

Task-linked Diurnal Brain Network Reorganization in Older Adults: A Graph Theoretical Approach

John A. E. Anderson^{1,2}, Saman Sarraf², Tarek Amer^{1,2}, Buddhika Bellana^{1,2}, Vincent Man¹, Karen L. Campbell³, Lynn Hasher^{1,2}, and Cheryl L. Grady^{1,2}

Abstract

■ Testing older adults in the morning generally improves behavioral performance relative to afternoon testing. Morning testing is also associated with brain activity similar to that of young adults. Here, we used graph theory to explore how time of day (TOD) affects the organization of brain networks in older adults across rest and task states. We used nodes from the automated anatomical labeling atlas to construct participant-specific correlation matrices of fMRI data obtained during 1-back tasks with interference and rest. We computed pairwise group differences for key graph metrics, including small-worldness and modularity. We found that older adults tested in the morn-

ing and young adults did not differ on any graph metric. Both of these groups differed from older adults tested in the afternoon during the tasks—but not rest. Specifically, the latter group had lower modularity and small-worldness (indices of more efficient network organization). Across all groups, higher modularity and small-worldness strongly correlated with reduced distractibility on an implicit priming task. Increasingly, TOD is seen as important for interpreting and reproducing neuroimaging results. Our study emphasizes how TOD affects brain network organization and executive control in older adults. ■

INTRODUCTION

Circadian rhythms are endogenous biological fluctuations entrained to the day–night cycle. These are found everywhere in nature and affect virtually all life, producing changes in metabolism, hormone expression, and, importantly, alertness, cognition, and behavior (Dibner, Schibler, & Albrecht, 2010; Hasher, Goldstein, & May, 2005). In humans, older adults have a circadian peak that occurs earlier in the day. The result is most older adults are “morning types” with physiological and mental peak earlier in the day than younger adults (Biss & Hasher, 2012; Yoon, May, & Hasher, 1999). Differences in chronotype (circadian preference) can be reliably measured using questionnaires (Roenneberg, Wirz-Justice, & Merrow, 2003; Adan & Almirall, 1991; Horne & Ostberg, 1976). Chronotype questionnaires correlate strongly with physiological measures of circadian rhythms, including melatonin levels, heart rate variability, blood pressure, actigraphy, midsleep point, and physical performance (Facer-childs & Brandstaetter, 2015; Adan et al., 2012; Kondratova & Kondratov, 2012; Roeser et al., 2012; Roenneberg et al., 2003; Horne & Ostberg, 1975). Evidence from our laboratory and others suggests that performance on highly demanding fluid cognitive tasks (i.e., not automatic or tests of crystallized/semantic

systems) is most affected by the time of testing and that these effects are particularly pronounced in older adults (Goldstein et al., 2007; Schmidt, Collette, Cajochen, & Peigneux, 2007; Winocur & Hasher, 2002; Hasher, Zacks, & May, 1999; Yoon et al., 1999).

Although research exists demonstrating the effects of time of day on behavior, few studies have examined the effects of time of testing on fMRI activity. Most of the latter studies have focused exclusively on younger adults and have shown an effect of both chronotype and time of testing on task-related fMRI activity, that is, a synchrony effect (Schmidt et al., 2012; Peres et al., 2011; Marek et al., 2010). We recently reported reduced differences between younger and older adults in task-related activations in a time-of-day paradigm. When we tested older adults at their optimal time of day, they showed a similar degree of activation in the brain regions associated with a cognitive control task in young adults. By contrast, older adults tested at an off-peak time showed no reliable activation in these regions (Anderson, Campbell, Amer, Grady, & Hasher, 2014). Thus, time of testing attenuates age effects in BOLD activity. However, little work has been done to explore time-of-day effects on brain networks in the context of aging (see Blautzik, Vetter, Peres, & Gutyrchik, 2013).

We attempted to bridge this gap using a graph theory approach. This analysis technique statistically describes the topological organization of anatomical and functional networks (Power, Fair, Schlaggar, & Petersen, 2010; Rubinov

¹University of Toronto, ²Rotman Research Institute, Toronto, Canada, ³University of Cambridge

& Sporns, 2010). Most biological systems follow an economical “small-world” organization (Bullmore & Sporns, 2009). Such networks have dense clusters of nodes with short path lengths (i.e., average distance between any node pair; Bullmore & Sporns, 2012; Latora & Marchiori, 2005; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; Watts & Strogatz, 1998). Analyses of network properties across the life-span have revealed age differences. Resting state studies show that old age predicts reduced small-world organization and modularity (Cao et al., 2014; Chan, Park, Savalia, Petersen, & Wig, 2014; Geerligs, Renken, Saliassi, Maurits, & Lorist, 2014; Schaefer et al., 2014; Song, Birn, et al., 2014; Song, Zhang, & Liu, 2014; Onoda & Yamaguchi, 2013; Tomasi & Volkow, 2012; Wu et al., 2012; Zuo et al., 2012; Chen, He, Rosa-Neto, Gong, & Evans, 2011; Meunier, Achard, Morcom, & Bullmore, 2009; Achard & Bullmore, 2007). Although graph analytic approaches have also been conducted on task-based data (e.g., Geib et al., 2015; Cao et al., 2014; Kitzbichler, Henson, Smith, Nathan, & Bullmore, 2011; Bassett, Meyer-Lindenberg, Achard, Duke, & Bullmore, 2006), this literature is especially lacking in the context of old age. Geerligs, Maurits, Renken, & Lorist, (2014) examined task-linked declines in functional connectivity in younger and older adults. They examined performance during a visual oddball task in a variety of functional networks. The authors reported a consistent decrease in connectivity within networks with age, especially in the default mode network (DMN) and somatomotor networks with a concomitant increase in functional connectivity across networks (see Grady, Sarraf, Saverino, & Campbell, 2016, for similar results). This decrease within network connectivity also was shown to correlate with worse cognitive ability. To our knowledge, no study has considered age differences across the day using this method.

Can time of day alter a functional system’s topological organization? Given the relevance of this question to the interpretation of cognitive performance in old age, we explored how time of day shapes rest and task-linked brain network organization in older adults. We predicted a similar pattern of network organization for younger adults and the older adults tested in the morning, particularly during task when the systems would experience more cognitive load. We expected that morning older adults and young adults should both have more economical (small-world) brain networks than older adults tested in the afternoon. This outcome would parallel previous behavioral advantages found for older adults tested in the morning. To preview our results, as predicted, during task states, network topology in older adults tested in the morning resembled that of younger adults. These two groups had similar levels of “small-world” network organization and greater modularity—both generally considered to be hallmarks of greater network efficiency (but see Kitzbichler et al., 2011). Compared with both young and morning old groups, older adults tested in the afternoon had lower network effi-

ciency measures. During resting states, however, no group differences were evident. Our findings suggest that age differences in brain organization are most apparent with increasing task demand and are exacerbated by sub-optimal testing contexts (i.e., nonoptimal times of day).

METHODS

Participants

Sixteen older and 16 younger adults were tested in the afternoon (3:00 p.m.; AO group), and 18 older adults were tested in the morning (8:00 a.m.; MO group; task-related activation from these participants was previously reported in Anderson et al., 2014). As demographic data did not differ across the older groups, (all t values were <0.4 , $ps > .5$), we present averaged descriptive statistics. Older adults’ average age was 70.35 ($SD = 7.68$) years, and they had an average of 15.94 ($SD = 2.36$) years of education. Younger adults, the AY group, were, on average, 23.94 ($SD = 4.17$) years old. All older participants had normal Mini-Mental State Examination ($M = 28.20$, $SD = 1.67$) and Shipley vocabulary scores ($M = 35.77$, $SD = 2.81$; Folstein, Folstein, & McHugh, 1975; Shipley, 1946) and were predominantly “morning types” as measured with the Morningness–Eveningness Questionnaire (MEQ; Horne & Ostberg, 1975). Consistent with previous research, younger participants had slightly lower Shipley scores ($M = 33.42$, $SD = 3.46$), $t(48) = 2.56$, $p = .01$, and were significantly more “evening-oriented” on the MEQ ($M = 46.6$, $SD = 11.3$) than their older peers ($M = 61.7$, $SD = 8.0$), $t(24.8) = 4.72$, $p \leq .001$. Note that, according to the MEQ, a score of 59–69 indicates a “moderate morning” type, whereas a score of 31–41 indicates a “moderate evening type.” Most of our older adults scored in the neutral-to-moderate morning range, whereas most of our young adults scored in the neutral-to-moderate evening range.

Procedure

During scanning, the participants did a 1-back task pressing a button for repeated picture stimuli of familiar objects. Stimuli contained irrelevant distractor text (word and nonwords) superimposed over the pictures, which participants were asked to ignore.

After an arrow flanker task (Eriksen & Eriksen, 1974), the participants were given a word fragment completion task containing some of the words that had previously been shown as distraction during the 1-back task to test for implicit access to those distracting items (the word fragment completion task was unscanned and is referred to as the “priming for distraction task” from this point forward). After the task described above, participants had a 7-min (eyes-closed) resting state scan in which they were instructed to relax, not think about anything in particular, and not fall asleep (full details can be found in Anderson et al., 2014; Campbell, Grady, Ng, & Hasher, 2012).

fMRI Data Acquisition and Preprocessing

Participants were scanned using a Siemens (Erlangen, Germany) Trio 3-T scanner 12-channel head coil. Anatomical scans were acquired with a 3-D magnetization prepared rapid gradient-echo sequence (repetition time = 2 sec, echo time = 2.63 msec, field of view = 25.6 cm², 256 × 256 matrix, 160 slices of 1 mm thickness). Functional runs were acquired with an EPI sequence, with 157 volumes for each of the 1-back runs (repetition time = 2 sec, echo time = 30 msec, flip angle = 70°, field of view = 20 cm², 64 × 64 matrix, 30 slices of 5 mm thickness, no gap). Measures of pulse and respiration were obtained during the scan.

Preprocessing of the image data was performed with the Analysis of Functional NeuroImages software (Cox, 1996). This included physiological motion correction using RETROICOR, rigid motion correction, spatial normalization to the Montreal Neurological Institute space, and smoothing with an 8-mm Gaussian filter (the final voxel size was 4 × 4 × 4 mm). We also used a mask-based approach to regress out the mean signals from the white matter, cerebral spinal fluid, vasculature, and motion time series from each voxel time series (Campbell, Grigg, Saverino, Churchill, & Grady, 2013; Grady et al., 2010).

As motion has been demonstrated to affect functional connectivity measures, even after standard correction procedures (e.g., Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), we followed a motion scrubbing procedure described in Campbell et al. (2013). Briefly, this procedure uses a multivariate technique to identify outliers in both the motion parameter estimates and fMRI signal itself. Where such outliers co-occurred (never more than 4% of the total volumes), we removed the fMRI volumes and replaced them with values interpolated with cubic splines. As reported by Campbell et al. (2013), this method has the advantage of suppressing spikes, yet keeping the length of the time course intact across participants. We found no differences between groups in the number of volumes removed for any scan type (smallest $p = .14$). Finally, the task effects (i.e., stimulus onsets) were regressed from the task run using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Graph Theory Analysis Using the GAT Toolbox

ROIs were defined using the ROIs from the automated anatomical labeling (AAL) atlas, which parcellates the brain into 90 regions (Whitfield-Gabrieli & Nieto-Castanon, 2012; Maldjian, Laurienti, Kraft, & Burdette, 2003). We extracted the average fMRI time series per condition within ROIs for each individual using the CONN toolbox. Individual participant correlation matrices were then input into the GAT Toolbox (Hosseini, Hoeft, & Kesler, 2012) and used to calculate graph metrics. Thresholding the association matrices of different groups at an

absolute threshold results in networks with a different number of nodes (and degrees) that might influence the network measures and reduce interpretation of between-group results. Two approaches were implemented for thresholding the constructed association matrices based on previous studies: (1) thresholding the constructed association matrices at a minimum network density (D_{min}) in which all nodes become fully connected in the brain networks of both groups (none of the networks are fragmented) and (2) thresholding the constructed association matrices at a range of network densities for comparing the network topologies across that range. The GAT toolbox allows the user to specify the range and the interval between densities.

For the initial step of calculating and displaying graph metrics, we set a wide density range (between 0.1 and 0.7) to form a binary adjacency matrix of 0s and 1s. The individual's graph is then constructed to have N nodes and degree equal to the number of edges (connections between regions). One of the advantages of using the GAT toolbox is that it avoids thresholding the adjacency matrices of individuals (which might arbitrarily remove nodes and degrees) and instead presents results across a range of correlation thresholds (densities).

Then, a smaller density range was obtained by a disconnectivity test and a small-worldness value of 1.5 (0.22–0.44; Hosseini et al., 2012)—these thresholds were used in subsequent calculations of group comparisons. Values smaller than 0.22 or larger than 0.44 should be interpreted with caution as they may be influenced by disconnected graphs or outlying values. We therefore only analyzed values falling within this range. To determine group level differences, individual graph metrics at each density were extracted per condition. We then ran separate mixed measures ANOVAs for each graph metric. Thus, each analysis consisted of a 3 (Group) × 3 (Condition) × 23 (Density) design, where group was the between-subject measure and density was the repeated within-subject measure. Post hoc two-way comparisons were run using Bonferroni corrections. Note that the number of edges is matched per density across individuals.

We focused our analyses on two primary measures: (a) small-worldness, a measure of overall network efficiency (Hosseini et al., 2012; Rubinov & Sporns, 2010), and (b) modularity, or how nodes hierarchically cluster into communities that are more highly connected with each other than nodes outside the community (module). In the GAT toolbox, modularity is calculated with the Louvain algorithm (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008). Modules are often regarded as signs of specialized processing within the network (e.g., Bullmore & Sporns, 2009, 2012; Stevens, Tappan, Garg, & Fair, 2012, but see Kitzbichler et al., 2011).

For visualization purposes, edge matrices were exported from the GAT toolbox and displayed for each group using iGraph (Csardi & Nepusz, 2006), a toolbox that can display 2-D spring-loaded graphs, and BrainNet

Viewer to help situate nodes in anatomical space (www.nitrc.org/projects/bnv/; Xia, Wang, & He, 2013).

RESULTS

Accuracy of *n*-Back Performance

n-back data for four participants was missing. Values for these participants (one morning older adult, one afternoon older adult, and two younger adults) were imputed in SPSS using age, Shipley scores, Mini-Mental State Examination, priming, and Flanker effect scores (i.e., incongruent–congruent RTs). Averages obtained with and without imputation were similar and did not change the results described below.

Accuracy on the *n*-back task was tested separately for each condition (word and nonword) using a simple between-group ANOVA. Accuracy did not differ between groups in the ignore-nonwords condition, $F(2, 47) = 0.92, p = .405$, but did differ on the ignore-words condition, $F(2, 47) = 6.549, p = .003, \eta_p^2 = 0.219$. Post hoc Bonferroni tests revealed that both the morning old ($M = 0.88, SD = 0.14$), $t(32) = 2.5, p = .047$, and afternoon old

($M = 0.82, SD = 0.17$), $t(30) = 3.54, p = .003$, groups differed significantly from the afternoon young group ($M = 0.99, SD = 0.03$), although they themselves did not differ, $t(32) = 1.14, p = .78$. Paralleling our previously reported findings of linearly increasing priming for distraction from afternoon old to morning old to young, we similarly found a significant linear trend describing accuracy on the ignore-words condition, $F(2, 47) = 6.549, p = .003, \eta_p^2 = 0.219$. In line with our previous findings, these results suggest that older adults tested in the afternoon were most distracted on the ignore-words condition.

Between-group Differences in Global Network Measures

In Figures 1 and 2, the group-averaged graph metrics contributing to small-worldness and modularity are displayed for a range of densities. To test for group differences in graph metrics across densities and conditions, we used two mixed-design ANOVAs. Each analysis (modularity and small-worldness) was a 3 (Group) \times 3 (Condition) \times 23 (Density) mixed-measures design. We then used within-condition analyses with post hoc two-way comparisons

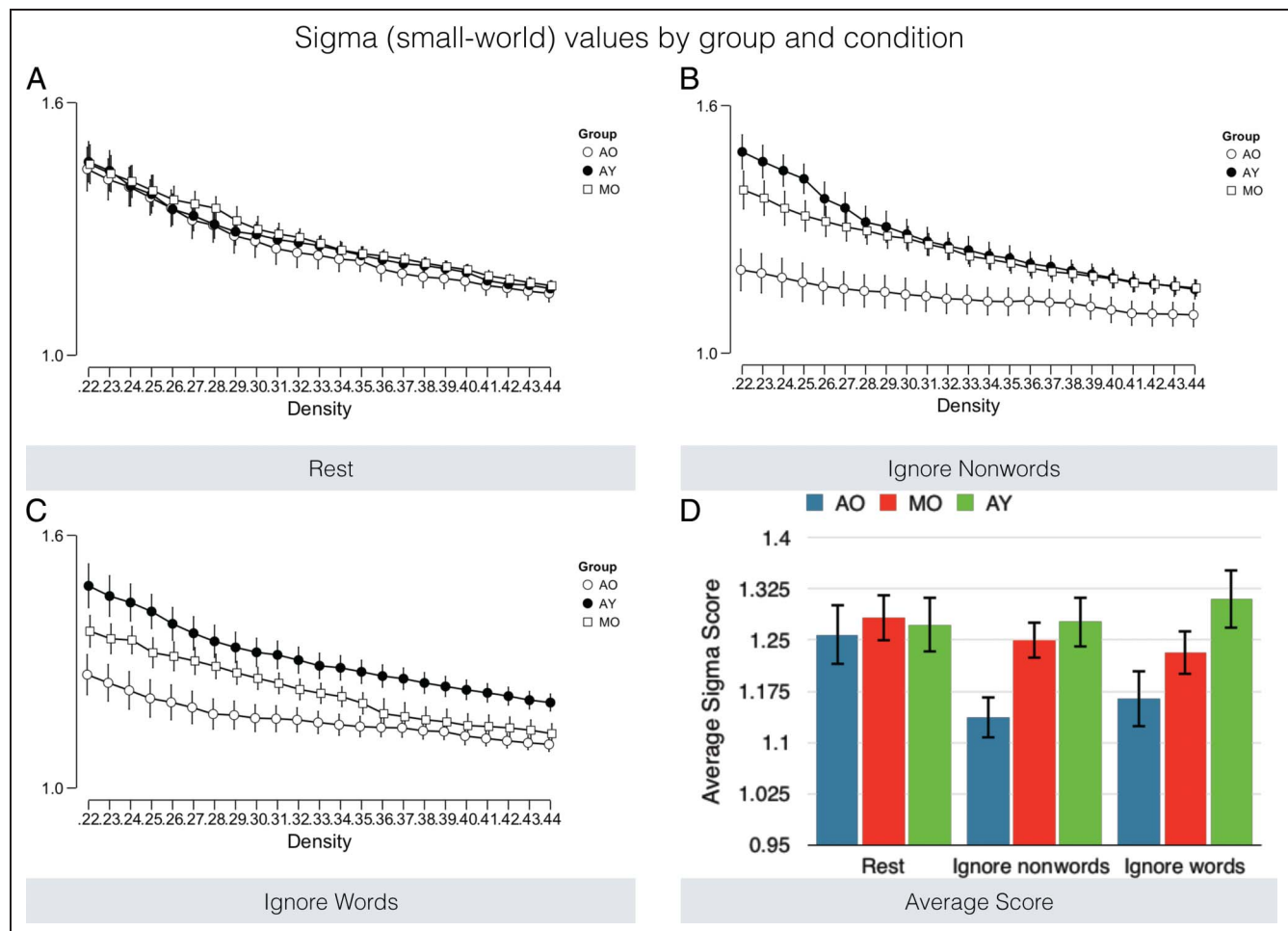


Figure 1. Group differences in global network values (sigma) by condition. Error bars are $\pm 1 SEM$. The graph in the lower right-hand corner of each panel shows the group averages across densities.

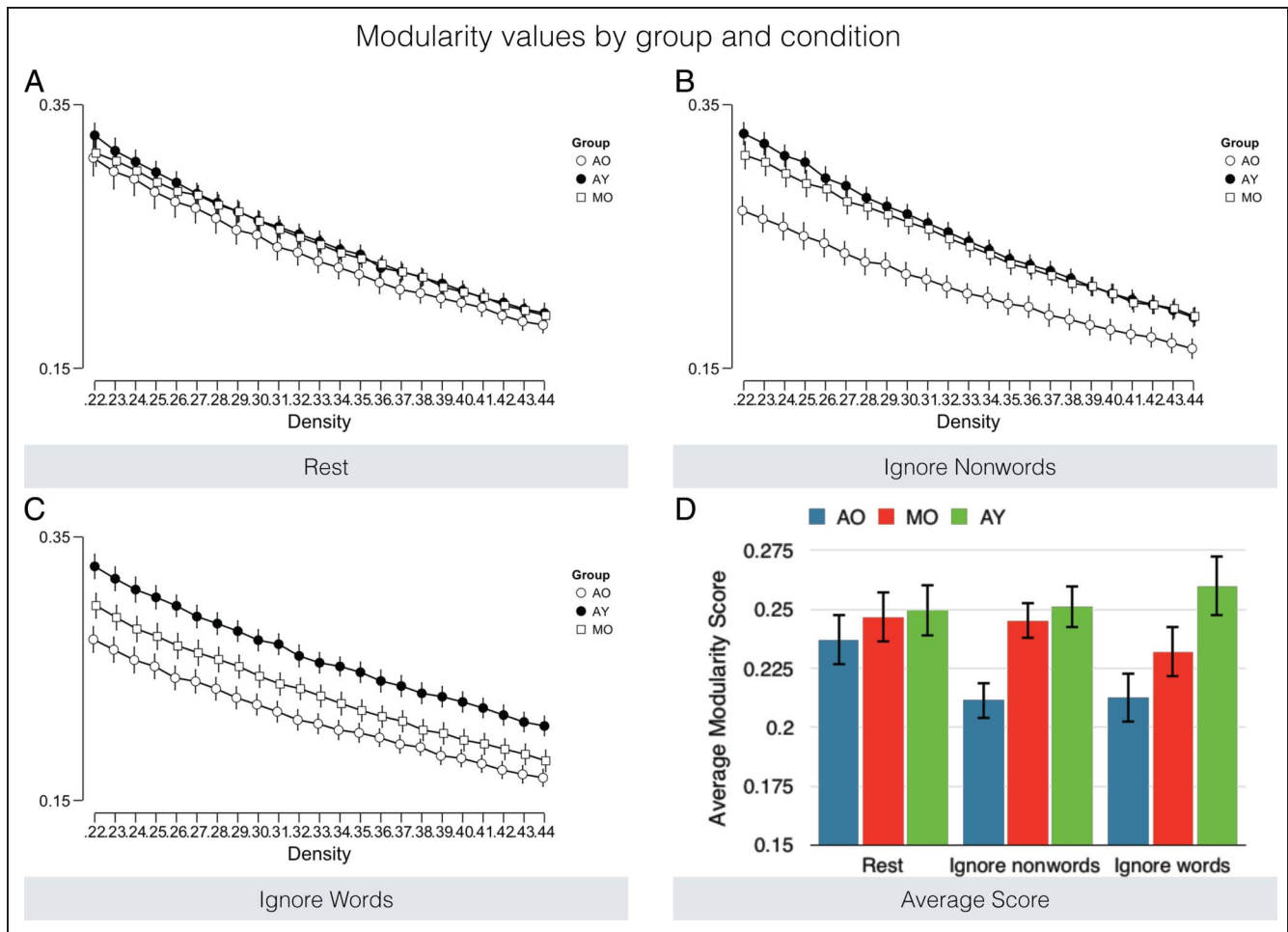


Figure 2. Group differences in global network values (modularity) by condition. Error bars are ± 1 SEM. The graph in the lower right-hand corner of each panel shows the group averages across densities.

to break apart interactions. For Bonferroni-corrected post hoc comparisons, adjusted p values are reported with the original df .

Group Differences in Small-worldness

The three-way interaction between Condition (ignore words, ignore nonwords, and rest), Group (MO, AO, and AY), and Density was significant, $F(88, 2068) = 2.08, p < .001, \eta_p^2 = 0.081$. This suggested that, across density values and conditions, the groups differed in small-worldness. To decompose this significant interaction, we ran three follow-up analyses. First, we assessed group differences in small-worldness at rest (Figure 1A). The main effect of Group was not significant, $F(2, 47) = 0.107, p = .898, \eta_p^2 = 0.005$, suggesting that the groups did not differ. The main effect of Density was significant, $F(22, 1034) = 87.85, p < .001, \eta_p^2 = 0.651$, suggesting that small-worldness during rest changed as a function of graph density. The two-way interaction between Group and Density was not significant, $F(44, 1034) = 0.159, p = 1.00, \eta_p^2 = 0.007$. The lack of significant interaction and the main effect of Group suggest that small-world values

were equivalent across groups during rest. Next, we assessed group differences in small-worldness in the ignore-nonwords condition (Figure 1B). For this condition, the main effect of Group was significant, $F(2, 47) = 5.677, p = .006, \eta_p^2 = 0.195$, as was the main effect of Density, $F(22, 1034) = 91.44, p < .001, \eta_p^2 = 0.661$. Here, the Group \times Density interaction was significant, $F(44, 1034) = 8.348, p < .001, \eta_p^2 = 0.26$. Post hoc Bonferroni tests carried out on mean sigma across densities revealed that the MO and AY groups both differed significantly from the AO group, $t(32) = 2.64, p = .034$, and $t(30) = 3.16, p = .008$, respectively. However, the MO and AY groups did not differ, $t(32) = 0.612, p = 1.00$. Finally, we assessed group differences in small-worldness in the harder ignore-word condition (Figure 1C). The main effect of Group was significant, $F(2, 47) = 3.458, p = .04, \eta_p^2 = 0.128$, as was the main effect of Density, $F(22, 1034) = 77.81, p < .001, \eta_p^2 = 0.623$. The two-way interaction between Group and Density was significant, $F(44, 1034) = 2.72, p < .001, \eta_p^2 = 0.104$. Post hoc Bonferroni tests revealed that the only significant difference was between the AY group and the AO group, $t(30) = 2.63, p = .035$. The values for the MO group fell in between those of the

other two groups but did not differ from either the AO group, $t(32) = 1.25, p = .65$, or the AY group, $t(32) = 1.45, p = .46$. Figure 1D summarizes these effects.

Group Differences in Modularity

The three-way interaction between Condition, Group, and Density was significant, $F(88, 2068) = 1.34, p = .021, \eta_p^2 = 0.054$. This suggested that, across density values and conditions, the groups differed in modularity. As above, to decompose this significant interaction, we ran three follow-up analyses. First, we assessed group differences in modularity at rest (Figure 2A). The main effect of Group was not significant, $F(2, 47) = 0.347, p = .709, \eta_p^2 = 0.015$, suggesting that the groups did not differ. The main effect of Density was significant, $F(22, 1034) = 452.87, p < .001,$

$\eta_p^2 = 0.906$, suggesting that modularity during rest changed as a function of graph density. Here, the two-way interaction between Group and Density failed to reach significance, $F(44, 1034) = 0.447, p = .99, \eta_p^2 = 0.019$. The above nonsignificant main effect of Group and the lack of interaction with Density suggest that, at rest, modularity values were equal across groups. Next, we assessed group differences in modularity during the easier ignore-nonword condition (Figure 2B). The main effect of Group was significant, $F(2, 47) = 6.109, p = .009, \eta_p^2 = 0.206$, as was the main effect of Density, $F(22, 1034) = 953.269, p < .001, \eta_p^2 = 0.953$. Here, the two-way interaction between Group and Density was significant, $F(44, 1034) = 7.159, p < .001, \eta_p^2 = 0.233$. Post hoc Bonferroni-corrected t tests revealed that the MO and AY groups both differed significantly in mean modularity from the AO group,

Table 1. AAL Atlas Regions

Figure Code	AAL Atlas Label	Figure Code	AAL Atlas Label	Figure Code	AAL Atlas Label	Figure Code	AAL Atlas Label
1	Amygdala (L)	26	Lingual (R)	51	SMA (L)	76	Frontal sup medial (R)
2	Amygdala (R)	27	Occipital inf (L)	52	SMA (R)	77	Precentral (L)
3	Caudate (L)	28	Occipital inf (R)	53	Supramarginal (L)	78	Angular (R)
4	Caudate (R)	29	Occipital mid (L)	54	Supramarginal (R)	79	Frontal inf tri (R)
5	Cingulum mid (L)	30	Occipital mid (R)	55	Temporal inf (L)	80	Frontal med orb (L)
6	Cingulum mid (R)	31	Occipital sup (L)	56	Temporal inf (R)	81	Frontal mid orb (L)
7	Cingulum post (L)	32	Occipital sup (R)	57	Temporal mid (L)	82	Precentral (R)
8	Cingulum post (R)	33	Olfactory (L)	58	Temporal mid (R)	83	Precuneus (L)
9	Frontal inf oper (L)	34	Olfactory (R)	59	Temporal pole mid (L)	84	Temporal pole sup (L)
10	Frontal inf oper (R)	35	Pallidum (L)	60	Temporal pole mid (R)	85	Frontal med orb (R)
11	Frontal inf orb (L)	36	Pallidum (R)	61	Temporal pole sup (R)	86	Frontal mid orb (R)
12	Frontal inf orb (R)	37	Paracentral lobule (L)	62	Temporal sup (L)	87	Precuneus (R)
13	Frontal sup (L)	38	Paracentral lobule (R)	63	Temporal sup (R)	88	Calcarine (R)
14	Frontal sup (R)	39	Parahippocampal (L)	64	Thalamus (L)	89	Frontal mid (L)
15	Frontal sup orb (L)	40	Parahippocampal (R)	65	Thalamus (R)	90	Frontal mid (R)
16	Frontal sup orb (R)	41	Parietal inf (L)	66	Rectus (L)		
17	Fusiform (L)	42	Parietal inf (R)	67	Rectus (R)		
18	Fusiform (R)	43	Parietal sup (L)	68	Angular (L)		
19	Heschl (L)	44	Parietal sup (R)	69	Calcarine (L)		
20	Heschl (R)	45	Postcentral (L)	70	Cingulum ant (L)		
21	Hippocampus (L)	46	Postcentral (R)	71	Cingulum ant (R)		
22	Hippocampus (R)	47	Putamen (L)	72	Cuneus (L)		
23	Insula (L)	48	Putamen (R)	73	Cuneus (R)		
24	Insula (R)	49	Rolandic oper (L)	74	Frontal inf tri (L)		
25	Lingual (L)	50	Rolandic oper (R)	75	Frontal sup medial (L)		

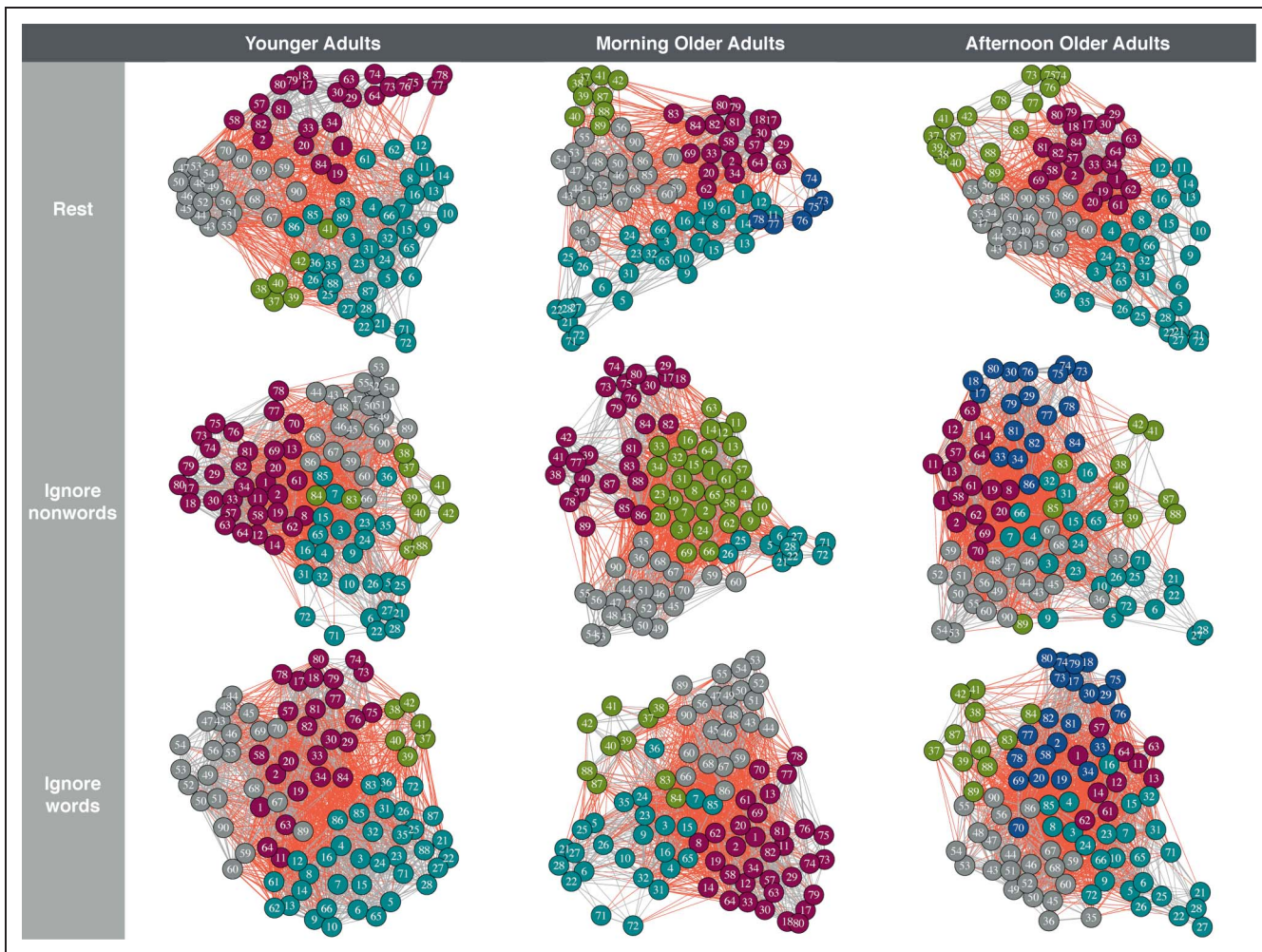


Figure 3. Spring-loaded graphs depicting differences in task-linked network topology by group and condition. Numbers refer to AAL atlas regions (see Table 1). Regions are colored by modularity affiliation (determined in Igraph using the Louvain algorithm; Blondel et al., 2008). To see modules in brain space, see Figure 4. Spring-loaded graphs are represented with the ForceAtlas2 algorithm with 2000 iterations (Jacomy, Venturini, Heymann, & Bastian, 2014). Within-module connections are depicted with gray lines; between-module connections are depicted with orange lines. To see the nodes in brain space, please go to [dx.doi.org/10.6084/m9.figshare.3502196.v1](https://doi.org/10.6084/m9.figshare.3502196.v1).

$t(32) = 2.83, p = .021$, and $t(30) = 3.217, p = .007$, respectively. Yet, the MO and AY groups did not differ, $t(32) = 0.48, p = 1.00$. Finally, we assessed group differences in modularity in the harder ignore-word condition (Figure 2C). The main effect of Group was significant, $F(2, 47) = 4.229, p = .020, \eta_p^2 = 0.153$, as was the main effect of Density, $F(22, 1034) = 856.498, p < .001, \eta_p^2 = 0.948$. The two-way interaction between Group and Density was significant, $F(44, 1034) = 1.736, p = .002, \eta_p^2 = 0.069$. Post hoc Bonferroni tests revealed that the only significant difference was between the AY group and the AO group, $t(30) = 2.89, p = .017$. The MO group did not differ from either the AO group, $t(32) = 1.23, p = .68$, or the AY group, $t(32) = 1.75, p = .26$. Thus, the results for small-worldness and modularity were similar in showing differences between the AO group and the other two groups (see Figure 2D). Note that, although there is a clear interaction between Modularity/sigma and Density \times Group suggesting that the graph metrics are changing differently across

graph densities, these interactions may be due to larger group effects at lower densities (i.e., in the strongest correlations). It is possible that older adults draw upon weaker connections in the higher-density networks to compensate; however, given that how density affects graph metrics is not our primary research question, we suggest that this is an avenue for future research.

Figure 3 illustrates how time of testing affected the topological organization of the functional networks during each of the three conditions. It should be noted that differences depicted in this figure are descriptive, and we have not carried out any statistical between-group comparisons because the node-to-module assignments differ across the groups.

Overall, the networks in the MO and AY groups can be classified into four main modules or subgraphs. Green modules predominantly involve the medial-temporal lobes bilaterally, bilateral insula, and SMA—in young adults, this subgraph resembles the salience network.

Gray modules are largely consistent with the visual/dorsal attention networks and are remarkably stable both across conditions and age groups. Purple regions include dorso-lateral pFC in young adults and are consistent with the frontoparietal control network in older adults (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Turquoise regions are consistent with a midline network/DMN (Raichle & Snyder, 2007).

Variations in modular organization are also apparent. In young adults, for example, the purple module appears to be localized to frontal regions and does not include parietal nodes as it does in the older groups. The turquoise midline/default module in young adults is much denser relative to older adults and includes nodes from both the frontoparietal (e.g., anterior cingulate) and default (e.g., angular gyrus and medial frontal cortex) networks. Another difference of some note is that older adults tested in the afternoon have an additional submodule representing the frontal and parietal regions in the two task conditions (dark blue module). This division is completely absent during the tasks in the AY and MO groups. This split in the AO group between frontal and parietal subgraphs occurring only in the two task conditions parallels the differences described in global metrics (i.e., older adults tested in the afternoon maintain network integrity at rest but not under the additional cognitive load of a task).

Correlations of Graph Metrics with Priming for Distraction

One motivation for examining how time of testing affects network changes during task was to predict behaviors that typically show large circadian variation. Previous research has demonstrated that tasks requiring top-down

control and especially those involving an inhibitory component are particularly susceptible to time-of-day influences, whereas measures of crystallized intelligence or semantic knowledge are not (Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1999; Yoon et al., 1999; May & Hasher, 1998; May, Hasher, & Stoltzfuz, 1993). We therefore predicted that graph metrics indicating better network performance (i.e., higher modularity and small-worldness) would correlate with better performance on tasks requiring attention regulation—in this case, inhibitory control of irrelevant information and the Flanker effect (for more information on this measure, please see Anderson et al., 2014)—but show little to no relationship with a measure of crystallized intelligence, the Shipley—which has been demonstrated not to vary with arousal (Park et al., 2002; Salthouse, 1996; Horn & Cattell, 1967).

We extracted individual graph metrics (small-worldness and modularity), averaged them across densities, and correlated them with priming for distraction (i.e., how likely participants were to generate previously seen distracting words relative to never before seen words in the fragment completion task; see Figure 4 and Table 2). Across groups, higher values of modularity and small-worldness (σ) predicted less priming for distraction—particularly at rest. In contrast, the Flanker effect was best predicted by modularity and σ during the ignore-words condition, as might be expected given that the latter was the most difficult condition. As expected, there was no relationship between the graph theory metrics and vocabulary. These correlations, as well as the graph metric data shown in Figures 1 and 2, indicate that adding a cognitive load not only appears to drive down levels of global modularity and small-worldness, particularly at nonoptimal times of day in the older adults, but also decreases the strength of correlations between these graph metrics and interference control.

Figure 4. Relationship between modularity and priming for distraction by condition. Dotted lines represent the 95% confidence ellipse for each group. Gray shaded regions indicate the 95% confidence estimate for the regression line. Modularity was chosen as an exemplar measure; similar relationships were observed with small-worldness (see text).

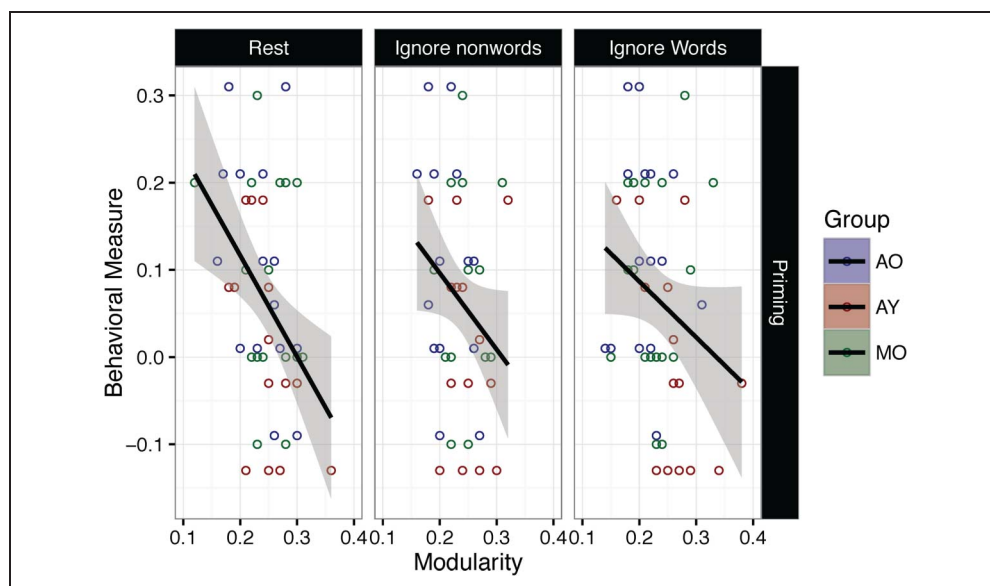


Table 2. Relationship between Graph Metrics and Behavior

			<i>Bayesian Pearson Correlation</i>			
<i>Correlation Between</i>			<i>r</i>	<i>BF₁₀</i>	<i>p</i>	<i>Strength of Evidence from Bayes Factor</i>
Rest	Modularity	Priming for distraction	-.408	11.915	.003	Decisive
	Sigma	Priming for distraction	-.328	2.454	.02	Substantial
	Modularity	Flanker effect	-.04	0.183	.784	Barely worth mentioning
	Sigma	Flanker effect	-.008	0.177	.955	Barely worth mentioning
	Modularity	Shiplay	-.01	0.177	.994	Barely worth mentioning
	Sigma	Shiplay	.036	0.182	.802	Barely worth mentioning
Ignore nonwords	Modularity	Priming for distraction	-.267	0.975	.061	Barely worth mentioning
	Sigma	Priming for distraction	-.285	1.246	.045	Barely worth mentioning
	Modularity	Flanker effect	-.172	0.352	.233	Barely worth mentioning
	Sigma	Flanker effect	-.213	0.513	.138	Barely worth mentioning
	Modularity	Shiplay	-.141	0.281	.328	Barely worth mentioning
	Sigma	Shiplay	-.122	0.249	.4	Barely worth mentioning
Ignore words	Modularity	Priming for distraction	-.253	0.807	.077	Barely worth mentioning
	Sigma	Priming for distraction	-.241	0.706	.091	Barely worth mentioning
	Modularity	Flanker effect	-.357	4.125	.011	Strong
	Sigma	Flanker effect	-.332	2.632	.018	Substantial
	Modularity	Shiplay	-.068	0.196	.638	Barely worth mentioning
	Sigma	Shiplay	-.031	0.18	.831	Barely worth mentioning

Bayes factors are provided along with strength of evidence for the effect. Note that the relationship between modularity at rest and priming for distraction is “decisive,” whereas the relationship between modularity during the ignore-words condition and the Flanker effect is “strong” (Jaynes, 2003).

DISCUSSION

Our research shows that time of testing in older adults affected their brain network organization. We used graph theory to show that the brain networks of older adults tested in the morning resembled those of younger adults. This was not the case for older adults tested in the afternoon. In particular, older adults tested in the morning have similar small-worldness to younger adults. Both of these groups had more small-world network organization than older adults tested in the afternoon. Given that ~75% of adults aged 66 years and older are morning types, our findings have relevance to an increasingly large demographic (Hasher, Goldstein, & May, 2005; May et al., 1993).

Although we did not explicitly define functional networks a priori, we did find functionally connected regions that resemble known networks. These data-driven clusters include the salience, visual/dorsal attention, and mid-line network/DMN. The DMN is more active during rest, unlike the task-positive network (Buckner, Andrews-Hanna, & Schacter, 2008; Toro, Fox, & Paus, 2008; Fox et al., 2005; Raichle et al., 2001). This latter network can

be further subdivided into the frontoparietal and dorsal attention networks. These task-related networks may mediate cognitive control and decision-making and externally oriented attention (Spreng et al., 2013; Vincent et al., 2008). Despite independent identification of networks for each group, we note a conservation of structure. Thus, most networks were identifiable for each group regardless of age and time of testing. These networks were also comparable with previously reported descriptions of the DMN and task networks (Buckner et al., 2008; Toro et al., 2008; Fox et al., 2005; Raichle et al., 2001).

A network with high modularity has dense intramodule connections and sparse intermodule connections. Older adults typically have lower modularity scores and different modular organization than younger adults (e.g., Onoda & Yamaguchi, 2013; Meunier et al., 2009). In our sample, older adults tested in the morning had equivalent modularity scores to young adults during the tasks, whereas older adults tested in the afternoon had modularity levels equivalent to those seen in young adults only at rest. In addition, the AY and MO groups had similar network topography across rest and task conditions, suggesting

maintenance of network integrity from rest to task states in these groups. We also observed that, for older adults tested in the afternoon, the frontoparietal submodule split into two components during the tasks (i.e., separate frontal and parietal modules). By contrast, the other two groups did not have the same degree of network reorganization in response to changing conditions. This implies that older adults tested in the afternoon were unable to maintain the rest network structure as task demands increased. Our findings broadly agree with theories of aging suggesting that older adults engage task-related brain regions at lower levels of cognitive load than younger adults, which then decrease as load increases (Reuter-Lorenz & Cappell, 2008). In short, older adults tested in the afternoon appear to show load-related increases in modularity and sigma values at lower levels of cognitive load than older adults tested in the morning. This suggests that older adults are better able to respond to cognitive demands when they are at peak levels of alertness.

Higher modularity scores in young adults derived from intrinsic control networks in resting state fMRI have been associated with greater working memory capacity (Stevens et al., 2012). Modularity also predicted the consistency of cognitive performance across multiple sessions. In this case, modularity's role may be to regulate signal or suppress noise before it propagates through the network (Stevens et al., 2012). The idea that noise propagation is reduced with higher modularity is interesting in light of the of inhibitory control theory of attention and memory (Lustig, Hasher, & Zacks, 2004; Hasher et al., 1999). This theory postulates that age differences emerge from a failure to suppress irrelevant environmental stimuli or errant thought processes. These irrelevant items then get integrated into the same representation as attended/to-be-remembered items. Memory failures thus result from having to process too much information rather than too little (Healey, Ngo, & Hasher, 2014; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Hasher et al., 1999; Anderson & Spellman, 1995). Higher modularity may therefore be an index of network inhibitory control of "noise"/irrelevant information. In support of this idea, we found that higher modularity reflected better on-task performance, as seen here in reduced priming from previously seen distraction. We note that others have found contradictory evidence for the role of modularity in working memory. Kitzbichler et al. (2011), for example, found that increasing levels of modularity were associated with worse performance in a young adult sample (mean age = 29.5 years) as task difficulty increased (they used a 1- and 2-back working memory tasks). A possible explanation for the discrepancy between the present results and those of Kitzbichler et al. is that the latter tested only young adults and used both a 1- and 2-back variant of the n-back task. Our study used only a 1-back variant, and our young adults were at ceiling levels of performance. In addition, our level of "difficulty" was in the distracting nature of the interfering

information, not working memory load per se. Thus, it is difficult to compare our results with those of Kitzbichler et al., and future work will need to assess modularity in young and older adults in relation to parametrically increasing task demand to fully address the conditions that lead to increased or decreased modularity as a function of cognitive load.

Our results agree with, and extend, previous studies examining circadian effects on behavioral and neuroimaging measures (Anderson et al., 2014; Blautzik et al., 2014; Peres et al., 2011; Schmidt et al., 2007; Hasher et al., 2005). We previously reported that time-of-day effects are observed in a task requiring inhibitory control, namely, priming for distraction, echoing previous research suggesting that time of testing selectively affects fluid cognitive processes rather than crystallized or semantic processes (Hahn et al., 2012; Goldstein et al., 2007; Schmidt et al., 2007; Hasher et al., 2005). In the analyses reported here, we found that priming for distracting verbal information (a measure reflecting inhibitory control over irrelevant information) correlated with graph metrics. Better inhibition of distraction was correlated with greater small-worldness and more highly modular networks. Importantly, the Shipley vocabulary score, a measure of crystallized intelligence, did not correlate with the graph metrics—nor would we expect it to be based on the previous literature cited above.

One limitation of our study is that the design was not fully crossed in that young adults were not tested at their nonoptimal times of day (the morning). Our rationale for this choice was that we wanted to focus on older adults in whom the synchrony effects on behavior are largest. That is, although younger adults show time-of-day-based performance differences in sentence recognition, working memory, long-term memory, forgetting of story materials, and priming for distraction (for a review, see Hasher, Goldstein, & May, 2005), across all of these effects, older adults typically show a synchrony effect that is twice as large as those seen in young adults. This suggests that young adults, although not immune to time-of-day effects, are less vulnerable to them than older adults. Given the decrease in magnitude of behavioral synchrony effects for young adults and the general lack of change in network topology that we observed across conditions in the young group, we suggest that detecting network changes in young adults across the day likely is possible but would require a very large sample and perhaps a more targeted approach with networks of interest chosen a priori.

Our study shows that functional networks respond dynamically to time of day as they would to an external stressor, such as a challenging task (Grady et al., 2010; Greicius, 2008; Wang et al., 2007). Indeed, we find that time of day interacts with task demands, such that there were no age differences evident at rest but marked reductions in modularity and small-worldness in the AO group in the most demanding condition. Given that circadian rhythms are known to affect heart rate (Roesser

et al., 2012) and glucose consumption in the brain (Buysse et al., 2004), both of which are known to impact the BOLD signal, it is unsurprising that we are able to observe circadian-driven differences in BOLD signal itself. Future research should investigate whether time of testing differentially influences the neural and vascular contributions to the BOLD signal. In addition, small-worldness and modularity are considered to be important indicators of disease processes, including mild cognitive impairment, Alzheimer's disease, and schizophrenia, (e.g., Fornito, Zalesky, Pantelis, & Bullmore, 2012; Sun, Tong, & Yang, 2012; Zhao et al., 2012; Sanz-Arigita et al., 2010; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Micheloyannis et al., 2006). Our data suggest that it would be useful to routinely measure time of testing and chronotype, especially when scanning cognitively demanding tasks with an elderly participant pool.

Conclusions

We show that, for older adults, both behavior and brain network characteristics are maintained in the morning and diminished in the afternoon and that these effects interact with task demands. There were no measurable age differences in the 1-back performance for the easier ignore-nonword condition as well as no age differences in network topology at rest. However, carrying out a task, especially one with a significant cognitive demand (i.e., inhibiting distracting words), was accompanied by robust differences between the AO group and younger adults in graph metrics but maintained levels of modularity and small-worldness in the MO group. Furthermore, across groups, higher levels of modularity and small-worldness were related to reduced priming for distraction and faster Flanker effects (in the ignore-words condition). Therefore, this study underscores the necessity of neuroimaging studies to take time of day into account, particularly when interpreting differences because of aging. This factor is vital for future replication studies because functional connectivity varies both within an experimental session and across the day (Calhoun, Miller, Pearlson, & Adali, 2014).

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Reprint requests should be sent to John A. E. Anderson, 5030 TEL Building, York University, 4700 Keele St., Toronto, ON M4P 1P3, Canada, or via e-mail: johnaeanderson@gmail.com.

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