate cognitive abilities to age-related differences in neural function. However, much of this literature has traditionally emphasized group-based differences in activity in circumscribed regions of the brain, and even with the development of functional connectivity methods, the focus has primarily been on a few select networks. As such, with a reliance on a priori regions and networks of interest and a tendency towards a group-level analysis approach, the majority of these studies have only been able to explain modest variance in behavioral performance.

Accumulating evidence suggests that the trajectories of cognitive and neural change across advancing age are markedly heterogeneous across individuals. Thus, more recently developed methods for predicting behavior from neuroimaging data at the individual level may be particularly well-suited for the aging context (Goh et al., 2012; Goh et al., 2013). Such individual difference approaches can offer insights into how age-related neural change may or may not impact cognitive function by examining associations between an individual's brain features (e.g., functional connectivity patterns) and their behavior. Recent work, for example, used data-driven techniques to identify a set of large-scale...
functional networks whose strength predicts over 70% of the variance in individual-level performance during a gradual-onset continuous performance task (gradCPT) in young adults (Rosenberg et al., 2016a). Subsequent work has provided evidence that this model captures a more task-general pattern of functional connectivity with successful prediction of other facets of attention in both healthy (Jangraw et al., 2018; Rosenberg et al., 2018; Rosenberg et al., 2016b) and clinical samples (e.g., attention-deficit/hyperactivity disorder; Rosenberg et al., 2016a). Although there is equivocal evidence for age-related differences on tasks of sustained attention similar to the gradCPT (see Stanb et al., 2013 for review), this model's predictive power is not reliant on, nor limited to, the gradCPT specifically. In order to extend this model to an aging sample, we were interested in applying it to an attentional task that more heavily taxes inhibitory control, on which age-related deficits are consistently observed (Jackson and Balota, 2013; Mutter et al., 2005; Spieler et al., 1996; West and Alain, 2000; Wolf et al., 2014). As such, the present study aims to test the ability of whole-brain networks derived during the gradCPT to predict performance on a Stroop task and to examine the generalizability of prediction across a sample of healthy young and older adults.

1. Age-related shifts in neural responses to cognitive demand

Studies investigating region-specific age-group differences in brain activation have laid the groundwork for understanding age-related changes in neural responding during cognitive tasks. For example, older adults as a group exhibit neural deactivation, or reduced specificity of neural recruitment in response to cognitive demand (Baltes and Lindenberger, 1997; Prakash et al., 2009; Prakash et al., 2012), and neural compensation, or increased recruitment of additional brain regions to compensate for functional deficits (Grady, 1998; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). These patterns have been observed in older adults engaged in tasks of attentional and executive control, including inhibitory control. Specifically, there is evidence of over-recruitment of various frontoparietal regions at lower levels of demand compared to young adults (Cabeza et al., 2004; Colcombe et al., 2005; Langenecker et al., 2004; Mattay et al., 2006; Milham et al., 2002; Nielson et al., 2002; Prakash et al., 2009; Vallesi et al., 2010) as well as increased recruitment of regions of the DMN (Grady et al., 2006; Lustig et al., 2003; Park and Reuter-Lorenz, 2011; Persson et al., 2007; Prakash et al., 2012; Sambataro et al., 2010). Although these studies provide consistent evidence that reduced DMN suppression is related to poorer performance, both positive and negative associations have been observed between increased frontoparietal recruitment and performance, generating significant interest in the functional implications of these altered patterns of neural activity. Importantly, more recent longitudinal data demonstrate that age-related increases in frontal activation are associated with declines in performance on several tasks of executive function, including inhibition (Goh et al., 2012). Therefore, it is unclear how age-related declines in attentional performance manifest in region-specific activation changes, particularly when assessed at the group level.

2. Age-related shifts in functional network topology

The understanding of brain-behavior relationships across aging has been augmented by the acknowledgment that complex cognitive functions are largely supported by coordinated, distributed networks of multiple brain regions (Yarkoni et al., 2011). Analysis of functional connectivity—correlations between blood oxygen-level-dependent timecourses in distinct regions of the brain—further supports a reduction in the selectivity and specificity of neural recruitment with age. During both exogenous and endogenous processing, there is strong evidence of age-related decreases in segregation, or increased functional connectivity between networks (Bernard et al., 2013; Betzel et al., 2014; Chan et al., 2014; Esposito et al., 2018; Geerligs et al., 2015a; Geerligs et al., 2014; Grady et al., 2016; Onoda et al., 2012; Spreng and Schacter, 2011; Spreng et al., 2016), as well as general age-related disconnection within many networks of the brain (Andrews-Hanna et al., 2007; Betzel et al., 2014; Damoiseaux et al., 2008; Geerligs et al., 2015a; Koch et al., 2010; Onoda et al., 2012; Song et al., 2014), which persist after controlling for age-related brain atrophy and structural changes (Ferreira and Busato, 2013; Ng et al., 2016). Declines in functional connectivity within networks implicated in higher-order cognition, such as the DMN, FPN, salience network, and dorsal attention network, begin to appear as early as middle age (Siman-Tov et al., 2017). Importantly, preserved network segregation and minimal intra-network disconnection are related to better performance on tasks of attentional control cross-sectionally (Andrews-Hanna et al., 2007; Avena-Pereira et al., 2017; Damoiseaux et al., 2008; Geerligs et al., 2015a; Geerligs et al., 2014; Grady et al., 2016; Onoda et al., 2012) and longitudinally over 4 years (Ng et al., 2016).

Recent work has moved beyond network-specific analyses to connectome-wide investigations, which also yield evidence of neural dedifferentiation in older adults. These studies have replicated findings of decreased connectivity within the DMN, attention networks, sensory-motor systems, and subcortical regions (Chan et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015a; Tomasi and Volkow, 2012), as well as increased positive inter-network correlations, and focal inter-network losses of anticorrelation, primarily between the DMN and attentional networks (Ferreira et al., 2016). Other whole-brain studies employing graph theory metrics provide convergent evidence for dedifferentiation, such that older adults exhibit less modularity (i.e., the degree to which a network can be divided into distinct functional groups), and shifts in modular composition, with some functionally distinct networks even merging with advancing age (Chan et al., 2014; Geerligs et al., 2015a; Iordan et al., 2017; Meunier et al., 2009; Onoda and Yamaguchi, 2013; Schlesinger et al., 2017; Song et al., 2014). Age-related deficits in attentional control appear to be related to several graph theory metrics representing dedifferentiation in the brain. For example, in a developmental sample (ages 19–78 years), those 42 years and older relied more on between-frontoparietal module connectivity to complete a conjunction search task (Monge et al., 2017). In a sample of older and younger adults who performed an n-back task with irrelevant word and non-word distractors, higher modularity and small-worldness (i.e., dense clustering between nodes with short connecting paths) at rest and during processing of distractor words predicted better performance, indexed by less priming for distraction and a reduced flanker effect (Anderson et al., 2017). In another study, older adults exhibited higher frontal participation coefficient in all conditions of an n-back task, whereas young adults only exhibited this increase during the most demanding condition (Gallen et al., 2016), indicating that frontal nodes with connections distributed more widely across networks were engaged to a greater extent in older adults. Interestingly, higher frontal participation coefficient was related to faster responses to the task for older adults, but not young adults. Additionally, preserved modularity and local efficiency (i.e., functional integration between neighboring regions) were found to be related to better learning during working memory training for older, but not younger, adults (Iordan et al., 2017). Together, this work suggests that age-related changes are fairly heterogeneous across networks and that shifts in connectivity can affect multiple networks, warranting a whole-brain approach to exploring neurocognitive aging.

3. Functional connectome modeling

Although there are broad patterns of functional brain organization that appear to be ubiquitous (Power et al., 2011), individuals possess distinct patterns of whole-brain functional connectivity, during both task execution and rest, that can be used to identify them from a group (Finn et al., 2015). These distinct patterns are maintained even when group-mean differences are observed (Shah et al., 2016). Connectome-based predictive modeling (CPM; Shen et al., 2017) was
developed as a method to identify connections within the whole-brain connectome that are predictive of individual-level behavior. This approach was recently used to derive a model that predicts sustained attention performance in previously unseen participants from functional connectivity data collected during performance of the gradual-onset continuous performance task (gradCPT; Esterman et al., 2013; Rosenberg et al., 2013), with subsequent successful prediction from resting-state data (Rosenberg et al., 2016a). This sustained attention connectome-based predictive model (saCPM) consists of two networks, a high-attention network and low-attention network, whose strengths predict better and worse performance, respectively, on the gradCPT. Interestingly, these two large-scale networks are widely distributed throughout the brain, including connections originating in the cortex, subcortex, and cerebellum. Initial generalizability of the saCPM has been demonstrated with prediction of attention-deficit/hyperactivity disorder (ADHD) symptom severity in children (Rosenberg et al., 2016a) and paragraph recall in a reading task (Jangraw et al., 2018).

Most pertinent to the present paper, these networks have also generalized to predict additional domains of attentional control. Specifically, the saCPM successfully predicted accuracy on a stop signal task (Rosenberg et al., 2016b), and accuracy, reaction time variability, and executive control on the Attention Networks Task (Rosenberg et al., 2018). Further, when healthy adults were given methylphenidate, a stimulant typically prescribed to ADHD patients, they showed connectivity patterns associated with better sustained attention (i.e., higher high-attention and lower low-attention network strength) compared to unmedicated controls, providing evidence of a relationship between changes in saCPM connectivity and changes in attentional control (Rosenberg et al., 2016b). This evidence of generalizability suggests that the saCPM may capture individual differences in general attentional ability, which can be represented in network properties of the brain during various attentional tasks and also at rest (Rosenberg et al., 2017). These results provide the impetus for testing the applicability of the saCPM to a task of higher-order attentional control in an aging sample.

4. Current study

The goal of the present study was to test the external validity of the saCPM to a novel task of attentional control and to the aging context. Specifically, we evaluated the ability of the saCPM networks to predict performance on a modified Stroop task in a previously unseen sample of healthy younger and older adults. The gradCPT and Stroop task share similar cognitive operations, requiring participants to sustain attention to changing stimuli over time and to stop or modulate prepotent responses, although the gradCPT has primarily been used as measure of sustained attention, and the Stroop task has traditionally been used as measure of response inhibition. Given these similarities, and the generalizability of this model to multiple tasks of attention demonstrated by previous studies reviewed above, we expected to observe successful prediction across age groups. Based on extensive evidence of age-related deficits on more demanding tasks of inhibitory control, we expected older adults to perform worse on the Stroop task. In order to investigate how age-related differences in performance might be represented within the connectome, we first examined whether connectivity strength of the saCPM networks mediated the effect of age on Stroop performance. Next, we employed a data-driven approach to identify subnetworks within the saCPM that exhibited age-related differences in connectivity strength. We then assessed the relation between these subnetworks and performance, and tested whether connectivity strength within these subnetworks accounted for age-related differences in Stroop performance through mediation.

5. Materials and methods

5.1. Participants

Forty-two healthy young adults (ages 18–30) and older adults (ages 60–80) participated in magnetic resonance imaging (MRI) sessions as part of a larger study, in which a total of 50 young adults (YA) and 50 older adults (OA) completed behavioral assessments of cognitive and emotional functioning. The parent study had two aims: 1) to identify age-related differences in emotion regulation and attentional control (Schirda et al., 2016) and 2) to examine the association between dispositional mindfulness and metrics of emotion regulation and attentional control (Prakash et al., 2013; Prakash et al., 2017). Of the subset of individuals who completed MRIs, eight participants were excluded from analyses: three young adults and two older adults who exhibited excessive head motion as described in the Motion Controls section below, one older adult and one young adult due to incidental anatomical abnormalities, and one additional young adult with functional network strength values >3 standard deviations from the age-group mean. Thirty-four participants were included in subsequent analyses: 16 young adults (age range: 18–30, M_age = 23.19 ± 3.67 years) and 18 older adults (age range: 60–77, M_age = 65.22 ± 4.76 years) were matched on sex (χ² = 0.034, p = .855; YA: 75% female, OA: 72% female) and education (t(32) = −0.503, p = .618; YA: M_age = 15.81 ± 2.43 years, OA: M_age = 16.22 ± 2.32 years). Demographic data can be found in Table 1.

Participants were considered eligible if they had corrected near and far visual acuity no worse than 20/20, were not colorblind (Ishihara, 2010), scored below 10 on the Geriatric Depression Scale for older adults or below 18 on the Beck Depression Inventory for young adults, and self-reported absence of neurologic disorders, psychiatric disorders, untreated hypertension, chronic inflammatory diseases, and denied regular use of steroid medication or replacement therapies. No older adults met exclusion criteria for low scores on the Mini Mental State Examination (Folstein et al., 1975; cutoff: ≤ 23; actual range: 27–30). Additionally, participants included in this analysis were suitable for the MRI portion of the study. Thus, all participants were right-handed, non-claustrophobic, had a BMI <30, and did not have implanted devices contraindicated for the MR environment. This study was approved by The Ohio State University Institutional Review Board, and informed consent was obtained from each participant.

5.2. Behavioral task

Participants performed a modified Stroop paradigm during MRI in which they were asked to press a button corresponding to the color of the word presented on the screen, which was either congruent or incongruent with the word meaning. Words were presented for 2000 ms

| Table 1: Study sample demographics and characteristics. |
|-----------------------------------------------|-----------------|-----------------|
|                                                | Young (n = 16)  | Old (n = 18)    |
|                                                | Mean ± SD       | Mean ± SD       |
| Full Sample                                    |                 |                 |
| Age (years)                                    | 23.19 ± 3.67    | 65.22 ± 4.76    |
| Education (years)                              | 15.81 ± 2.43    | 16.22 ± 2.32    |
| % Female                                       | 75.00 ± 0.00    | 72.22 ± 0.00    |
| Stroop Task                                    |                 |                 |
| RT cost MC block (ms)                          | 157.90 ± 71.74  | 252.41 ± 108.12 |
| RT cost MI block (ms)                          | 86.43 ± 77.78   | 185.21 ± 83.44  |
| Framewise Displacement (mm)                    | 0.14 ± 0.05     | 0.21 ± 0.07     |
| CPM                                            |                 |                 |
| High-Attention Network                         |                 |                 |
| Mean Strength                                  | 0.008 ± 0.032   | −0.005 ± 0.028  |
| Predicted d'                                   | 2.205 ± 1.97e-4 | 2.205 ± 1.74e-4 |
| Low-Attention Network                          |                 |                 |
| Mean Strength                                  | 0.015 ± 0.032   | 0.037 ± 0.029   |
| Predicted d'                                   | 2.171 ± 2.28e-4 | 2.171 ± 2.10e-4 |
| NBS                                            |                 |                 |
| OA Low1 Mean Strength                          | −0.184 ± 0.109  | 0.018 ± 0.134   |
| OA Low2 Mean Strength                          | −0.282 ± 0.127  | −0.003 ± 0.127  |

Note. MC: Mostly Congruent block, MI: Mostly Incongruent block.
followed by a 500 ms fixation and a jittered inter-trial interval of 1500–4500 ms. The task was divided into 12 task blocks (lasting approximately 110 s), consisting of 20 trials each. The proportion of congruent stimuli within a block was manipulated to a 70:30 ratio, such that six blocks were mostly congruent and six blocks were mostly incongruent. The blocks and trials within them were pseudo-randomized to counterbalance trial and block presentation order and to prevent repeat trials. Each block was followed by an inter-block fixation of 16,000 ms.

The primary dependent variable of interest was reaction time cost (RT cost), calculated as the difference in RT for incongruent vs. congruent trials of the mostly congruent blocks. This calculation was based on correct trials of mostly congruent blocks only; accuracy for incongruent trials was 96.25% (34.65 out of 36 trials on average) and accuracy for congruent trials was 96.36% (80.94 out of 84 trials on average). This variable was derived solely from the mostly congruent blocks, which is the more challenging of the two blocks, given that participants must resolve interference from infrequent incongruent stimuli in the context of frequent non-conflict trials. Therefore, the mostly congruent block places greater demands on working memory processes in service of maintaining task set across longer durations of congruent trials (Botvinick et al., 2001). Previous work manipulating list-level proportion congruency (i.e., within blocks) has found that Stroop interference is greater for mostly congruent than mostly incongruent lists (Bugg et al., 2011; Hutchison, 2011) and that the mostly congruent block accentuates differences in performance between high and low working memory capacity individuals (Hutchison, 2011; Kane and Engle, 2003). These findings suggest that the mostly congruent block might be more sensitive to age-related deficits, providing a basis for our choice of focusing on the mostly congruent block. In addition, RT cost values calculated from the mostly congruent and incongruent blocks separately are highly correlated (rho = 0.739, p < .001), suggesting that this choice of dependent variable is not the sole driver of the individual differences results we observed. Higher RT cost is considered to reflect poorer performance, given that it indicates more slowing to incongruent trials relative to the participant’s average RT to congruent trials.

5.3. Imaging parameters

Data were collected at the Center for Cognitive and Behavioral Brain Imaging at The Ohio State University on a 3T Siemens MAGNETOM TrioTim system using a 12-channel head coil. Participants completed the 22-minute Stroop task in a single run during which 658 volumes were acquired using an echo-planar imaging (EPI) sequence which had the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 28 ms, flip angle = 73°, field of view: 220 mm × 220 mm, acquisition matrix = 64 × 64, 34 axial slices, slice thickness = 3.4 mm (voxel size = 3.4 × 3.4 × 3.4 mm), GRAPPA acceleration factor = 2. MPRAGE images had the following parameters: TR = 1900 ms, TE = 4.68 ms, flip angle = 9°, field of view: 256 mm × 256 mm, acquisition matrix = 256 × 256, slice thickness = 1.00 mm (voxel size = 1.0 mm²), 160 sagittal slices.

5.4. Motion controls

Older adults exhibit greater head motion than young adults on average during both task-based and resting-state scans, raising concerns about how to adequately control for these differences in studies of age-related differences (Cao et al., 2014; D’Esposito et al., 1999; Geerligs et al., 2015a; Geerligs et al., 2015b; Geerligs et al., 2017; Van Dijk, Sabuncu and Buckner, 2012). In our study, we also found evidence for greater mean framewise displacement (FD) in older adults (M = 0.207 mm, SD = 0.071) than young adults (M = 0.144 mm, SD = 0.049; U = 226.00, p = .004). Although differences in head motion can introduce confounds in studies of functional connectivity, there is increasing evidence that in-scanner motion reflects neurobiological, or trait-level characteristics that may also be related to true differences in functional connectivity and cognition (Wylie et al., 2014; Zeng et al., 2014). Therefore, attempts to remove motion artifacts, particularly at the group level, may obscure real and meaningful effects of age, cognitive ability, and behavior on functional connectivity along with artificial ones (Geerligs et al., 2017; Wylie et al., 2014).

Another factor of concern is that age-related changes in vascular health contribute to brain-wide differences in mean functional connectivity. In light of these issues, we followed the recommendations of Geerligs et al. (2017) set forth specifically for studies examining individual differences in functional connectivity including healthy older adults. These included regression of motion parameters at the participant level; regression of cerebrospinal fluid (CSF) and white matter (WM) signal and low-pass filtering, found to reduce the effects of age-differences in motion and vascular health; high-pass filtering and pre-whitening; use of a larger smoothing kernel found to minimize the effects of age-related differences in the location of functional regions; and Pearson correlation to compute functional connectivity estimates. These steps are described in more detail in the Image Preprocessing section. Five participants (two older adults and three young adults) were excluded for excessive head motion, defined as mean absolute displacement > 1.5 mm (Jenkinson et al., 2002) and mean FD > 0.2 mm (Power et al., 2012). Additionally, we corrected for head motion through nuisance regression as described below.

5.5. Image preprocessing

Data were preprocessed using FMRIB’s software library (FSL; Smith et al., 2004). Images were motion corrected using FMRIB’s Linear Image Registration Tool (MCFLIRT; Jenkinson et al., 2002), as well as slice time corrected, brain extracted (BET; Smith, 2002), spatially smoothed with a 6-mm kernel, and pre-whitened. Data were also band-pass filtered (frequency = 0.01–0.1 Hz) to remove the effects of high- and low-frequency noise. Of note, low-pass filtering in the current study was included to align the preprocessing steps with the original study in which saCPM was derived (Rosenberg et al., 2016a) as well as to mirror other studies examining the generalizability of these connectome models (Jangraw et al., 2018). Additionally, low-pass filtering was included in order to mitigate the impact of physiological noise. It is important to note that low-pass filtering of task-based data may potentially reduce the degree to which task-evoked signals drive functional connectivity patterns.

Each individual’s 4D data was then registered to the corresponding high resolution MPRAcE. Images were segmented into WM, CSF, and grey matter using FMRIB’s Automated Segmentation Tool (FAST; Zhang et al., 2001). Nuisance regressors included mean signal from CSF and WM, a 24-parameter motion model (six motion parameters, six temporal derivatives, and their squares), and global signal, which has been found to reduce the effects of both physiological signals and head motion in functional connectivity data (Ciric et al., 2017; Parkes et al., 2018; Power et al., 2014; Power et al., 2017; Power et al., 2015; Weissenbacher et al., 2009). Following the recommendation of Power et al. (2012), volumes with mean FD over 0.5 mm were added as confounds in the regression model.

5.6. Whole-brain functional connectivity

We warped a whole-brain functional atlas, the 268-node Shen functional atlas (Shen et al., 2013) that includes cortical, subcortical, and cerebellar regions (i.e., nodes), from MNI space to each participant’s functional space. Given that functional scans did not include full cerebellum coverage, nodes were excluded from further analysis if they were missing in more than 3 participants. Nodes were considered missing if less than 50% of their original volume was retained after masking. This resulted in 32 excluded nodes, primarily from the brainstem and cerebellum bilaterally. Whole-brain functional connectivity was computed using the Graph Theory GLM toolbox (GT; Spielberg et al., 2015).
Activity in each node was calculated by averaging the time courses of all voxels within the node for the full duration of the Stroop task. Functional connectivity between nodes (i.e., edges) was calculated as the mean Pearson correlation coefficients ($r$) between the time courses of each node pair. Each coefficient was then normalized using Fisher’s r-to-z transformation and the resulting $236 \times 236$ fully connected matrices were used in all analyses.

As in previous work examining the predictive power of connectome-based models (Jangraw et al., 2018; Rosenberg et al., 2016a; Rosenberg et al., 2016b), functional connectivity patterns were calculated using data from the full task run, rather than from individual blocks or block contrasts, for several reasons. First, collapsing across the full task facilitates the translation of the saCPM model across various contexts of interest (i.e., across tasks and at rest). Second, this method maximizes the amount of data used in the analysis, increasing the reliability of functional connectivity estimates (Birn et al., 2015; Noble et al., 2017). Finally, there is evidence that extended task paradigms are useful in investigations of individual differences as they modulate functional connectivity in systematic, task-related ways while also preserving individual differences in connectivity throughout (Shah et al., 2016). Performing demanding attentional tasks engages attention-related brain circuitry, potentially magnifying behaviorally relevant individual differences in functional connectivity from which we can extract patterns that are useful for prediction of performance (Finn et al., 2017).

5.7. Sustained attention CPM networks

Previous work identified two large-scale functional networks, comprising the saCPM, whose strength during performance of a sustained attention task was related to individual differences in sustained attention: a high-attention network (757 edges) that was predictive of better attentional abilities, and a low-attention network (630 edges) that was predictive of poorer attention (Rosenberg et al., 2016a). A model based on strength in these networks, the sustained attention connectome-based predictive model (saCPM), has generalized to predict individual differences in attention in several independent datasets including children, adolescents, and young adults (Rosenberg et al., 2017). However, its predictive power in older-adult samples is unknown.

To test the generalizability of the saCPM to this dataset, we calculated high-attention and low-attention network strength for each participant using custom Matlab scripts (The MathWorks, Inc.; version r2017b). First, the high- and low-attention network masks ($268 \times 268$ symmetrical, binary matrices including 1s for edges that belong in the network and 0s elsewhere) were modified by removing vectors corresponding to excluded nodes. Then, for each of the 34 participants and each network, connectivity strength was computed by averaging all edge values in the respective mask. Given that our dataset contained missing nodes due to limitations in brain coverage, we chose to compute mean edge strength as it is less sensitive to missing edge values than summing. However, the two metrics were highly correlated (High: $\rho = 1.00$, $p < .001$; Low: $\rho = 0.998$, $p < .001$).

5.8. Prediction of behavioral performance

5.8.1. Effects of head motion

All subsequent analyses were performed using SPSS version 24.0 (IBM Corp., 2016) and the PROCESS macro (Hayes, 2012). Given that motion can introduce significant confounds in studies of functional connectivity, we evaluated the extent to which head motion was related to individual differences of interest. After excluding participants with excessive head motion and correcting for head motion during preprocessing through regression of motion parameters and confound regression of volumes with high motion (see Image Preprocessing section), we assessed whether estimates of head motion (mean FD) were correlated with RT cost, high-attention network strength, and low-attention network strength in our dataset. We found that motion was not related to RT cost in either age group (OA: $\rho = 0.176$, $p = .484$; YA: $\rho = 0.235$, $p = .380$). Motion was also not related to high-attention network strength in either age group (Old: $\rho = -0.131$, $p = .604$; Young: $\rho = 0.256$, $p = .339$) or low-attention network strength in young adults ($\rho = 0.288$, $p = .279$). However, higher motion was associated with greater connectivity of the low-attention network in older adults ($\rho = 0.583$, $p = .011$). Therefore, for analyses involving connectivity strength within the low-attention network or subnetworks, we conducted additional analyses with mean FD as a covariate. None of the reported results changed as a result of covarying mean FD (see Results section).

5.8.2. Age-related differences

We checked each variable of interest for normality using the Shapiro-Wilk test of normality (Shapiro and Wilk, 1965), of which mean FD, connectivity strength of one of the age difference subnetworks (OA Low2), high-attention network connectivity strength, and predicted performance values from the high-attention network were not normally distributed. Age-related differences in RT cost were assessed using an independent samples t-test. A generalized estimating equation (GEE) approach, an extension of the GLM that allows for correlation among dependent variables and that does not assume homoscedasticity, was used to investigate group differences in high- and low-attention network strength. Bonferroni corrected significance values were used for all GEE analyses to correct for multiple comparisons.

5.8.3. Connectome-based predictions

To generate a predicted measure of attention for each participant, network strength values for the high-attention network and low-attention network were entered into general linear models, the coefficients of which were derived in the initial saCPM validation (Rosenberg et al., 2016a). These models generated estimates of predicted performance on the gradCPT (sensitivity or $d’$), a test of sustained attention and inhibitory control (Esterman et al., 2013). Models included the high- and low-attention network models with one predictor each to index high- or low-attention network strength, as well as a full model with one predictor indexing the difference in low-attention and high-attention network strength. The predictive ability of the saCPM was assessed using two-tailed Spearman rank correlation ($r_s$) between observed RT cost and predicted $d’$. These results are presented as the percent variance explained ($\rho^2$), calculated as $100 \times$ the correlation coefficient squared. Age-group differences in predictive power were assessed using two-tailed Fisher’s z tests, which compares the independent correlation coefficients. Given that multiple variables of interest were not normally distributed, we chose to use Spearman rank correlation for all correlational analyses to improve consistency and to allow us to more easily compare correlations. Because individuals with better attention and inhibitory control abilities should perform better on the Stroop task, we expect saCPM predictions to be inversely correlated with RT cost. In other words, individuals who would hypothetically perform better on the gradCPT should show less slowing on incongruent relative to congruent Stroop trials.

5.9. Mediation models

Given that the primary aim of the study was to assess the generalizability of the saCPM to older adults, we next examined whether connectivity strength in the high- and low-attention networks mediated age-related differences in Stroop performance. For this analysis, we constructed mediation models to assess the indirect effect of age-group (X) on RT cost (Y) through network strength (M). For multiple mediation models, the total indirect effect is the sum of all specific indirect effects, an index of the effect of X on Y through all mediating mechanisms. The direct effect (c’) is the estimated mean difference in Y between two cases.
that differ by one unit on X but who are equal on the mediator. The total effect (c) is the sum of the direct and indirect effects, providing an estimate of the effect of X alone on Y. We employed bias-corrected bootstrapping (5000 samples) that does not assume a normally distributed indirect effect (Preacher and Hayes, 2004). Point estimates are standardized coefficients and were considered significant if the 95% confidence interval did not contain zero.

5.10. Age-difference subnetworks

The saCPM networks, which were derived from whole-brain functional connectivity data, contain edges spanning the cortex, subcortex, and cerebellum. To identify age-related differences in functional connectivity within these networks, we employed the Network Based Statistics (NBS) method using the NBS Toolbox (NBS; Zalesky et al., 2010). Using this approach, we searched for group differences amongst the widely distributed edges of the high-attention and low-attention networks to discover age-difference subnetworks. NBS conducts independent, one-tailed t-tests at every edge to identify edges whose strength is significantly different between groups at a threshold of $t = 3.1$. Next, NBS controls for multiple comparisons by considering the brain as a graph and searching for connectivity amongst suprathreshold edges that are connected to each other (i.e., fully connected graph components) and comparing the size of these age-difference subnetworks to the size of 5000 random network permutations. Age-difference subnetworks larger than 95% of null difference networks are considered significantly different between groups, and $p$-values were computed as $(1 + \text{the number of random networks with fully connected components})/5001$.

We ran four NBS models by specifying contrasts to test age-related differences between older adults (OA) and younger adults (YA; OA > YA and YA > OA) separately for the high-attention and low-attention networks. Connectivity strength within identified age-difference subnetworks was calculated as the mean connectivity across all edges of the component. Spearman rank correlation was used to assess the relation between subnetwork strength and RT cost. Mediation models were constructed as outlined above to examine whether the strengths of age-difference subnetworks mediate the effect of age on Stroop performance.

6. Results

6.1. Behavioral performance

Descriptive statistics for all variables are presented in Table 1. The dependent variable of interest was reaction time cost (RT cost), calculated as the difference in RT for incongruent and congruent trials of the mostly congruent task blocks. This metric assesses the interference experienced by participants when presented with infrequent incongruent stimuli in the context of frequent congruent stimuli, and RT cost reflects the degree of slowing in response to incongruent stimuli relative to that participant’s baseline RT (i.e., average RT to non-conflict trials). Higher cost is considered to be reflective of poorer inhibitory control as a greater latency presumably represents greater difficulty resolving interference. As expected, older adults exhibited higher RT cost ($M = 252.41$ ms, $SD = 108.12$ ms) than young adults ($M = 157.90$ ms, $SD = 71.74$ ms; $t(32) = -2.962$, $p = .006$).

6.2. CPM-based predictions

We examined the generalizability of the saCPM, previously identified in Rosenberg et al. (2016a), to a novel context: groups of younger and older adults who completed a Stroop inhibitory control task. To do so, the high-attention and low-attention saCPM networks were assessed for the ability to predict observed RT cost in previously unseen individuals.

6.2.1. Network application

We applied network masks for the high-attention and low-attention networks to individual functional connectivity matrices and computed individuals’ network strength values. Across age groups, connectivity within the low-attention network was significantly stronger, when compared with the high-attention network (Wald $\chi^2 = 7.679$, $p = .006$, 95% CI = 0.007, 0.042). Older and younger adults did not differ in overall connectivity strength (Wald $\chi^2 = 0.604$, $p = .437$, 95% CI = –0.006, 0.014), but there was a significant age-group X network-type interaction (Wald $\chi^2 = 3.860$, $p = .049$, 95% CI = 0.818$ to $0.069$) such that older adults exhibited greater connectivity within the low-attention network than young adults (Wald $\chi^2 = 4.332$, $p = .037$, 95% CI = 0.001, 0.041).

![Fig. 1. saCPM-Based Predictions of Stroop Performance. Predicted performance on the x-axis represents participants’ expected performance on the gradCPT, indexed as $d'$. Observed performance on the y-axis represents participants’ observed performance on the Stroop task (RT cost in ms, transformed by multiplying by -1 so that a negative association represents a relation to poorer performance). All values were standardized to z-scores for visualization purposes. We observed that the saCPM networks successfully predicted RT cost in the full sample, demonstrated by the positive relation between predicted and observed performance based on (A) the GLM indexing the difference in low-attention and high-attention network strength (B) the high-attention network, and (C) the low-attention network. All correlations are Spearman rank correlations. The percent variance explained ($r^2$) is presented for each. **$p \leq .01$, ***$p \leq .001$.](image-url)
worse attentional performance. In Fig. 1, RT cost scores have been on the gradCPT (measured as higher predicted scores correspond to better hypothetical performance. between predicted and observed performance were expected given that the magnitude of these associations did not differ by age-group (OA: \[ r^2 = 0.354, p < .001 \]; low-attention model with mean FD covaried: \[ r^2 = 22.5\%, p = .005 \]), as did a GLM with one predictor indexing the difference in low-attention and high-attention network strength (\[ r^2 = 38.4\%, p < .001 \]; with mean FD covaried: \[ r^2 = 26.9\%, p = .002 \]), suggesting that prediction was successful when applied to a Stroop inhibitory control task.

When predictive power was examined within each age group separately, predictions of the high-attention network model were not significantly related to RT cost in either group (OA: \[ r^2 = 2.89\% \], \[ p = .499 \]; YA: \[ r^2 = 16.5\%, p = .119 \]) and did not differ by age-group (\[ Z = 0.68, p = .497 \]; Fig. 1a). Predictions of the low-attention network model reached significance for older adults (\[ r^2 = 34.7\%, p = .010 \]; with mean FD covaried: \[ r^2 = 37.0\%, p = .010 \]), but not young adults (\[ r^2 = 6.4\%, p = .345 \]; with mean FD covaried: \[ r^2 = 4.0\%, p = .477 \]), however, the magnitude of these associations did not differ by age-group (\[ Z = -1.1, p = .271 \]; Fig. 1b). The full GLM model successfully predicted performance for older adults (\[ r^2 = 24.8\%, p = .035 \]; with mean FD covaried: \[ r^2 = 22.8\%, p = .053 \]) but not young adults (\[ r^2 = 18.7\%, p = .094 \]; with mean FD covaried: \[ r^2 = 15.3\%, p = .149 \]), but again the magnitude of these associations did not differ by age-group (\[ Z = -0.22, p = .826 \]; Fig. 1c). These negative correlations between predicted and observed performance were expected given that higher predicted scores correspond to better hypothetical performance on the gradCPT (measured as \( d' \)), whereas higher RT cost corresponds to worse attentional performance. In Fig. 1, RT cost scores have been transformed to display the positive predictive ability of these models. These results suggest that the saCPM accounts for a considerable amount of variance in Stroop performance across age groups, with successful prediction from only the low-attention network when the groups were examined separately. These findings suggest that this underlying sustained attention factor represented in the brain’s functional connections is robust to both task and age contexts.

6.2.3. Accounting for age-related differences

Given that connectivity in the low-attention network was the more consistent predictor of behavioral performance, we examined whether its connectivity strength mediated the effect of age-group on performance (Table 2). There was no significant indirect effect of age-group on RT cost through low-attention network strength (point estimate = \(-0.338, 95\% \text{ CI} = -0.765, 0.004 \)). This result remained when mean FD was entered into the model as a covariate (point estimate = \(-0.160, 95\% \text{ CI} = -0.578, 0.177 \)). Thus, although the saCPM can successfully predict performance across age groups, it may not be sensitive to age-related differences in performance.

6.3. Age-difference subnetworks

Given that connectivity of saCPM networks did not account for age-related differences in Stroop performance, we employed a data-driven approach to identify age-related difference subnetworks within the saCPM networks that may potentially explain these observed differences. We identified connected edges within the high-attention and low-attention networks that differed significantly between age-groups using NBS (Zalesky et al., 2010).

6.3.1. Subnetwork anatomy

Details regarding the specific nodes and edges belonging to the age-difference subnetworks, as well as their locations and anatomical labels, can be found in Table 3. For the high-attention network (whose strength predicts better attention), no age-difference subnetworks were identified. For the low-attention network (whose strength predicts worse attention), there were no subnetworks identified in which younger adults exhibited greater connectivity than older adults. However, older adults exhibited greater connectivity than young adults in two subnetworks, which were larger than subnetworks found in 99.02–99.92% of randomizations (associated \( p \)-values: OA Low1 \( p = .01 \); OA Low2 \( p < .001 \)). The first subnetwork consisted of three edges between four nodes of the FPN and motor networks (’OA Low1’; Fig. 2a). The second subnetwork consisted of seven edges between eight nodes of the FPN, DMN, medial frontal (MF), and motor networks (’OA Low2’; Fig. 2b).

6.3.2. Accounting for age-related differences

Connectivity strengths within these age-difference subnetworks were tested as simultaneous mediators of the effect of age-group on performance in a parallel multiple mediation model (Fig. 3, Table 4). Connectivity within the OA Low1 subnetwork (point estimate = \(-0.580, 95\% \text{ CI} = -1.097, -0.102 \)) and the OA Low2 subnetwork (point

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Simple mediation model for the relationship between age-group (X) and RT cost (Y) through low-attention network strength.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediator (M)</td>
<td>X on M (a)</td>
</tr>
<tr>
<td>Low-Attention</td>
<td>-0.666</td>
</tr>
</tbody>
</table>

Note: Effects are standardized coefficients. \( ^* p < .05, ^* * p < .01, ^* * * p < .001 \).

6.2.2. Behavioral prediction

We next evaluated the correlation between observed and predicted performance to assess the predictive power of the saCPM. Given that our aims were to test the generalizability of these markers to a novel task context as well as to older adults, correlations were assessed first in the full sample and then within the individual age groups.

In the full sample, both networks successfully predicted observed RT cost (high-attention model: \( r^2 = 16.6\%, p = .016 \); low-attention model: \( r^2 = 35.4\%, p < .001 \); low-attention model with mean FD covaried: \( r^2 = 22.5\%, p = .005 \)), as did a GLM with one predictor indexing the difference in low-attention and high-attention network strength (\( r^2 = 38.4\%, p < .001 \); with mean FD covaried: \( r^2 = 26.9\%, p = .002 \)), suggesting that prediction was successful when applied to a Stroop inhibitory control task.

We identified connected edges within the high-attention and low-attention networks that differed significantly between age-groups using NBS (Zalesky et al., 2010).

Table 3

<table>
<thead>
<tr>
<th>Age-Difference Subnetwork</th>
<th>Node#</th>
<th>Anatomical Label</th>
<th>Network</th>
<th>Edges in Subnetwork</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Low1</td>
<td>10</td>
<td>Right superior frontal gyrus</td>
<td>FPN</td>
<td>10 (FPN)–46 (Motor)</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>Right parietal operculum</td>
<td>Motor</td>
<td>10 (FPN)–61 (Motor)</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>Right superior temporal gyrus</td>
<td>Motor</td>
<td>46 (Motor)–193 (FPN)</td>
</tr>
<tr>
<td></td>
<td>193</td>
<td>Left middle temporal gyrus</td>
<td>FPN</td>
<td></td>
</tr>
<tr>
<td>OA Low2</td>
<td>21</td>
<td>Right inferior temporal gyrus</td>
<td>FPN</td>
<td>21 (FPN)–138 (DMN)</td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>Left medial frontal cortex</td>
<td>DMN</td>
<td>21 (FPN)–141 (DMN)</td>
</tr>
<tr>
<td></td>
<td>141</td>
<td>Left frontal pole</td>
<td>DMN</td>
<td>181 (Motor)–182 (FPN)</td>
</tr>
<tr>
<td></td>
<td>168</td>
<td>Left insular cortex</td>
<td>Motor</td>
<td>21 (FPN)–183 (MF)</td>
</tr>
<tr>
<td></td>
<td>181</td>
<td>Left somatosensory cortex</td>
<td>Motor</td>
<td>168 (Motor)–183 (MF)</td>
</tr>
<tr>
<td></td>
<td>182</td>
<td>Left angular gyrus</td>
<td>FPN</td>
<td>181 (Motor)–183 (MF)</td>
</tr>
<tr>
<td></td>
<td>183</td>
<td>Left temporoparietal junction</td>
<td>MF</td>
<td>21 (FPN)–225 (DMN)</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>Left precuneus</td>
<td>DMN</td>
<td></td>
</tr>
</tbody>
</table>

Note: DMN = default-mode network; FPN = frontoparietal network; MF = medial frontal network.

estimate = $-0.658$, 95% CI = $-1.297, -0.054$) were significant mediators, such that older adults had greater subnetwork connectivity which was related to poorer performance. There was also a significant total indirect effect, or combined effect of all mediators (point estimate = $-1.238$, 95% CI = $-1.935, -0.513$). These results remained when mean FD was entered into the model as a covariate (OA Low1 point estimate = $-0.542$, 95% CI = $-1.094, -0.078$; OA Low2 point estimate = $-0.717$, 95% CI = $-1.396, -0.100$; Total Indirect Effect point estimate = $-1.259$, 95% CI = $-2.063, -0.471$). These findings suggest that older and younger adults exhibit significant group-based differences in connectivity within components of the low-attention network, and that age-related differences in Stroop performance may be accounted for by a limited number of specific connections within the more widely distributed saCPM.

7. Discussion

The ability to sustain attention critically supports many higher-order
To predict sustained attention would also predict inhibitory control of attentional control, we hypothesized that functional networks derived based on features. Unique networks have been derived to successfully predict sustained attention in both laboratory-based and real-world tasks of higher-order processes of goal maintenance and inhibition. These methods have also been applied to clinical contexts, providing support for the generalizability of the saCPM to a higher-order task of attentional control. Successful application of the saCPM across multiple task states, and to resting-state data in this and previous studies, provides support for the idea that there is some consistent signal in the brain allowing for individual-level prediction. This is corroborated by evidence that individual differences in connectivity are maintained across task contexts and between rest and task states, even when differences in group-mean connectivity are observed (Shah et al., 2016). These effects may be subserved by “intrinsic” patterns of functional connectivity that are largely preserved from rest to task as well as task-general network changes that are consistent across many task states (Cole et al., 2014; Krienen et al., 2014). However, it is important to acknowledge that there is systematic reorganization of functional connectivity in response to task demands. Because higher-order cognition requires coordinated and dynamic interactions among multiple brain regions, task execution produces system-level changes to functional connectivity (see Gonzalez-Castillo and Bandettini, 2018 for review). Such task-evoked alterations in regional brain activation manifest as altered functional connections. When measured using correlation, as in the present study, connectivity estimates capture the correspondence between regional activity throughout the task. These estimates thus contain some information relevant to task-evoked patterns in addition to “intrinsic” connectivity. As such, functional connectivity estimates in this study should be interpreted as representing both intrinsic patterns and modulations that are tied to exogenous demands. Importantly, task-evoked functional connectivity contains useful information, as shifts in functional connectivity from rest to task have been found to be associated with behavioral outcomes on multiple tasks of attentional control (Braun et al., 2015; Spadone et al., 2015).

Together, our results suggest that functional connectivity within the saCPM can be used to predict performance on a novel Stroop task. In conjunction with previous external validation studies, these findings contribute to the proposal that the saCPM captures patterns of connectivity in the brain that represent an individual’s ability to engage attentional processes more generally and at various levels of complexity (Rosenberg et al., 2017). Future work is needed to further establish whether this model indexes sustained attention and attentional control specifically or a general attention factor more broadly.

### 7.1. Generalizability of prediction to a novel task

There is growing support for the utility of CPM, and similar data-driven predictive modeling approaches, for elucidating brain-based signatures of nuanced cognitive constructs. Based on the recognition that there are individual differences in functional connectivity patterns that are reliable across time and task context, these methods have been increasingly applied to predict behavior from functional connectome-based features. Unique networks have been derived to successfully predict a range of traits, including fluid intelligence (Finn et al., 2015), creativity (Beatty et al., 2018), neuroticism, and extraversion (Hsu et al., 2018). These methods have also been applied to clinical contexts, including for the prediction of cognitive impairment in a sample of healthy controls and individuals with mild cognitive impairment or Alzheimer’s disease (Lin et al., 2018). The saCPM, which was initially derived to predict sustained attention abilities (Rosenberg et al., 2016a), has generalized to predict ADHD symptom severity in children (Rosenberg et al., 2016a), recall in a reading task (Jangraw et al., 2019), accuracy on a stop signal task (Rosenberg et al., 2016b) as well as accuracy, reaction time variability, and executive control scores on the Attention- Network Task (Rosenberg et al., 2018).

Given this evidence of generalizability of the saCPM to various tasks of attentional control, we hypothesized that functional networks derived to predict sustained attention would also predict inhibitory control during a Stroop task. Performance during the Stroop task requires both active maintenance of a goal set (i.e., to report the color of the presented stimuli) and inhibition of an automatic response (i.e., word reading). More successful task execution minimizes the difference in response time to incongruent compared with congruent trials, and this measure of RT cost served as the dependent variable of interest in this study. These higher-order processes of goal maintenance and inhibition require continuous monitoring of the presented stimuli and the internal goal set, and this shared reliance on sustained attention provided the basis for our hypothesis. In line with this expectation, we observed that both high- and low-attention saCPM networks predicted RT cost in the full sample, providing support for the generalizability of the saCPM to a higher-order task of attentional control.

Table 4

<table>
<thead>
<tr>
<th>Mediators (M)</th>
<th>X on M (a)</th>
<th>M on Y (b)</th>
<th>Indirect Effect</th>
<th>95% CI (ab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Low1</td>
<td>−1.274***</td>
<td>0.456*</td>
<td>−0.580</td>
<td>[−1.097, −0.102]*</td>
</tr>
<tr>
<td>OA Low2</td>
<td>−1.476***</td>
<td>0.446*</td>
<td>−0.658</td>
<td>[−1.279, −0.054]*</td>
</tr>
</tbody>
</table>

**Note.** Effects are standardized coefficients. *p ≤ .05, **p ≤ .01, ***p ≤ .001.

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Successful application of the saCPM across multiple task states, and to resting-state data in this and previous studies, provides support for the idea that there is some consistent signal in the brain allowing for individual-level prediction. This is corroborated by evidence that individual differences in connectivity are maintained across task contexts and between rest and task states, even when differences in group-mean connectivity are observed (Shah et al., 2016). These effects may be subserved by “intrinsic” patterns of functional connectivity that are largely preserved from rest to task as well as task-general network changes that are consistent across many task states (Cole et al., 2014; Krienen et al., 2014). However, it is important to acknowledge that there is systematic reorganization of functional connectivity in response to task demands. Because higher-order cognition requires coordinated and dynamic interactions among multiple brain regions, task execution produces system-level changes to functional connectivity (see Gonzalez-Castillo and Bandettini, 2018 for review). Such task-evoked alterations in regional brain activation manifest as altered functional connections. When measured using correlation, as in the present study, connectivity estimates capture the correspondence between regional activity throughout the task. These estimates thus contain some information relevant to task-evoked patterns in addition to “intrinsic” connectivity. As such, functional connectivity estimates in this study should be interpreted as representing both intrinsic patterns and modulations that are tied to exogenous demands. Importantly, task-evoked functional connectivity contains useful information, as shifts in functional connectivity from rest to task have been found to be associated with behavioral outcomes on multiple tasks of attentional control (Braun et al., 2015; Spadone et al., 2015).

Together, our results suggest that functional connectivity within the saCPM can be used to predict performance on a novel Stroop task. In conjunction with previous external validation studies, these findings contribute to the proposal that the saCPM captures patterns of connectivity in the brain that represent an individual’s ability to engage attentional processes more generally and at various levels of complexity (Rosenberg et al., 2017). Future work is needed to further establish whether this model indexes sustained attention and attentional control specifically or a general attention factor more broadly.

### 7.2. Generalizability of prediction to an aging sample

Critically, these findings also provide novel evidence of generalizability of this marker to an aging sample, as strength in the high-attention network, low-attention network, and full model all successfully predicted observed RT cost. An expansive literature has documented age-related shifts in patterns of neural activity and connectivity, including increased frontal and reduced posterior activity, reduced connectivity within large-scale functional networks, and reduced functional segregation between networks (Ferreira and Busatto, 2013; Ferreira et al., 2016; Gerrigys et al., 2015a). Despite these well-documented changes that accompany age, we found that the saCPM, which was derived from functional connectivity data in a group of young adults, was able to successfully predict performance in a sample of older adults. This is in line with previous evidence that these networks also generalize to...
samples of children and adolescents (Rosenberg et al., 2016a) and middle-aged adults (Jangraw et al., 2018). Thus, the present study contributes to accumulating evidence supporting the status of the saCPM as a neural biomarker that is robust across the developmental spectrum.

When predictions were examined in each age group separately, predictions based on the high-attention network were no longer significant in either group. However, the low-attention network appeared to remain the primary driver of prediction. Although the lack of successful prediction by the high-attention network is likely driven in part by a small sample size used in the current study, this finding may suggest that the low-attention network might be more robust to task context. That is, connectivity patterns related to poorer performance may be more similar across task contexts, possibly representing fluctuating attention or mind-wandering, whereas connectivity implicated in better performance might be expected to vary more considerably with varying task requirements. However, this finding is tentative and would require replication prior to drawing strong conclusions about the relative generalizability of the high- and low-attention networks.

### 7.3. Accounting for age-related differences in performance

Consistent with previous studies, we found that older adults exhibited poorer performance on the Stroop task than young adults (Jackson and Balota, 2013; Mutter et al., 2005; Spieler et al., 1996; West and Alain, 2000; Wolf et al., 2014). Additionally, older adults exhibited greater connectivity within the low-attention network, a network that was initially derived based upon its negative association with sustained attention performance (Rosenberg et al., 2016a). As such, we were interested in whether the low-attention network of the saCPM, when applied to this task-based functional connectivity data, might contain information that could help account for these age-related differences in performance. Despite age-related differences in both connectivity and performance, connectivity within the low-attention network did not mediate the effect of age-group on RT cost. Thus, the saCPM demonstrates successful prediction across age groups, but this model may not be sensitive to age-related differences in connectivity related to attentional control. Although it is possible that a model derived from a sample including older adults would be better able to account for age-related differences than this original saCPM, there is also some evidence that predicted scores are not related to age (Rosenberg et al., 2016a). Thus, this remains an empirical question to be explored in future studies.

Based on the saCPM’s inability to explain age-related differences in performance, we hypothesized that subnetworks of the saCPM that significantly differed in connectivity strength between groups may better account for observed age-related differences in inhibitory control. To identify these subnetworks, we conducted exploratory analyses using the Network-Based Statistics method (NBS; Zalesky et al., 2010), which yielded two discrete age-difference subnetworks. We found that connectivity strengths within two age-difference subnetworks were related to performance in expected ways. Connectivity strengths in both subnetworks of the low-attention saCPM in which older adults exhibited greater connectivity were associated with poorer performance, or greater RT cost. These subnetworks were composed of inter-network edges between the FPN and motor network (“OA Low1”) and between the MF, FPN, DMN, and motor networks (“OA Low2”). The composition of these age-difference subnetworks is consistent with a dedifferentiation model of neurocognitive aging, as both subnetworks involve greater connectivity between bilateral nodes from two different networks in older compared to younger adults, but is not supportive of a compensatory role of these age-related shifts, as increased connectivity between these nodes was related to poorer, rather than preserved, performance. Instead, these results fit with existing evidence of decreased network segregation, harkening back to the strong evidence of reduced differentiation between the FPN and DMN in particular, which is related to poorer attentional control performance in older adults (Andrews-Hanna et al., 2007; Avelar-Pereira et al., 2017; Damoiseaux et al., 2008; Geerligs et al., 2015a; Geerligs et al., 2014; Grady et al., 2016; Onoda et al., 2012).

Both age-difference subnetworks of the low-attention saCPM significantly mediated the relation between age-group and Stroop RT cost. These subnetworks both contained edges connecting nodes in the FPN and motor networks. It is notable that FPN nodes emerged from a data-driven, whole-brain analytic approach. Although many previous functional connectivity studies have selected the FPN a priori, several recent studies that also employed whole-brain, data-driven approaches provide corroborating evidence that this network exhibits important shifts in connectivity with age (Chan et al., 2014; Geerligs et al., 2015a; Tomasi and Volkow, 2012). In addition, our finding that age-related increases in connectivity between FPN and motor nodes partially explain age-related decrements in performance is supported by previous observations of increased connectivity between nodes of these networks with age when measured at rest (Roski et al., 2013) and during tasks of selective attention (Geerligs et al., 2014). Interestingly, increased resting-state connectivity between these networks has been observed early in the developmental trajectory, during the transition between young and middle adulthood (Siman-Tov et al., 2017), potentially representing initial stages of neurocognitive aging. These preliminary results warrant future study to determine their robustness and replicability. However, they also demonstrate one of the primary benefits of data-driven, whole-brain analysis approaches—the elucidation of connectivity features that are important for explaining behavior, such as interactions between FPN and motor nodes, that have traditionally been somewhat neglected.

### 7.4. Limitations and conclusions

The results of this study should be considered in light of several limitations. First, replication of these findings in a larger sample is warranted to support their reliability and potential generalizability to the broader aging population. Accordingly, analyses performed separately within young and older adults were likely limited in power by smaller sample sizes. Similarly, non-significant effects in complex models, such as mediations, may underestimate the true effect. Second, findings from connectivity analyses were limited by the fact that 32 nodes were missing, primarily from the brainstem and cerebellum, due to incomplete brain coverage during image acquisition. Although previously associated with sensorimotor function only, the cerebellum is increasingly recognized as a critical player in the modulation of attention (Buckner, 2013; Kellermann et al., 2012; Strick et al., 2009). Further, connectivity involving cortico-cerebellar networks has been found to be disrupted with age and implicated in cognitive function (Bernard et al., 2013). Therefore, replication of these results using images acquired with full brain coverage is needed for a full inquiry into generalizability to the aging context. Finally, given the cross-sectional design of the current study, causal inferences cannot be drawn with regards to the links between connectivity and performance or the mediating effects of connectivity between age-group and performance. Longitudinal assessment of age-related alterations in the saCPM and corresponding changes in attentional performance is required to establish these networks as true mechanisms of cognitive change.

This study provides evidence that the saCPM, comprised of two large-scale functional networks derived to predict sustained attention in young adults, generalizes to predict performance on a task of inhibitory control within an aging sample. These results support the possibility that attention is represented in the brain’s functional architecture and that patterns of functional connectivity exhibit individual variability that can be harnessed to predict individual-level behaviors. The saCPM appears to be a robust neurorouter of attentional ability that can produce useful predictions in older adults despite the presence of age-related changes in behavior and neural functioning. However, the saCPM networks did not appear to be sensitive to age-related differences in performance. Instead, exploratory analyses revealed two subnetworks within the low-attention saCPM, containing nodes from the MF, FPN, DMN and motor networks,
that were more strongly connected in older adults and accounted for age-related differences in inhibitory control. This suggests that there are localized age-differences in particular edges within the connectome, and our results draw attention to some features that have previously been understudied. Thus, data-driven, whole-brain approaches to functional connectivity analysis appear to yield results consistent with well-established patterns of age-related neural change while also providing insights into age-related shifts in neural and behavioral function.

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Declarations of interest

None.

References


West, R., Alain, C., 2000. Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. Psychophysiology 37 (2), 179–189.


