NeuroImage 209 (2020) 116521

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Aging relates to a disproportionately weaker functional architecture of brain networks during rest and task states

Colleen Hughes [a,*], Joshua Faskowitz [a], Brittany S. Cassidy [b], Olaf Sporns [a], Anne C. Krendl [a]

[a] Psychological and Brain Sciences Department, Indiana University, 1101 East 10th Street, Bloomington, IN, 47405, USA
[b] Department of Psychology, The University of North Carolina at Greensboro, 296 Eberhart Building, Greensboro, NC, 27412, USA

ARTICLE INFO

Keywords:
Functional connectivity
Aging
Network neuroscience
Functional magnetic resonance imaging
Resting-state
Default mode network

ABSTRACT

Functional connectivity – the co-activation of brain regions – forms the basis of the brain's functional architecture. Often measured during resting-state (i.e., in a task-free setting), patterns of functional connectivity within and between brain networks change with age. These patterns are of interest to aging researchers because age differences in resting-state connectivity relate to older adults' relative cognitive declines. Less is known about age differences in large-scale brain networks during directed tasks. Recent work in younger adults has shown that patterns of functional connectivity are highly correlated between rest and task states. Whether this finding extends to older adults remains largely unexplored. To this end, we assessed younger and older adults' functional connectivity across the whole brain using fMRI while participants underwent resting-state or completed directed tasks (e.g., a reasoning judgement task). Resting-state and task functional connectivity were less strongly correlated in older as compared to younger adults. This age-dependent difference could be attributed to significantly lower consistency in network organization between rest and task states among older adults. Older adults had less distinct or segregated networks during resting-state. This more diffuse pattern of organization was exacerbated during directed tasks. Finally, the default mode network, often implicated in neurocognitive aging, contributed strongly to this pattern. These findings establish that age differences in functional connectivity are state-dependent, providing greater insight into the mechanisms by which aging may lead to cognitive declines.

1. Introduction

Functional connectivity – the co-activation of brain regions within brain networks – is a hallmark feature of the functional architecture of the brain (Buckner et al., 2013). A growing body of research has begun to characterize changes in functional connectivity associated with healthy aging (for a review, see Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). These changes are of interest to aging researchers because functional connectivity relates to how the brain gives rise to myriad cognitive functions (Stevens and Spreng, 2014), and may inform how aging negatively impacts older adults' cognition (e.g., Hughes et al., 2019b). Functional connectivity is examined either during resting-state (e.g., task-free setting; Greicius et al., 2003; Raichle, 2011), or when individuals are engaged in directed tasks. Research in younger adults suggests that the underlying functional architecture of brain networks remains relatively consistent between these two types of states (Cole et al., 2014). This relative overlap between states suggests a shared functional architecture underlying and even shaping brain function (Chan et al., 2017; Cole et al., 2016). However, it remains largely unexplored whether the same is true for older adults (but see Geerligs et al., 2015b; Monteiro et al., 2019). This is an important topic because aging may disproportionately affect functional connectivity in one state (e.g., during task), thus disrupting how brain networks interact in a way that is detrimental for cognition. The current study addresses this gap in the literature.

Younger adults' resting-state connectivity patterns are highly correlated with task-evoked connectivity patterns (e.g., Cole et al., 2014; Smith et al., 2009). This finding has been interpreted as evidence for a shared functional architecture present during resting-state and many directed tasks, and minimally modulated in response to task demands (Cole et al., 2014). A potential implication of this overlap is that resting-state connectivity constraints the activation of brain regions in response to task demands (Chan et al., 2017; Cole et al., 2016). Brain organization facilitating precise modulation makes sense from an efficiency perspective. The organization of brain regions into distinct and strongly internally-connected networks increases the amount of

* Corresponding author. Department of Psychological and Brain Sciences, Indiana University, 1101 E. 10th St, Bloomington, IN, 47405, USA.
E-mail address: collhugh@iu.edu (C. Hughes).

https://doi.org/10.1016/j.neuroimage.2020.116521
Received 8 October 2019; Received in revised form 2 January 2020; Accepted 3 January 2020
Available online 8 January 2020
1053-8119/© 2020 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

information that can be communicated within a short window of time (Bullmore and Sporns, 2012). Thus, highly correlated functional connectivity reflects functional architecture underlying rest and task states that may be well-adapted for integrating information in the course of cognition.

Although younger adults' functional connectivity between resting and task states is highly correlated, the relationship between these states may be degraded in older adults. Research using resting-state data have shown age-related declines in functional connectivity within well-characterized brain networks (for a review, see Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). A hallmark of older adults' brain organization is that there is weaker within-network connectivity coupled with stronger between-network connectivity (Spreng and Turner, 2019). These connectivity patterns reflect a weaker network organization (i.e., assignment of brain regions into distinct networks). As a result, networks are less distinct and less well-organized in older adults versus younger adults (Chan et al., 2014; Geerligs et al., 2015a). This "de-differentiation" (Goh, 2011) across neural systems during resting-state has negative implications for older adults. De-differentiation, for example, has been linked to older adults' worse performance than younger adults in several cognitive domains (e.g., memory, Andrews-Hanna et al., 2007; theory of mind, Hughes et al., 2019b). Altered functional connectivity among large-scale brain networks in aging (Spreng and Turner, 2019) may thus be implicated in a variety of cognitive deficits in older adults because the baseline (resting-state) functional architecture of the brain is less efficiently organized to respond differentially to task demands (e.g., Zebrowitz et al., 2016).

Despite well-documented findings at rest, less is known about how, or if, functional connectivity patterns are different between resting-state and directed tasks in older adults (but see Geerligs et al., 2015b; Monteiro et al., 2019). One possibility is that age differences in functional connectivity during resting-state may constrain connectivity during directed tasks. In this case, connectivity between task and rest would still be highly correlated for older adults, but the network organization would be different between older adults and younger adults due to de-differentiation during resting-state. Alternatively, aging may further exacerbate functional connectivity changes during task. This would result in a lower correlation of functional connectivity between rest and task for older adults (versus younger adults), as well as different network organization for older adults than younger adults. The latter possibility may indicate that older adults' age deficits in cognition relative to younger adults are more strongly related to age differences in task-evoked, rather than resting-state, connectivity. This possibility would raise the important conceptual issue of whether rest is truly the ideal condition under which to examine how age differences in brain connectivity relate to behavioral differences.

Participant age might indeed exacerbate individual differences in functional connectivity between rest and task states (Finn et al., 2017; Geerligs et al., 2015b). For example, a recent study examined the overlap between functional connectivity patterns during resting-state and a directed sensorimotor task (responding to bilateral visual and auditory input) in a lifespan sample (ages 18–88; Geerligs et al., 2015b). Functional connectivity was less correlated between resting-state and the sensorimotor task with increasing age. This pattern of results occurred because older participants (vs. younger) had less distinct networks during resting-state – i.e., weaker within-network and stronger between-network connectivity. Critically, this pattern was even more pronounced during task. Similar age differences were obtained using motor tasks (Monteiro et al., 2019) and passive movie-watching (Geerligs et al., 2015b). Moreover, a greater magnitude of difference between rest and task states related to age deficits in task performance (Monteiro et al., 2019). Certain network-level effects were task-specific (Archer et al., 2016; Geerligs et al., 2015b). However, it is unclear what task features may be driving particular network-level effects because few types of task states have been examined. To understand how, if at all, the relationship between resting-state and task-evoked connectivity might contribute to age deficits in cognitive function, it is thus important to examine functional connectivity during tasks that are cognitively demanding.

The current study addresses this gap in the literature by investigating whether age differences are exacerbated when comparing resting-state to a higher-order cognition task – a reasoning judgment (Moran, 2013). We used a reasoning task as the comparison task to rest because the same reasoning task has illustrated age differences in both network and brain function (Hughes et al., 2019b; Moran et al., 2012). Moreover, judgments in the reasoning task mirrored the types of judgments that older adults make in everyday life (e.g., Moran et al., 2012). Higher-order cognition, such as reasoning judgments (McKinnon and Moscovitch, 2007), also elicits more variable neural activity from associative brain regions that facilitate communication across networks (e.g., in contrast to sensorimotor regions; Mueller et al., 2013). The associative nature of these networks is important because their connectivity has been widely related to many of the cognitive functions that decline in older versus younger adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Hampson et al., 2006; Hughes et al., 2019b; Reineberg et al., 2015). We hypothesized that connectivity between rest and task states will be less correlated in older versus younger adults (Hypothesis 1). Furthermore, we predicted this pattern would emerge because functional network organization (i.e., assignment of brain regions into distinct networks) would be less consistent between rest and task states for older versus younger adults (Hypothesis 2).

A final question was whether particular networks would be more susceptible to age differences in functional connectivity between rest and task states. We anticipated that the default mode network (DMN) would demonstrate a disproportionate magnitude of difference in connectivity strength between states in older adults. DMN connectivity is particularly vulnerable to aging; older adults, versus younger adults, exhibit particularly weaker resting-state connectivity within the DMN when older adults are healthy and when older adults exhibit signs of pathological aging (Andrews-Hanna et al., 2007; Betzel et al., 2014; Campbell et al., 2013; Damoiseaux et al., 2008; Geerligs et al., 2015a; Hafkemeijer, van der Grond and Rombouts, 2012). Furthermore, the DMN is often considered a "task-negative" network because it exhibits stronger functional connectivity during rest and appears suppressed during demanding task states (Raichle et al., 2001). These findings support the possibility that DMN connectivity should be stronger during rest and weaker during task states. Age differences also occur in the extent that the DMN is suppressed during task states (Reuter-Lorenz and Cappell, 2008). We predicted that the magnitude of difference in functional connectivity between rest and task states would be greater for particular networks (e.g., the DMN) among older versus younger adults (Hypothesis 3).

2. Material and methods

2.1. Participants

Forty young adults (18–33 years old, $M_{age} = 21.58$, $SD = 2.82$; 25 female; years of education: $M = 15.24$, $SD = 1.88$) and 35 older adults (61–86 years old, $M_{age} = 71.66$, $SD = 6.09$; 22 female; years of education: $M = 16.96$, $SD = 2.19$) who were right-handed, White, not Hispanic, and had no recent history of neurological problems gave informed consent to participate. We recruited younger adults from Indiana University in Bloomington and older adults from the Bloomington, Indiana community via newspaper and electronic advertisements. The study was approved by the Indiana University Institutional Review Board. Older adults and younger adults were normal functioning, as evidenced by a score of 26 or higher on the Mini-Mental State Exam (MMSE; Folstein et al., 1975).

2.2. Procedure

Participants completed the study across two testing sessions that were approximately one week apart. The first session included behavioral

testing that lasted approximately 2 h. During this session, participants completed initial screening for eligibility to undergo fMRI, measures of cognitive function (e.g., the MMSE), and other measures unrelated to the current research.

The second testing session, occurring approximately one week later, included MRI. Participants completed an anatomical scan and one resting-state scan. The resting-state scan was collected over one run that lasted 15 min; a common scan duration for assessing functional connectivity estimates within and across participants (Shah et al., 2016). Participants were instructed to remain still, stay awake, and keep their eyes open. No stimuli were presented during this scan and the projector was off. After the resting-state scan, participants completed three separate tasks during fMRI. The three tasks were (1) a reasoning task in which participants made judgments based on written stories about objects and people, (2) an evaluative judgment task in which participants rated faces based on their likability, and (3) a face perception task. The order of the three tasks was counterbalanced across participants. A prior publication (Hughes et al., 2019b) reported analyses based on the resting-state and reasoning task data from this sample of participants that were unrelated to the current hypotheses.

Given that a greater quantity of data results in more reliable functional connectivity estimates (Laumann et al., 2015; Shah et al., 2016) and discrimination between task and rest (Anderson et al., 2011), our primary focus was on the reasoning task, which had the greatest total quantity of data of the task scans (totaling 10 min and 40 s). To assess the generalizability of our results, we then replicated the analyses using the data from the face evaluation task (totaling 6 min and 48 s; see Supplementary Materials).

The reasoning task included false belief (theory of mind) and false photo (control) conditions (Hughes et al., 2019b). Participants responded to statements about stories referring to either a person's beliefs (false belief condition) or to physical representations (false photo condition). Both conditions required that participants make an inference. For example, during one false belief trial, participants viewed the story, "When Lisa left Jacob, he was deep asleep on the beach. A few minutes later, a wave woke him. Seeing Lisa was gone, Jacob decided to go swimming." This story was then followed by a true or false inference (e.g., "Lisa now believes that Jacob is sleeping"). Participants were instructed to indicate whether the inference was true or false. The false photo condition was similar to the false belief condition, but differed only in that participants were not asked to make an inference about another person's mental states. For example, participants viewed the story "When the picture was taken of the house, it was one story tall. Since then, the renovators added an additional story and a garage" followed by the true or false inference "In the picture, the house is two stories tall and has a garage."

In the current work, we collapsed our analyses of task-evoked functional connectivity across task conditions (false belief, false photo) for two reasons. First, the focus of the current work was to compare rest to task states (see also the face evaluation task results in the Supplementary Materials) at the level of large-scale brain systems. Condition-specific effects in functional connectivity might be expected to emerge at a more localized scale (e.g., among specific connections; Cole et al., 2014; Hughes et al., 2019b). Therefore, our primary interest was to focus on a task state in which participants read similar amounts of information and were asked to make similar types of reasoning judgments (true or false) about the statements presented (Moran, 2013; Saxe and Kanwisher, 2003). We thus refer to this combined task state as a reasoning task. Second, there is limited work on the validity of functional connectivity estimates from event-related (vs. blocked) designs (but see Barch et al., 2013) which, given the relatively low number of trials per condition, may negatively impact the reliability of any condition-specific analyses. Collapsing across task conditions therefore had the second purpose of reducing noise in the analyses (i.e., by doubling the number of trials and length of the task).

In total, participants responded to 24 stories (12 per condition) across two runs lasting, in total, 10 min and 40 s. The false belief and false photo trials were presented in an event-related fashion that was pseudorandomized across participants. Each trial began with a story presented for 10 s. The story was followed by a fixation cross at the centre of the display, which was presented at a variable delay of 0–6 s. Finally, a statement that was true or false was presented for 6 s. In each run, there were three 0 s delays, three 2 s delays, three 4 s delays, and three 6 s delays ($M_{delay} = 3$ s, $SD = 2.34$), with 8 s of fixation at the beginning of the run and 10 s of fixation at the end, for a total of 128 s of fixation and 192 s of stimulus presentation.

2.3. fMRI data acquisition and analysis

Whole-brain imaging was performed on a Siemens 3.0T Prisma MRI Scanner using a 20-channel phase arrayed head coil at the Indiana University Imaging Research Facility in Bloomington, Indiana. Stimuli were presented using a back projector (Sony WUXGA VPL-FH30) and behavioral data were collected on a Dell laptop running Windows 7. The scanner was synced to the data collection equipment via scanner TTL. Anatomical images were acquired with a high-resolution 3-D magnetization prepared rapid gradient echo sequence (sagittal rotation; 160 slices, TE = 2.7 ms, TR = 1800 ms, TI = 900 ms, flip angle = 9°, 1.0 mm isotropic voxels; with no fat suppression).

Functional images for resting-state were collected over one run consisting of 450 time points. Subsequently, participants completed two runs of 160 time points each (320 total) of the reasoning task in counterbalanced order. All functional scans were collected using an echo-planar image (EPI) sequence sensitive to blood oxygen level dependent contrast (T2*; 54 slices with 2.2 mm thickness and no gap, TE = 30 ms, TR = 2000 ms, flip angle = 52°, FOV = 242 mm, in-plane matrix size = 110 × 110, A/P phase encoding direction). Slices were collected in an interleaved order (multi-band acceleration factor = 2). These slices provided partial-brain coverage (i.e., the entire cortex with partial cerebellum, but not brainstem).

2.3.1. Preprocessing

Resting-state and task data were preprocessed identically, except where noted, for straightforward comparison. Preprocessing was conducted in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm). Images were slice-time corrected, realigned to correct for motion, normalized to the Montreal Neurological Institute (MNI) template, and smoothed using an 8 mm FWHM isotropic Gaussian kernel (for similar preprocessing parameters in aging research, see Cassidy et al., 2016; Castle et al., 2012; Krendl et al., 2016; Zebrowitz, Ward, Boshyounger adultsn, Gutchess and Hadjikhani, 2018; Zebrowitz, Ward, Boshyounger adultsn, Gutchess and Hadjikhani, 2016). Data were resampled to 3 mm-isotropic voxels.

2.3.2. Network construction

The preprocessed resting-state and task data were submitted to the CONN functional connectivity toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). This toolbox was used to test for motion artifacts and to estimate functional connectivity for each participant during each state (i.e., across the full time-series for rest and for task). Motion artifacts were detected on a participant-by-participant basis using custom software that detected outlier time points (http://www.nitrc.org/projects/artifact_detect). Volumes were recorded as an outlier if the signal for that time point fell three standard deviations outside the mean global signal for the entire run or if the scan-to-scan head motion exceeded .5 mm in any direction. Based on these analyses, two older adults were excluded from further analyses because they did not meet our *a priori* cut-off of having at least 150 non-outlier volumes of data (approximately 5 min) for either resting-state or task data, which prior work suggests is the minimum amount of data needed to compute stable correlations from resting-state functional scans (Power et al., 2014; Van Dijk et al., 2010). This criterion is also appropriate for task-evoked connectivity based on

the quantity of data observed in similar research (Archer et al., 2016; Barch et al., 2013; Cole et al., 2014; Geerligs et al., 2015b; Monteiro et al., 2019; Murphy et al., 2019). Like past research, older adults (M_{rest} = 51.76, SD_{rest} = 49.69; M_{task} = 49.73, SD_{task} = 34.63) had more outlier volumes than younger adults (M_{rest} = 31.95, SD_{rest} = 20.56; M_{task} = 31.50, SD_{task} = 23.63) during resting-state, t (73) = 2.31, p = .02, d = 0.54, 95% CI [0.07, 1.01]; and task, t (73) = 2.66, p = .01, d = 0.63, 95% CI [0.15, 1.10]. Excluding these outlier volumes, older adults retained an average of 13.27 min (SD = 1.66; 88%) at rest and 9.01 min (SD = 1.15; 84%) at task; whereas younger adults retained an average of 13.94 min (SD = 0.69; 93%) at rest and 9.62 min (SD = 0.79; 90%) at task.

Outlier time points were excluded from analysis using participant-specific regressors. Other nuisance regressors included motion regressors from realignment and noise estimates from white matter and cerebrospinal fluid (CSF) from a PCA-based approach to noise reduction as described by Whitfield-Gabrieli and Nieto-Castanon (2012). Because noise patterns vary across brain areas, global signal regression, the average signal across all voxels in the brain, has less sensitivity to non-artifactual functional connectivity (Chai et al., 2012). The PCA-based approach to noise reduction implemented in CONN, which regresses out physiological noise from areas of non-interest (e.g., white matter and CSF), is advantageous because it controls for inflation of negative functional connectivity estimates while preserving valid positive estimates (for more information, see Chai et al., 2012; Whitfield-Gabrieli and Nieto-Castanon, 2012).

Another possible confound is that higher frequencies may contain task signals that confound measurement of the lower frequency fluctuations that typically comprise functional connectivity estimates (Biswal et al., 1995; Fox et al., 2005). We addressed this possible confound in two ways. First, we applied a high-pass filter (0.008 Hz) to both rest and task data, as has been done in other work directly comparing functional connectivity from rest and task states (Cole et al., 2014) to filter task signals at high frequencies. Also, for task data only, we conducted a general linear model regression of task events and used the residuals to compute functional connectivity (Cole et al., 2014; Fair et al., 2007). This step limits the spurious inflation of functional connectivity estimates by task activations (for more information, see Cole et al., 2019), allowing us to conclude that state differences in functional connectivity were not due to task-related global changes in neural activity.

Whole-brain functional connectivity estimates were calculated across the time series using Fisher's z coefficients between the 114 cortical regions of interest (ROIs) from the Yeo 17 network split-label parcellation (Yeo et al., 2011) and an additional 14 subcortical ROIs isolated using the maximum likelihood subcortical FSL Harvard-Oxford Atlas (Desikan et al., 2006). This parcellation has been used in prior aging research (Cao et al., 2014; Hughes et al., 2019b). Cerebellum ROIs were not included as it only had partial coverage in most participants. This procedure generated a matrix of Fisher's z coefficients between all pairs of brain regions in the parcellation (128 × 128 regions) for each participant at rest and at task. Self-connections were excluded from analysis.

2.4. Data and code availability

Because participants did not consent to having their data stored in a specific public repository, the de-identified data (e.g., functional connectivity matrices) and code that support the findings of this study are available from the corresponding author, C.H., upon request. No formal data-sharing agreement is necessary.

3. Results

3.1. Hypothesis 1: The correlation of functional connectivity between rest and task states is lower for older adults versus younger adults

Our first goal was to determine the correlation of the functional connectivity between rest and task states – similar to Cole et al. (2014) – for younger adults and older adults. We expected this correlation to be lower in older versus younger adults. We calculated the rest-task correlation by conducting a Pearson's correlation between the rest and task whole-brain matrices for each participant. To test for age differences, we conducted a t-test on the r-values between older adults and younger adults. We compared the observed t-value to a permuted null distribution to determine significance. Specifically, we permuted group assignment, preserving the sample sizes of the original older adults and younger adults groups (N_1 = 33, N_2 = 40), and recalculated the t-values from these comparisons across 10,000 iterations. We then recorded the number of null observations equal to or greater than the observed statistic divided by the number of iterations, thus obtaining a p-value. All further significance testing for age differences used this permutation testing approach, except where noted. The permutation testing approach is suitable because it tests for group differences within our data specifically attributed to age (for similar approaches, see Contreras et al., 2019; Hughes et al., 2019b).

Replicating past work (Cole et al., 2014), we found relatively high correspondence between rest and task states across all participants, M_{corr} = 0.68, SD = 0.09 (see Fig. 1 for a visualization of the averaged connectivity for each age group and state). Supporting Hypothesis 1, older adults (M_{corr} = 0.61, SD = 0.08) had lower rest-task correlation than younger adults (M_{corr} = 0.73, SD = 0.04), t (71) = 8.45, p < .001 (see Fig. 2).[1]

3.2. Hypothesis 2: Network organization is less consistent between resting-state and task for older adults versus younger adults

A lower correlation between rest and task states in older adults may arise because the organization of their networks changes between states to a greater extent than in younger adults. We next tested for this possibility. Specifically, we characterized the network organization – assignment of brain regions into distinct networks – for each participant group (older adults, younger adults) and state (rest, task). Then, we compared key features of those organizations (Sporns and Betzel, 2016). This method allowed us to test whether older adults' lower rest-task correlation in functional connectivity emerged because older adults' network organization is less consistent across states relative to younger adults' network organization.

3.2.1. Deriving network organization

For each participant, we applied the Louvain modularity algorithm (Blondel et al., 2008; Rubinov and Sporns, 2011) to each state to identify a network organization of their respective data. We employed the "community_louvain" function from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/; Rubinov and Sporns, 2011) to do this. The algorithm was run over a range of the resolution parameter gamma (γ) from 0.5 to 2.5 in increments of 0.05 (250 repeats for each setting of gamma). We varied gamma, a free parameter, to ensure robustness. This approach has the benefit of capturing the reliability of differences in network organization on multiple spatial scales (for details, see Geerligs et al., 2015b; Ji et al., 2019; Sporns and Betzel, 2016). The network organization with the highest modularity value (Q) – reflecting strong within-network connectivity and weak between-network connectivity – at each level of gamma (evaluated 250 times) was retained for analysis. Age differences in network organizations were predicted to emerge at intermediate values of gamma, given that very low values and very high values of gamma are less biologically meaningful (i.e., likely to result in subnetworks corresponding to entire brain hemispheres or to singleton brain regions, respectively).

[1] Note that the magnitude of the age difference in the rest-task correlation did not differ between conditions (false belief, false photo) in the reasoning task, t(71) = 0.57, p > .28 (see Supplementary Materials Fig. 10); therefore we collapsed across conditions.

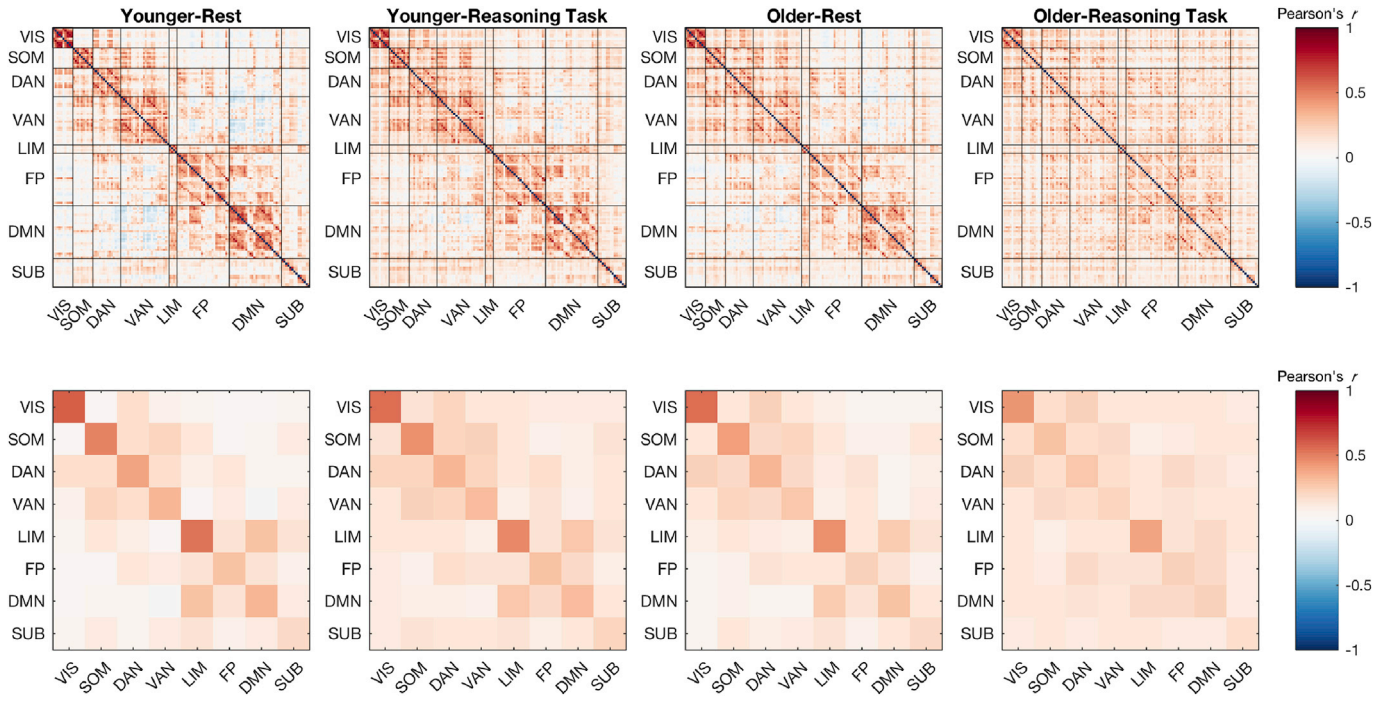


Fig. 1. Functional connectivity for each age group (older adults, younger adults) from each state (rest, reasoning task) sorted by common functional brain networks. Fisher's *z* coefficients were transformed to Pearson's *r* coefficients for visualization for their ease of interpretation. The top row shows the functional connectivity between each pair of brain regions. The bottom row down-samples the top row by showing the averaged functional connectivity within and between networks. VIS = visual network; SOM = Somatomotor network; DAN = dorsal attention network; VAN = ventral attention network; LIM = limbic network; CON = frontoparietal control network; DMN = default mode network; SUB = subcortical network.

3.2.2. *Comparing network organizations*

We first examined age differences in the total number of subnetworks detected between states. This metric reflects the average number and size of subnetworks that parse the overall organization into coherent subsystems. We recorded the total number of subnetworks for each participant and state across the range of gamma values. The number of subnetworks describing the organization of both states was higher for older adults than younger adults (see Fig. 3A; see Supplementary

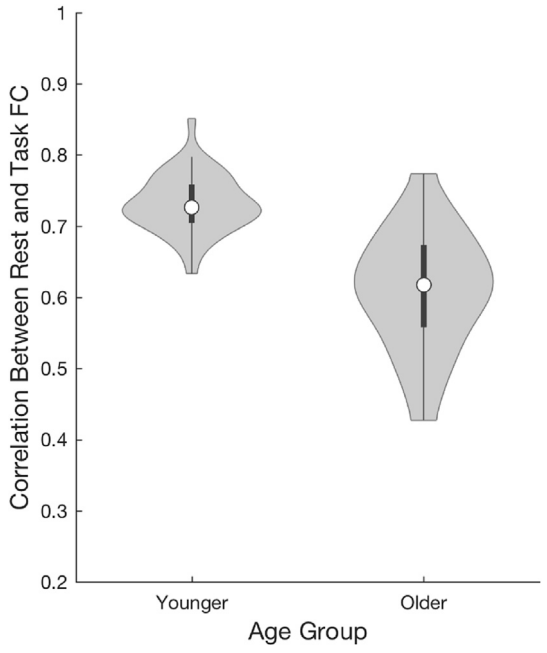


Fig. 2. Violin plot of the Pearson's correlations between task and rest functional connectivity for each age group. White dots reflect the median, thick black lines indicate the first and third quartile range, and the thin black lines indicate the maximum and minimum of the data. The shape of each is determined by the density of values.

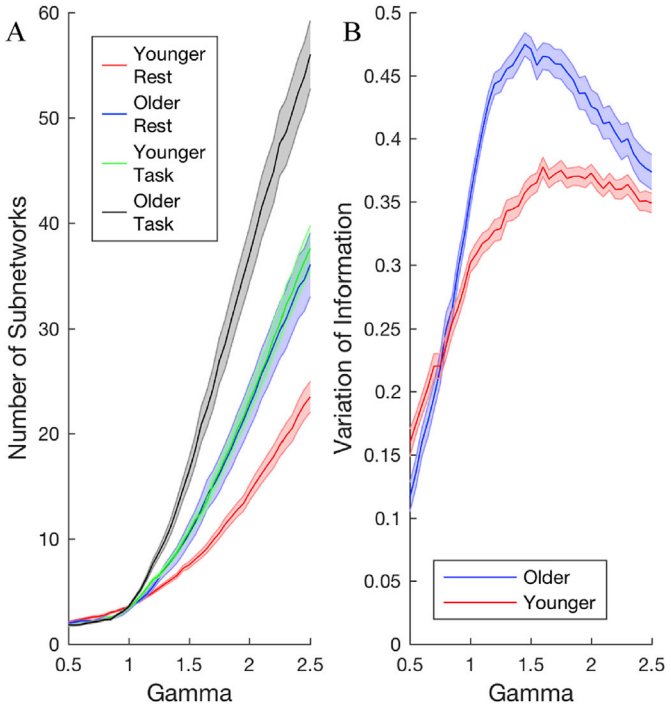


Fig. 3. Fig. 3A shows the number of subnetworks detected by modularity maximization across a range of the resolution parameter gamma for each group at each state. Fig. 3B shows the variation of information between rest and task network organizations for each group across the same range of gamma. In both plots, shaded areas represent ± 1 standard error from the mean (solid line).

Materials Fig. 1 for individual-level results). However, it may be possible that older adults' network organization resolves into more subnetworks regardless of the particular state, reflecting less distinct networks in general. In other words, these results might have been conflated by individual variation in network organization overall. To address this potential confound, we recorded the number of networks detected for task minus rest for each participant (within-subjects) and then permuted the age comparison. By doing so, we were able to conclude that age group differences were state-specific. Consistent with our hypothesis that older adults' (vs. younger adults') network organization is more diffuse (i.e., less distinct) during task versus rest, older adults had a higher number of subnetworks detected during the reasoning task than at rest compared to younger adults at most values of gamma (0.70, $t = 1.89$; 0.90–0.95, t-values range: [3.13, 3.95]; 1.05–2.15, t-values range: [1.75, 2.69], 2.25, $t = 1.77$).

Variation of information is a normalized information-theoretic measure of distance (i.e., consistency) between network organizations (Meilă, 2007). Comparing variation of information in older adults versus younger adults provides converging evidence to the prior analysis by establishing age differences in the consistency with which brain regions are assigned to the same networks between rest and task states. We calculated variation of information using the "partition_distance" function from the Brain Connectivity Toolbox. Because older adults and younger adults might have different network organizations in general, we calculated the variation of information between each participant's rest and task partitions (within-subjects) and permuted the age difference. Overall, the results most often showed that older adults' functional brain networks exhibit more change between rest and task states. Specifically, older adults had a higher variation of information between rest and task network organizations than younger adults (see Fig. 3B; see Supplementary Materials Fig. 1 for individual-level results) at intermediate values of gamma from 0.90 to 2.40 (t-values range: [1.87, 9.18]), as predicted. Ancillary, younger adults had a greater variation of information than older adults at the lowest levels of gamma from 0.5 to 0.60 (t-values range: [2, 2.55]), and no significant age differences emerged for gamma values between 0.65 and 0.85 or gamma values at the highest two values of gamma – 2.45 to 2.50. That age differences in network organization emerged across a wide range of intermediate gamma values indicates that the findings are reliable across multiple spatial scales.

3.3. Hypothesis 3: Particular networks, such as the DMN, have a greater magnitude of difference between rest and task states in older adults versus younger adults

Finally, we assessed whether age differences in the magnitude of change between states emerged within or between particular networks (e.g., the DMN). To examine age differences in the magnitude of change between rest and task, we created a difference matrix for each participant of the connectivity for the reasoning task minus the connectivity for rest between each pair of brain regions (i.e., each connection). Then, we took the absolute value of the difference matrix such that all values were zero or positive. This resulted in a 128 × 128 region-by-region matrix of the *magnitude of state difference* for each participant. Using the absolute difference matrices, we conducted a network contingency analysis described in Contreras et al. (2019) and similar to the procedure described in Sripada et al. (2014a; 2014b) to detect within or between which networks the age differences in the magnitude of rest-task difference were most prominent. This non-parametric method is suitable because it yokes rest and task at each connection, which accounts for the possibility that older adults have overall weaker connectivity across states. Moreover, by comparing connection counts within and between network blocks, we can reduce the number of significance tests performed.

The network contingency analysis was conducted in three stages. First, we conducted a t-test between older adults and younger adults at each connection. Next, brain regions in the parcellation were assigned to one of eight functional brain networks, including the seven cortical networks from Yeo et al., 2011; Visual, Somatomotor, Dorsal Attention, Ventral Attention, Limbic, Frontoparietal, and Default) and the collection of subcortical regions. This divided the connectivity matrices into an 8 × 8 matrix with 36 unique sub-blocks (8 within network and 28 between networks). The t-value from all connections were thresholded across a range from ± 2 to ± 6 in increments of 0.10 to ensure robustness. Values greater than the threshold indicate connections whose magnitude of difference between states was greater for older adults and values less than the threshold indicate connections whose magnitude of difference between states was greater for younger adults. We counted the number of connections surviving the t-threshold – either $t > t_{thr}$ or $t < -t_{thr}$ for each block. We calculated the p-value for each block as the number of significant connections in our data greater than in a permuted null distribution. We accounted for multiple comparisons by applying a Bonferroni correction to the alpha ($p = .05$) for analysis across 8 functional brain networks, resulting in a Bonferroni-corrected p-value of .0014 (0.05/36).

The network contingency analysis confirmed our hypothesis that older adults, compared to younger adults, had a greater *magnitude of difference between states* in the functional connectivity of particular brain networks. This finding held across multiple t-value thresholds; to ease discussion, we focus on the blocks identified using the t-value threshold of 3.50. We found that older adults and younger adults differed in the magnitude of functional connectivity at a significant number of connections within the DMN (as predicted), ventral attention network (VAN), somatomotor network (SOM), and between the DMN and VAN (see Fig. 4). The DMN, VAN, SOM, and DMN-VAN age differences also passed Bonferroni-correction across a broad range of t-values thresholds (DMN: $t = [2, 3]$ and [3.30, 3.70]; VAN: $t = [2, 6]$; SOM: $t = [2.40, 2.50]$ and [3, 3.50]; DMN-VAN: $t = [2.70, 4.80]$ and [5.10, 5.80]). Overall, older adults had greater magnitude of difference in the functional connectivity between states than younger adults within or between the aforementioned networks. No networks had a greater magnitude of difference between states in younger adults.

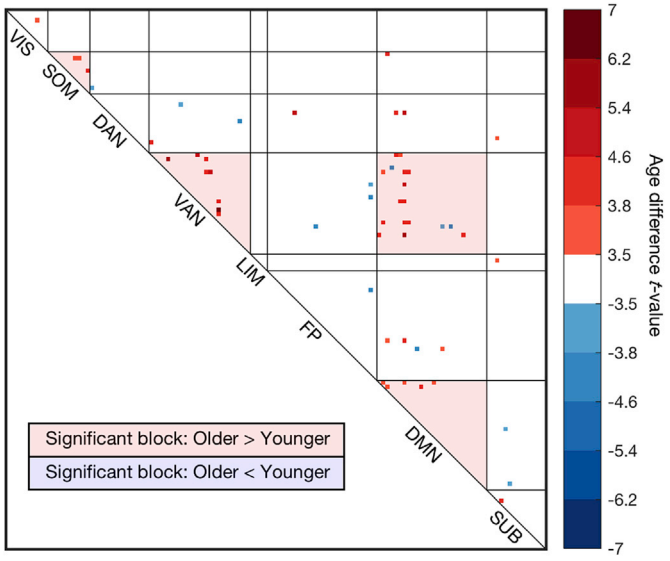


Fig. 4. Results from the network contingency analysis using an example t-value threshold of 3.50. Each dot represents a functional connection whose age difference exceeds the threshold, and the color indicates whether the functional connectivity of that connection was stronger in older adults (positive, red) or younger adults (negative, blue). The shading represents blocks where the number of connections that showed an age difference was statistically significant. VIS = visual network; SOM = Somatomotor network; DAN = dorsal attention network; VAN = ventral attention network; LIM = limbic network; FP = frontoparietal control network; DMN = default mode network; SUB = subcortical network.

To characterize the direction of these differences, we averaged the functional connectivity of all connections within each block (i.e., not just the connections surviving a particular *t*-value threshold). The DMN, VAN, and SOM exhibited a similar pattern of results (see Fig. 5). Using an alpha threshold of 0.05 to determine significance, older adults had weaker functional connectivity within these networks during the reasoning task compared to rest, DMN: $t\,(32) = 140.72$, $p < .001$; VAN: $t\,(32) = 106.00$, $p < .001$; SOM: $t\,(32) = 87.78$, $p < .001$. Younger adults also had weaker connectivity during the reasoning task versus rest but to a lesser degree than older adults, DMN: $t\,(39) = 36.31$, $p = .015$; VAN: $t\,(39) = 18.92$, $p = .13$; SOM: $t\,(39) = 29.94$, $p = .011$. For the DMN-VAN block, older adults had stronger connectivity during the reasoning task versus rest, $t\,(32) = 81.87$, $p < .001$; as did younger adults, $t\,(39) = 89.04$, $p < .001$.

3.4. Replication task results

The same sample of participants completed an evaluative judgment task in which participants rated faces based on how much they liked the individual pictured. This task was chosen to assess another type of explicit judgment in which older adults and younger adults differ: evaluative judgments based on forming impressions (e.g., Ng et al., 2016). We replicated the analyses reported in the main text with the face evaluation task to assess the generalizability of our results. Methods and detailed results from the face evaluation task are included in the Supplementary Materials. The analysis procedures were the same between the tasks. Although the face evaluation task had a lower quantity of data (see Method), restricting the sample whose data met our *a priori* inclusion criteria (27 older adults, 38 younger adults), we replicated the key results reported in the main text. Specifically, using the face evaluation task we found that older adults had a lower rest-task correlation of functional connectivity than younger adults (Hypothesis 1, Supplementary Materials Figs. 3–4), and that older adults' network organization is less consistent between rest and task compared to younger adults (Hypothesis 2, Supplementary Materials Figs. 5–7). We did not find evidence that the DMN exhibited a larger magnitude of difference in functional connectivity from resting-state versus the face evaluation task in older adults versus younger adults (Hypothesis 3, Supplementary Materials Figs. 8–9).

4. Discussion

The current study revealed the extent of age differences in functional

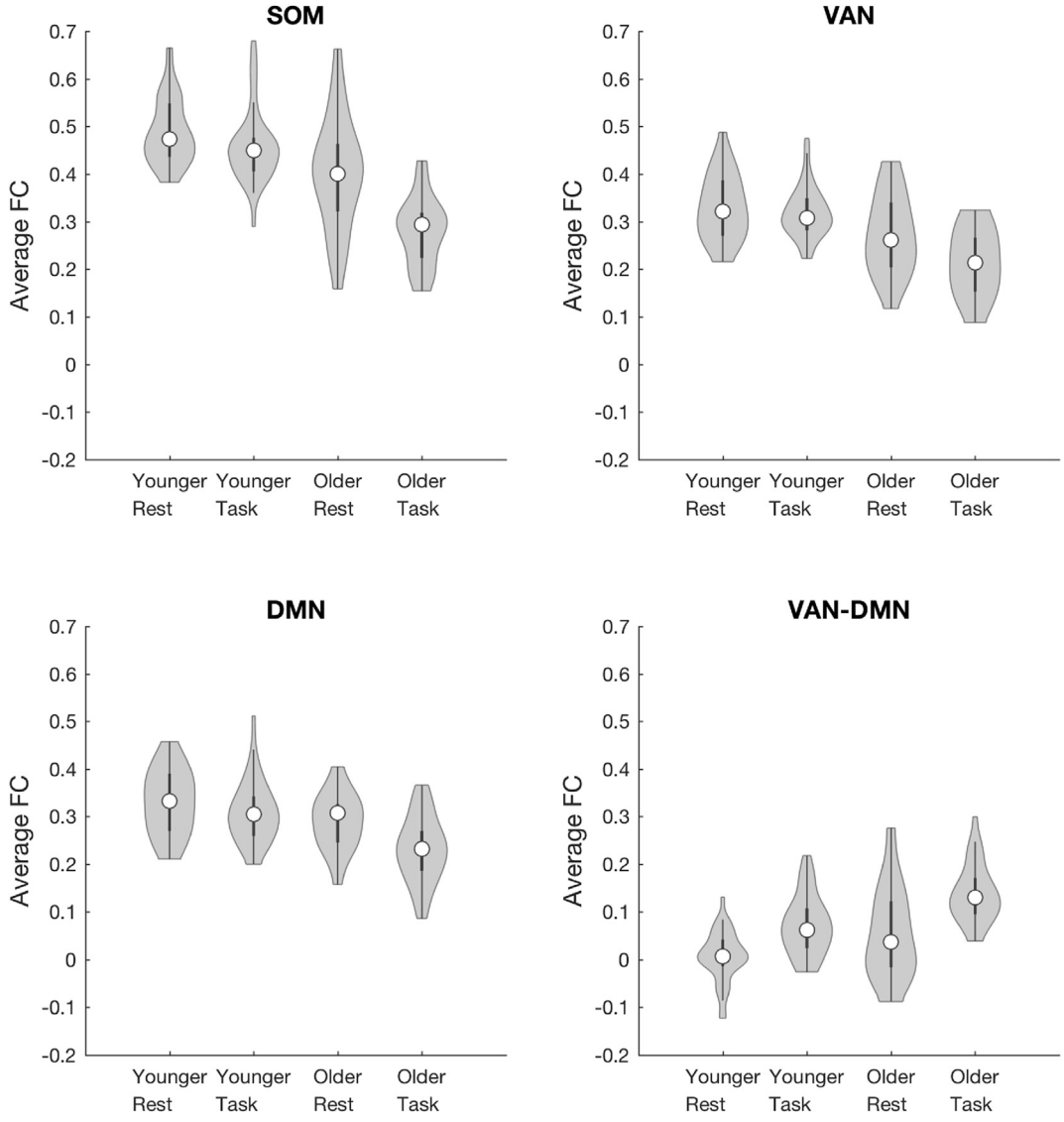


Fig. 5. Violin plot of the averaged functional connectivity of blocks identified as having significant age differences in the magnitude of rest-task connectivity based on the network contingency analysis. White dots reflect the median, thick black lines indicate the first and third quartile range, and the thin black lines indicate the maximum and minimum of the data. The shape of each is determined by the density of values.

connectivity to be state-dependent. That is, although we found that older adults had less distinct networks than younger adults during resting-state, this effect was exacerbated during two types of directed tasks – reasoning and evaluative judgments. Reasoning judgments involve higher-order cognition (McKinnon and Moscovitch, 2007; Moran, 2013) of interest to aging researchers. Examining age effects on the functional connectivity between rest and task states within this domain extends past work in other domains (e.g., sensorimotor tasks; Monteiro et al., 2019), potentially generating novel insight for mechanisms of cognitive declines often observed in older adults versus younger adults.

While showing that connectivity across rest and task states is less correlated among older adults versus younger adults, the current work also illustrated a potential explanation for this effect. In principle, lower similarity of networks across rest and task may be due to subtle randomizations of connection weights within subnetworks that leave the overall organization intact. Here, we found that the lower correlation between rest-task states among older adults versus younger adults was driven by lower consistency in the network organization (i.e. the assignment of brain regions to distinct networks) between these states. The organization of brain regions into distinct and strongly internally-connected networks is thought to promote information flow and neural communication (Bullmore and Sporns, 2012). That older adults had less distinct or differentiated networks versus younger adults may reflect disturbed communication processes that in turn gives rise to age differences in task performance and cognition.

An important consideration of these findings is that age differences emerge in functional connectivity and network organization during resting-state, which could contribute to – if not fully account for – age differences in task-evoked functional connectivity. However, by controlling for age differences at rest, we showed that task-evoked network organization is disproportionately weaker among older adults. The important theoretical contribution of this finding is that it shows that the extent of older adults' relative dysfunction in connectivity versus younger adults depends on the behavioral state (rest, task) in which a participant is engaged. The current work extends previous findings that support this assertion (Geerligs et al., 2015b; Monteiro et al., 2019) by demonstrating this effect in a reasoning task that involve higher-order cognitive abilities.

Although age differences in the relationship between rest and task states emerged across the whole brain, certain networks were disproportionately affected. Here, the DMN demonstrated a greater magnitude of difference in connectivity between rest and task states for older adults compared to younger adults. Specifically, connectivity within the DMN was more strongly attenuated during task versus rest states in older adults as compared to younger adults.[2] It is important to note that components of the reasoning task (false belief trials involving theory of mind) have been previously associated with age differences in DMN activation and connectivity (Hughes et al., 2019b; Moran et al., 2012). It is therefore possible that age deficits in theory of mind might have driven the DMN differences we observed when collapsing across the false belief and false photo conditions. However, the magnitude of the age difference in average DMN connectivity between rest and each task condition did not differ. This finding indicates that the false belief condition involving theory of mind did not solely account for age differences in DMN connectivity between rest and task states.

It is also possible that engaging in any reasoning may disproportionately affect the DMN. In support of this possibility, despite that the face evaluation task replicated the whole-brain findings, it did not show age differences in DMN connectivity between states. This conclusion would suggest that the whole-brain findings may be task-general (see Cole et al., 2014), whereas network-level effects may best relate to specific tasks. Typically, less distinction between networks occurs in response to task demands (Bertolero, Yeo, & D'Esposito, 2015). Yet, the fact that decreased segregation of brain networks during tasks occurs to a greater extent among older adults within the DMN during reasoning may help identify an age-specific mechanism of dysregulation. That is, cognitive decline among some older adults may be attributed to the extent that the functional architecture of brain networks changes from rest in response to task demands, rather than its dysregulation during either state alone. The dynamic aspect of functional connectivity represented by changes in connectivity from rest to task may thus provide a novel mechanism by which aging impacts cognition. Although beyond the scope of the current investigation, one particularly fruitful area of future research would be to examine how the magnitude of difference in functional connectivity between rest and task states relates to age differences in behavior.

Intriguingly, another brain network implicated in this analysis was the VAN (within-network), which also showed stronger attenuation during task versus rest states in older adults versus younger adults. Beyond age differences within the VAN and DMN, older adults (vs. younger adults) had increased task-evoked connectivity between the DMN and VAN during the reasoning task versus rest. These findings are perhaps unsurprising given that emerging theories of aging (Spreng and Turner, 2019), supported by experimental work (Grady et al., 2016), emphasize how the DMN's communication with other brain networks represents a fundamental shift in the functional architecture of brain networks in aging. Here, increased task-evoked connectivity between the DMN and VAN may reflect older adults' greater difficulty in the reasoning task and the shift from rest to focused attention during a goal-directed task (Grady et al., 2016). Functional brain interactions (i.e., between-network connectivity) best captured by task-evoked processes may thus be an understudied characteristic of neurocognitive aging. However, a limitation of these conclusions is that the network-specific results were not replicated using the evaluative judgment task (see Supplementary Materials). Because some network-level effects are task-specific (Geerligs et al., 2015b), it is not clear what task features elicited these differences. Future work should thus characterize age effects on the relationship between resting-state and a wider variety of cognitive and behavioral tasks.

A final consideration is that our estimates of rest-task overlap may be more conservative than those in Cole et al. (2014) because we calculated the correlation at the participant-level to examine age differences, whereas their procedure was to compare the correlation between group-averaged rest and task connectivity. Following the group-level procedure reported in Cole et al. (2014), we find similarly high correlation between states across participants, $r = 0.92$, as well as within each group (older adults: $r = 0.84$; younger adults: $r = 0.93$). This distinction may be important for understanding how individual variability in the correlation between rest and task connectivity relates to cognitive ability. Limited work shows that older adults' exacerbated age differences during task versus rest related to higher error rates on a motor task (Monteiro et al., 2019). While outside the scope of the current paper, our findings may generate new insights as to why resting-state connectivity predicts cognitive abilities via its relationship with task-evoked connectivity. Future work should investigate how the relationship of connectivity between rest and task states contributes to age-related declines in cognitive abilities.

5. Conclusions

Healthy aging is associated with a less consistent functional architecture of brain networks across states. Because older adults' networks are disproportionately affected by task demands versus rest, studying the dynamic mechanism of change between states (relative to static differences at rest and task separately) is a theoretically important method by which to understand negative impacts of aging. Because age negatively relates to reasoning ability (Moran, 2013), the reasoning judgement task

[2] The age difference in DMN average connectivity between rest and task states did not differ between conditions (false belief, false photo) in the reasoning task, $t(71) = 0.48$, $p > .32$ (see Supplementary Materials Fig. 11).

involving higher-order cognition studied here extends work in which few behavioral states (motor tasks, passive movie-watching; Geerligs et al., 2015b; Monteiro et al., 2019) have been characterized. That task and rest are consistently less related across behavioral states may reflect a broader shift in the functional architecture in response to any directed task or elucidate mechanisms of age differences in the corresponding behavioral state. The findings of the current work thus broadens our understanding of aging's impact on the functional architecture of brain networks and calls to action the need for future work testing a wider variety of cognitive and behavioral states.

Acknowledgments

The authors wish to thank the Indiana University Imaging Research Facility, Rachel Brown, Lindsey Fisher, Jaclyn Lisnek, and Lauren Lu for assistance with data collection. This work was supported in part by the National Institute of Mental Health grant T32MH103213 (C.H.) and by grant numbers KL2TR002530 and UL1TR002529 (A. Shekhar, PI) from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award (PI: A.C.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was also supported by the National Science Foundation Graduate Research Fellowship under Grant No. 1342962 (J.F.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116521.

Author Contributions

Colleen Hughes: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Joshua Faskowitz**: Formal analysis, Writing – review & editing, Visualization. **Brittany Cassidy**: Conceptualization, Methodology, Investigation, Writing – review & editing. **Olaf Sporns**: Formal analysis, Writing – review & editing, Visualization, Supervision. **Anne Krendl**: Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

References

Fair, D.A., Schlaggar, B.L., Cohen, A.L., Miezin, F.M., Dosenbach, N.U.F., Wenger, K.K., et al., 2007. A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. Neuroimage 35 (1), 396–405. https://doi.org/10.1016/j.neuroimage.2006.11.051.

Anderson, J.S., Ferguson, M.A., Lopez-Larson, M., Yurgelun-Todd, D., 2011. Reproducibility of single-subject functional connectivity measurements. AJNR. American Journal of Neuroradiology 32 (3), 548–555. https://doi.org/10.3174/ajnr.A2330.

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 (5), 924–935. https://doi.org/10.1016/j.neuron.2007.10.038.

Archer, J.A., Lee, A., Qiu, A., Chen, S.-H.A., 2016. A comprehensive analysis of connectivity and aging over the adult life span. Brain Connect. 6 (2), 169–185. https://doi.org/10.1089/brain.2015.0345.

Barch, D.M., Burgess, G.C., Harms, M.P., Petersen, S.E., Schlaggar, B.L., Corbetta, M., et al., 2013. Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage 80, 169–189. https://doi.org/10.1016/j.neuroimage.2013.05.033.

Bertolero, M.A., Yeo, B.T.T., D'Esposito, M., 2015. The modular and integrative functional architecture of the human brain. Proc. Natl. Acad. Sci. U.S.A. 112 (49), E6798–E6807. https://doi.org/10.1073/pnas.1510619112.

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. https://doi.org/10.1016/j.neuroimage.2014.07.067.

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med. 34 (4), 537–541. https://doi.org/10.1002/mrm.1910340409.

Blondel, V.D., Guillaume, J.-L., Lambiotte, R., Lefebvre, E., 2008. Fast unfolding of communities in large networks. J. Stat. Mech. Theory Exp. 2008 (10), P10008. https://doi.org/10.1088/1742-5468/2008/10/P10008.

Buckner, R.L., Krienen, F.M., Yeo, B.T., 2013. Opportunities and limitations of intrinsic functional connectivity MRI. Nat. Neurosci. 16 (7), 832–837. https://doi.org/10.1038/nn.3423.

Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13 (5), 336–349. https://doi.org/10.1038/nrn3214.

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. https://doi.org/10.3389/fnagi.2013.00073.

Cao, M., Wang, J.H., Dai, Z.J., Cao, X.Y., Jiang, L.L., Fan, F.M., et al., 2014. Topological organization of the human brain functional connectome across the lifespan. Developmental Cognitive Neuroscience 7 (16), 76–93. https://doi.org/10.1016/j.dcn.2013.11.004.

Cassidy, B.S., Lee, E.J., Krendl, A.C., 2016. Age and executive ability impact the neural correlates of race perception. Soc. Cogn. Affect. Neurosci. 11 (11), 1752–1761. https://doi.org/10.1093/scan/nsw081.

Castle, E., Eisenberger, N.I., Seeman, T.E., Moons, W.G., Boggero, I.A., Grinblatt, M.S., Taylor, S.E., 2012. Neural and behavioral bases of age differences in perceptions of trust. Proc. Natl. Acad. Sci. U.S.A. 109 (51), 20848–20852. https://doi.org/10.1073/pnas.1218518109.

Chai, X.J., Castañón, A.N., Ongür, D., Whitfield-Gabrieli, S., 2012. Anticorrelations in resting state networks without global signal regression. Neuroimage 59 (2), 1420–1428. https://doi.org/10.1016/j.neuroimage.2011.08.048.

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 (46), E4997–E5006. https://doi.org/10.1073/PNAS.1415122111.

Chan, M.Y., Alhazmi, F.H., Park, D.C., Savalia, N.K., Wig, G.S., 2017. Resting-state network topology differentiates task signals across the adult life span. J. Neurosci.: The Official Journal of the Society for Neuroscience 37 (10), 2734–2745. https://doi.org/10.1523/JNEUROSCI.2406-16.2017.

Cole, M.W., Bassett, D.S., Power, J.D., Braver, T.S., Petersen, S.E., 2014. Intrinsic and task-evoked network architectures of the human brain. Neuron 83 (1), 238–251. https://doi.org/10.1016/j.neuron.2014.05.014.

Cole, M.W., Ito, T., Bassett, D.S., Schultz, D.H., 2016. Activity flow over resting-state networks shapes cognitive task activations. Nat. Neurosci. 19 (12), 1718–1726. https://doi.org/10.1038/nn.4406.

Cole, M.W., Ito, T., Schultz, D., Mill, R., Chen, R., Cocuzza, C., 2019. Task activations produce spurious but systematic inflation of task functional connectivity estimates. Neuroimage 189, 1–18. https://doi.org/10.1016/j.neuroimage.2018.12.054.

Contreras, J.A., Avena-Koenigsberger, A., Risacher, S.L., West, J.D., Tallman, E., McDonald, B.C., et al., 2019. Resting state network modularity along the prodromal late onset Alzheimer's disease continuum. Neuroimage: Clinic 22, 101687. https://doi.org/10.1016/J.NICL.2019.101687.

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J.S., Barkhof, F., Scheltens, P., Stam, C.J., et al., 2008. Reduced resting-state brain activity in the "default network" in normal aging. Cerebr. Cortex 18 (8), 1856–1864. https://doi.org/10.1093/cercor/bhm207.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., et al., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31 (3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.

Ferreira, L.K., Busatto, G.F., 2013. Resting-state functional connectivity in normal brain aging. Neurosci. Biobehav. Rev. 37 (3), 384–400. https://doi.org/10.1016/J.NEUBIOREV.2013.01.017.

Finn, E.S., Scheinost, D., Finn, D.M., Shen, X., Papademetris, X., Constable, R.T., 2017. Can brain state be manipulated to emphasize individual differences in functional connectivity? Neuroimage 160, 140–151. https://doi.org/10.1016/j.neuroimage.2017.03.064.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. *12*, 189–198.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U.S.A. 102 (27), 9673–9678. https://doi.org/10.1073/pnas.0504136102.

Geerligs, L., Renken, R.J., Saliasi, E., Maurits, N.M., Lorist, M.M., 2015a. A brain-wide study of age-related changes in functional connectivity. Cerebr. Cortex 25 (7), 1987–1999. https://doi.org/10.1093/cercor/bhu012.

Geerligs, L., Rubinov, M., Cam-Can, Henson, R.N., 2015b. State and trait components of functional connectivity: individual differences vary with mental state. J. Neurosci.: The Official Journal of the Society for Neuroscience 35 (41), 13949–13961. https://doi.org/10.1523/JNEUROSCI.1324-15.2015.

Goh, J.O.S., 2011. Functional dedifferentiation and altered connectivity in older adults: neural accounts of cognitive aging. Aging & Disease 2 (1), 30–48. Retrieved from. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3066008&tool=pmcentrez&rendertype=abstract.

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. https://doi.org/10.1016/j.neurobiolaging.2016.02.020.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U.S.A. 100 (1), 253–258. https://doi.org/10.1073/pnas.0135058100.

Hafkemeijer, A., van der Grond, J., Rombouts, S.A.R.B., 2012. Imaging the default mode network in aging and dementia. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (3), 431–441. https://doi.org/10.1016/J.BBADIS.2011.07.008.

Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T., 2006. Brain connectivity related to working memory performance. J. Neurosci. 26 (51), 13338–13343. https://doi.org/10.1523/JNEUROSCI.3408-06.2006.

Hughes, Colleen, Cassidy, B.S., Faskowitz, J., Avena-Koenigsberger, A., Sporns, O., Krendl, A.C., 2019b. Age differences in specific neural connections within the Default Mode Network underlie theory of mind. Neuroimage 191, 269–277. https://doi.org/10.1016/J.NEUROIMAGE.2019.02.024.

Ji, J.L., Spronk, M., Kulkarni, K., Repovš, G., Anticevic, A., Cole, M.W., 2019. Mapping the human brain's cortical-subcortical functional network organization. Neuroimage 185, 35–57. https://doi.org/10.1016/J.NEUROIMAGE.2018.10.006.

Krendl, A.C., Kensinger, E.A., Wang, X., Han, S., Brammer, M., David, A., 2016. Does older adults' cognitive function disrupt the malleability of their attitudes toward outgroup members?: an fMRI investigation. PLoS One 11 (4), e0152698. https://doi.org/10.1371/journal.pone.0152698.

Laumann, T.O., Gordon, E.M., Adeyemo, B., Snyder, A.Z., Joo, S.J., Chen, M.-Y., et al., 2015. Functional system and areal organization of a highly sampled individual human brain. Neuron 87 (3), 657–670. https://doi.org/10.1016/J.NEURON.2015.06.037.

McKinnon, M.C., Moscovitch, M., 2007. Domain-general contributions to social reasoning: theory of mind and deontic reasoning re-explored. Cognition 102 (2), 179–218. https://doi.org/10.1016/J.COGNITION.2005.12.011.

Meilă, M., 2007. Comparing clusterings—an information based distance. J. Multivar. Anal. 98 (5), 873–895. https://doi.org/10.1016/J.JMVA.2006.11.013.

Monteiro, T.S., King, B.R., Zivari Adab, H., Mantini, D., Swinnen, S.P., 2019. Age-related differences in network flexibility and segregation at rest and during motor performance. Neuroimage 194, 93–104. https://doi.org/10.1016/J.NEUROIMAGE.2019.03.015.

Moran, Joseph M., 2013, January 15. Lifespan Development: the Effects of Typical Aging on Theory of Mind. Behavioural Brain Research. Elsevier. https://doi.org/10.1016/j.bbr.2012.09.020.

Moran, J.M., Jolly, E., Mitchell, J.P., 2012. Social-cognitive deficits in normal aging. J. Neurosci. 32 (16), 5553–5561. https://doi.org/10.1523/JNEUROSCI.5511-11.2012.

Mueller, S., Wang, D., Fox, M.D., Yeo, B.T.T., Sepulcre, J., Sabuncu, M.R., et al., 2013. Individual variability in functional connectivity architecture of the human brain. Neuron 77 (3), 586–595. https://doi.org/10.1016/J.NEURON.2012.12.028.

Murphy, A.C., Bertolero, M.A., Papadopoulos, L., Lydon-Staley, D.M., Bassett, D.S., 2019. Multiscale and multimodal network dynamics underpinning working memory. Retrieved from. https://arxiv.org/pdf/1901.06552.pdf.

Ng, S.Y., Zebrowitz, L.A., Franklin, R.G., 2016. Age differences in the differentiation of trait impressions from faces. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 71 (2), 220–229. https://doi.org/10.1093/geronb/gbu113.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84, 320–341. https://doi.org/10.1016/J.NEUROIMAGE.2013.08.048.

Raichle, Marcus E., 2011. The restless brain. Brain Connect. 1 (1), 3–12. https://doi.org/10.1089/brain.2011.0019.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A. 98 (2), 676–682. https://doi.org/10.1073/pnas.98.2.676.

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. https://doi.org/10.1016/J.NEUROIMAGE.2014.09.045.

Reuter-Lorenz, P.A., Cappell, K.A., 2008. Neurocognitive aging and the compensation hypothesis. Curr. Dir. Psychol. Sci. 17 (3), 177–182. https://doi.org/10.1111/j.1467-8721.2008.00570.x.

Rubinov, M., Sporns, O., 2011. Weight-conserving characterization of complex functional brain networks. Neuroimage 56 (4), 2068–2079. https://doi.org/10.1016/J.NEUROIMAGE.2011.03.069.

Sala-Llonch, R., Bartres-Faz, D., Junque, C., 2015. Reorganization of brain networks in aging: a review of functional connectivity studies. Front. Psychol. 6, 663. https://doi.org/10.3389/fpsyg.2015.00663.

Saxe, R., Kanwisher, N., 2003. People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind. Neuroimage 19 (4), 1835–1842.

Shah, L.M., Cramer, J.A., Ferguson, M.A., Birn, R.M., Anderson, J.S., 2016. Reliability and reproducibility of individual differences in functional connectivity acquired during task and resting state. Brain and Behavior 6 (5), e00456. https://doi.org/10.1002/brb3.456.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. 106 (31), 13040–13045. https://doi.org/10.1073/pnas.0905267106.

Sporns, O., Betzel, R.F., 2016. Modular brain networks. Annu. Rev. Psychol. 67, 613–640. https://doi.org/10.1146/annurev-psych-122414-033634.

Spreng, R.N., Turner, G.R., 2019. The shifting architecture of cognition and brain function in older adulthood. Perspect. Psychol. Sci. 14 (4), 523–542. https://doi.org/10.1177/1745691619827511.

Sripada, C., Kessler, D., Fang, Y., Welsh, R.C., Prem Kumar, K., Angstadt, M., 2014a. Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 35 (9), 4693–4705. https://doi.org/10.1002/hbm.22504.

Sripada, C.S., Kessler, D., Angstadt, M., 2014b. Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder. Proc. Natl. Acad. Sci. 111 (39), 14259–14264. https://doi.org/10.1073/pnas.1407787111.

Stevens, W.D., Spreng, R.N., 2014. Resting-state functional connectivity MRI reveals active processes central to cognition. Wiley Interdisciplinary Reviews: Cogn. Sci. 5 (2), 233–245. https://doi.org/10.1002/wcs.1275.

Van Dijk, K.R.A., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321. https://doi.org/10.1152/jn.00783.2009.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2 (3), 125–141. https://doi.org/10.1089/brain.2012.0073.

Yeo, B.T.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., et al., 2011b. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.

Zebrowitz, L., Ward, N., Boshyan, J., Gutchess, A., Hadjikhani, N., 2016. Dedifferentiated face processing in older adults is linked to lower resting state metabolic activity in fusiform face area. Brain Res. 1644, 22–31. https://doi.org/10.1016/j.brainres.2016.05.007.

Zebrowitz, L.A., Ward, N., Boshyan, J., Gutchess, A., Hadjikhani, N., 2018. Older adults' neural activation in the reward circuit is sensitive to face trustworthiness. Cognit. Affect Behav. Neurosci. 18 (1), 21–34. https://doi.org/10.3758/s13415-017-0549-1.