



Dissociable Effects of Aging on Salience Subnetwork Connectivity Mediate Age-Related Changes in Executive Function and Affect

Alexandra Touroutoglou^{1,2*}, Jiahe Zhang³, Joseph M. Andreano^{2,4},
Bradford C. Dickerson^{2,5†} and Lisa Feldman Barrett^{2,3,4†}

¹Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States,

²Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, ³Department of Psychology, Northeastern University, Boston, MA, United States, ⁴Psychiatric

Neuroimaging Division, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, ⁵Frontotemporal Disorders Unit, Department of Neurology, Massachusetts General Hospital, Harvard Medical

School, Boston, MA, United States

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*Correspondence:

Alexandra Touroutoglou
atouroutoglou@mgh.harvard.edu

[†]These authors have contributed
equally to this work and share senior
authorship

Received: 21 September 2018

Accepted: 28 November 2018

Published: 17 December 2018

Citation:

Touroutoglou A, Zhang J,
Andreano JM, Dickerson BC and
Barrett LF (2018) Dissociable Effects
of Aging on Salience Subnetwork
Connectivity Mediate Age-Related
Changes in Executive Function
and Affect.
Front. Aging Neurosci. 10:410.
doi: 10.3389/fnagi.2018.00410

Aging is associated with both changes in affective experience and attention. An intrinsic brain network subserving these functions, the salience network, has not shown clear evidence of a corresponding age-related change. We propose a solution to this discrepancy: that aging differentially affects the connectivity of two dissociated subsystems of the salience network identified in our prior research (Touroutoglou et al., 2012). We examined the age-related changes in intrinsic connectivity between a dorsal and a ventral salience subsystem in a sample of 111 participants ranging in age from 18 years to 81 years old. We predicted that connectivity within the ventral subsystem is relatively preserved with age, while connectivity in the dorsal subsystem declines. Our findings showed that the connectivity within the ventral subsystem was not only preserved but it actually increased with age, whereas the connectivity within the dorsal subsystem decreased with age. Furthermore, age-related increase in arousal experience was partially mediated by age-related increases in ventral salience subsystem, whereas age-related decline in executive function was fully mediated by age-related decreases in dorsal salience subsystem connectivity. These findings explain previously conflicting results on age-related changes in the salience network, and suggest a mechanism for relatively preserved affective function in the elderly.

Keywords: resting-state fMRI, salience network subsystems, aging, executive function, arousal

INTRODUCTION

Substantial evidence indicates that both affect and executive function change as people age, and these changes offer challenges for healthy aging. Elderly people are more easily aroused than are young people and tend to experience arousal as unpleasant (Smith et al., 2005; Gavazzeni et al., 2008; Gruhn and Scheibe, 2008; Moriguchi et al., 2011; Sands and Isaacowitz, 2017). Intense, unpleasant arousal is linked to an increased risk of illness (Cacioppo, 1994; Ong and Allaire, 2005), including cardiovascular disease (Steptoe and Kivimaki, 2012), stroke (Henderson et al., 2013), metastasis of cancer (Garssen, 2004) and metabolic syndrome (Tamashiro, 2011). Age-related decline in

attention and executive function (Verhaeghen and Cerella, 2002; Lustig and Jantz, 2015; Hedden et al., 2016) impairs cognitive performance across diverse domains (Wascher et al., 2011; Clapp and Gazzaley, 2012) and increases the risk for injury when walking or driving (Sheridan and Hausdorff, 2007). Understanding the mechanisms of age-related changes in affect and attention may help to identify factors important for healthy aging, as well as shed light on normal brain function throughout the lifespan.

Both affective processing and executive function are linked to the brain's salience network, a group of structures connected at rest including the anterior insula (AI), dorsal anterior and mid-cingulate cortex (ACC/MCC) and amygdala (Seeley et al., 2007; Touroutoglou et al., 2012).

The strength of connectivity within this network in young adults predicts subjective experiences of anxiety (Seeley et al., 2007), cortisol responsivity (Thomason et al., 2011) and feelings of arousal (Touroutoglou et al., 2012, 2014). Major nodes of the salience network, particularly the AI and ACC/MCC, have also been implicated in various features of executive function, including the orienting of attention (Corbetta and Shulman, 2002), cognitive control (Cole et al., 2013) and performance monitoring (Dosenbach et al., 2007).

This diversity of brain-behavioral relationships within the salience network may be explained by recent evidence suggesting that the salience network is composed of two dissociable subsystems, defined by their connectivity to the dorsal and ventral AI (vAI). These two regions of insula have different patterns of connectivity in macaques (Touroutoglou et al., 2016) and humans (Taylor et al., 2009; Kurth et al., 2010; Cauda et al., 2011; Deen et al., 2011; Kelly et al., 2012; Touroutoglou et al., 2012; Chang et al., 2013; Uddin et al., 2014). In healthy young adults, connectivity within the ventral salience subsystem has been associated with affect whereas connectivity within the dorsal salience subsystem has been associated with executive function (Touroutoglou et al., 2012).

Studies of age-related changes in the integrity of the salience network have shown conflicting results, with decreased age-related connectivity in some cases (Allen et al., 2011; Onoda et al., 2012; He et al., 2013, 2014; Roski et al., 2013; Langner et al., 2015), but preserved or increased connectivity in others (Wang et al., 2012; Cao et al., 2014; Sakaki et al., 2016; Xiao et al., 2018); this is in contrast to clear reductions in connectivity with age in default mode and fronto-parietal networks (Andrews-Hanna et al., 2007; Esposito et al., 2008; Biswal et al., 2010; Wang et al., 2010, 2012; Campbell et al., 2012; Onoda et al., 2012; Betzel et al., 2014; He et al., 2014; Zhang et al., 2014; Shaw et al., 2015; Ward et al., 2015). A closer look at these studies show that those reporting preserved or increased connectivity with age have focused on connectivity to limbic structures within the ventral salience subnetwork such as the amygdala (Wang et al., 2012; Cao et al., 2014; Sakaki et al., 2016; Xiao et al., 2018). In contrast, studies showing decreased salience network connectivity with aging have focused on nodes within the dorsal salience network (Allen et al., 2011; Onoda et al., 2012; He et al., 2013; Roski et al., 2013; Langner et al., 2015). The differential rates of age-related functional connectivity changes are consistent with

rates of atrophy. The ventral salience subnetwork contains more agranular cortex, which atrophies more slowly with age when compared to cortex with a granular cytoarchitecture, such as the lateral frontal and parietal regions in the dorsal salience, default mode or fronto-parietal networks (Salat et al., 2004; Fjell et al., 2009, 2014; McGinnis et al., 2011).

In the present study, we hypothesized that the dorsal and ventral salience subnetworks are differentially affected by aging. We predicted that connectivity within the ventral subsystem is relatively preserved with age, while connectivity in the dorsal subsystem declines. We further predicted that age-related changes in stimulus-evoked arousal and executive function are mediated by differences in functional connectivity in the ventral and dorsal salience subsystems, respectively.

MATERIALS AND METHODS

Participants

One hundred eleven adults ranging in age from 18 to 81 (mean age = 46.6, SD = 18.89; 56 females) participated in this study, which involved the collection of resting-state blood oxygenation-level dependent (BOLD) data as well as behavioral and task-evoked data. All participants were right-handed, native English speakers and had normal or corrected-to-normal vision. No participant reported a history of neurological or psychiatric disorders. The protocol of this study was approved by the Institutional Review Board of the Massachusetts General Hospital. All subjects gave written informed consent.

Behavioral Data Acquisition

Affective Experience

Ninety full-color images were selected from the International Affective Picture System (IAPS) to induce affective experiences (Lang et al., 2008). Participants viewed each of the IAPS images on a 120 × 75 cm high definition (Sharp, Aquos) screen placed 2 m from the participant. The images represented five combinations of valence and arousal (i.e., negative valence-high arousal, positive valence-high arousal, negative valence-low arousal, positive valence-low arousal, neutral valence-low arousal). Images were grouped into three blocks of 30 images. Each block contained six images from each of the five valence and arousal categories. To avoid order effects, we randomized the order of the blocks and the order of images within each block during stimulus presentation. For each stimulus, participants viewed the IAPS image for 6 s, then rated the valence and arousal of the image using the Self-Assessment Manikin (SAM; Bradley and Lang, 1994). Only the arousal ratings are reported here, which ranged from "Very calm" (1) to "Very activated" (5). A variable inter-trial interval of 10–15 s followed the rating prior to presentation of the next image. Before beginning the task, participants were familiarized with the SAM rating procedure and practiced by rating five images. The images and rating scales were administered via E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA).

Because the ventral salience network connectivity has been associated with high arousal states such as anxiety

TABLE 1 | Demographic and neuropsychological characteristics.

Measure	Mean	Minimum	Maximum	Std. Dev.	Std. Error
N	111				
Sex (% female)	49.5				
Age (years)	46.65	18.00	81.00	18.90	1.79
Education (years)	16.10	12.00	20.00	2.21	0.21
Trail Making Test B (s)	57.59	19.00	165.00	21.89	2.08
Arousal ratings (5-point scale)	4.58	3.60	5.00	0.40	0.04

Note: $N = 110$ for education; $N = 108$ for arousal ratings. We applied a negative log transformation to Trail Making Test B scores for subsequent analyses.

(Seeley et al., 2007) or high arousal responses to negative images (Touroutoglou et al., 2012), we focused on high arousal stimuli. For each participant, we obtained a high arousal rating in response to negative evocative images (referred to hereafter as arousal ratings in response to negative images) by calculating the average arousal ratings for all high arousal negative images. In addition, we obtained a high arousal rating in response to positive evocative images (referred to hereafter as arousal ratings in response to positive images) by calculating the average arousal ratings for all high arousal positive images. We removed data for three participants whose arousal ratings were outliers (3 standard deviations below the group mean). We conducted subsequent analyses including arousal ratings with the remaining 108 participants.

Executive Function

Executive function, processing speed and set-switching was measured with the Trail Making Test administered before the scans (Reitan, 1958; Strauss et al., 2006). For each participant, the Trail Making Test B (Trails B) score reflected the time in seconds taken to complete the part B of the test, which is thought to require processing speed, visuomotor speed and set-shifting (Strauss et al., 2006). Because the distribution of the Trails B completion time was positively skewed (skewness >1.32), we performed a log transformation on this data. We also inverted the log of Trails B time such that higher Trails B scores indicate better performance. Demographic and neuropsychological characteristics are summarized in **Table 1**.

Magnetic Resonance Imaging (MRI) Data Acquisition and Preprocessing

Participants underwent brain imaging on a different day, on average less than 1 week after the behavioral session. Imaging data were collected on a 3T Magnetom Tim Trio system (Siemens Medical Systems, Iselin, NJ, USA) at Massachusetts General Hospital, equipped for echo planar imaging (EPI) with a 12-channel phased-array head coil. Head motion was minimized using head restraints, including a pillow and foam padding. Noise was attenuated with ear plugs. Structural magnetic resonance imaging (MRI) data were acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2,530 ms/3.48 ms/7°, resolution = 1.0 mm isotropic, FoV = 256 mm, 0% slice gap).

Whole-brain resting state functional MRI (fMRI) data were acquired with echo-planar sequence (TR = 5,000 ms; TE = 30 ms; FA = 90°, FoV = 256 mm, 0% slice gap). These parameters allowed us to obtain 55 slices and have a spatial resolution of

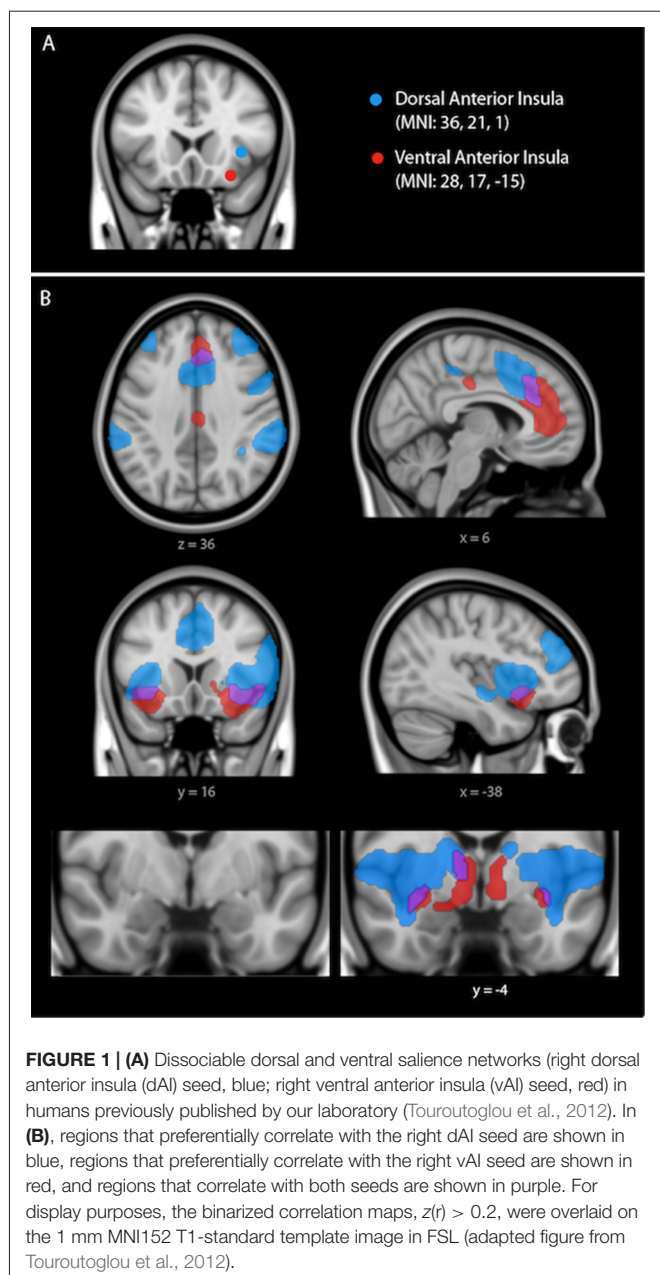
2.0 mm isotropic voxels. The resting state scan was 6.40 min long and the data involved one run of 76 volumes. During all resting-state fMRI (rs-fMRI) runs, participants were directed to keep their eyes open without fixating and to remain as still as possible. Resting state fMRI runs preceded the task-based fMRI runs.

Preprocessing of the resting state fMRI data involved a series of previously established resting state functional connectivity MRI (rs-fcMRI) procedures (Biswal et al., 1995; Vincent et al., 2007; Van Dijk et al., 2010). After removing the first four functional volumes, the following steps were completed: correction for slice-dependent time shifts (SPM2, Wellcome Department of Cognitive Neurology, London, UK), correction for head motion with rigid-body transformation in three translation and three rotations (FMRIB, Oxford, UK), spatial normalization to Montreal Neurological Institute (MNI) atlas space, re-sampling to 2 mm isotropic voxels, spatial smoothing using a 6 mm full width at half-maximum (FWHM) Gaussian kernel, and temporal band-pass filtering to remove frequencies >0.08 Hz. We then removed sources of spurious variance and their temporal derivatives from the data through linear regression (six parameters derived from the rigid-body head motion correction, the signal averaged over the whole brain, the signal averaged over a region within the deep white matter, and the signal averaged over the ventricles) and the residual BOLD time course was retained for functional connectivity analysis.

Resting State fMRI Analysis

To examine the intrinsic functional connectivity strength within the dorsal and ventral salience subsystems, we used seed-based rs-fcMRI analysis. We took a hypothesis-driven approach and created spherical regions of interest (ROIs; 4-mm radius) around major nodes within each salience subsystem as determined in Touroutoglou et al. (2012; see **Figure 1**). In that study of young adults, the strength of connectivity within the dorsal salience subsystem predicted individual differences in executive function and the strength of connectivity within the ventral salience subsystem predicted individual differences in the intensity ratings of arousal in response to negative images.

We computed Pearson's product moment correlations, r , for the mean signal time courses of each pair of ROIs. Fisher's r -to- z correlation coefficients were then calculated between each ROI pair. To calculate the connectivity within the dorsal salience subsystem, we computed the pairwise connectivity measure of $z(r)$ values between the dorsal anterior insula (dAI; right dAI coordinates: +36, 21, 1, MNI) and a bilateral region in the mid



cingulate (MCC; right MCC coordinates: +4, 16, 46; left MCC coordinates: -2, 14, 46) as determined in Touroutoglou et al. (2012). To calculate the connectivity within the ventral salience subsystem, we computed a pairwise connectivity measure of $z(r)$ values between the right vAI (right vAI coordinates: +28, 17, -15) and a region in the dorsal amygdala (right amygdala coordinates: +30, -2, -18) found in Gerdes et al. (2010) to predict feelings of arousal during task. This region has been shown to be critical for subjective arousal in a variety of other studies (Phan et al., 2004; Barrett et al., 2007; Wilson-Mendenhall et al., 2013; Touroutoglou et al., 2014). The averaged pairwise connectivity measure of $z(r)$ values of each pair of ROIs was then used for the analyses of the brain-behavioral relationships with aging.

Brain-Behavior Relationships

Using a series of linear regression analyses, we first examined the entire sample to determine whether the dissociable relationships between salience subsystem connectivity and behavior that we previously found in an independent sample of young adults (Touroutoglou et al., 2012) would replicate in this sample of adults spanning a broad age range. Specifically, to examine the relationship between ventral salience subsystem connectivity and arousal ratings in response to negative images, we conducted a linear regression analysis using vAI connectivity to amygdala (pairwise connectivity measure of $z(r)$ values of the right vAI with right amygdala) and arousal ratings as the dependent variable. Additionally, to investigate the possibility that ventral salience connectivity might similarly influence arousal responses to positively valenced stimuli, we repeated this analysis using high arousal, positively valenced stimuli. To examine the relationship between dorsal salience subsystem connectivity and executive function, we conducted a linear regression analysis using dAI connectivity to MCC (averaged pairwise connectivity measure of $z(r)$ values of the right dAI with left and right MCC) as independent variable and executive function as the dependent variable. We then examined the effects of age on connectivity and behavior. For all these analyses, we controlled for potential effects of sex and education. Brain-behavior analyses were conducted using PASW Statistics 21, Release Version 21.0.0 (SPSS Inc., 2009, Chicago, IL, USA¹). Results were considered statistically significant at $p < 0.05$.

Salience Subsystem Connectivity Mediation of the Relationship Between Age and Behavior

We first examined the potential mediating effects of ventral salience subsystem connectivity on the relationship between age and arousal ratings. In Step 1 of our mediation analysis, arousal ratings were regressed on age to examine the total effect of age on subjective arousal (path a). We conducted a linear regression analysis using age as the independent variable and arousal ratings as the dependent variable. Next, we tested whether ventral salience subsystem connectivity mediated the above relationship between age and ratings of arousal. Specifically, in Step 2 of the analysis, the ventral salience subsystem connectivity was regressed on age (path b). We conducted a linear regression analysis using age as the independent variable and ventral salience subsystem connectivity values as the dependent variable. In Step 3 of our mediational analysis, we performed another multiple regression analysis where we regressed the arousal ratings on both age (path a') and ventral salience subsystem connectivity (path c). In Step 4, we compared the standardized regression coefficients (beta) of the age predictor computed at Step 1 (path a: total effect) and Step 3 (path a': direct effect) to test the amount of mediation (path bc: indirect effect) by the ventral salience subsystem connectivity predictor (Baron and Kenny, 1986). A Sobel test (Sobel, 1982; Preacher and Hayes, 2008) was conducted to test the significance of mediation. Results were considered statistically

¹www.spss.com

significant at $p < 0.05$. We repeated the same analysis procedure to examine whether dorsal salience subsystem connectivity mediated the relationship between age and executive function. Mediation analyses were conducted using PASW Statistics 21, Release Version 21.0.0 (SPSS Inc., 2009, Chicago, IL, USA¹).

Data Availability

The data for this study are available on request.

RESULTS

Brain-Behavior Relationships

As in our previous study (Touroutoglou et al., 2012), we used rs-fMRI analyses and replicated the dissociable relationships between salience subsystems and behavior in our independent sample including young, middle-aged and older individuals (see **Figure 2**). As in Touroutoglou et al. (2012), the strength of connectivity within the ventral salience subsystem predicted individual differences arousal ratings in response to negative images ($R^2 = 0.06$, $r = 0.25$, $p = 0.000$) but not in Trails B performance ($R^2 = 0.005$, $r = -0.07$, $p = 0.48$), whereas the dorsal salience subsystem predicted individual differences in Trails B performance ($R^2 = 0.06$, $r = 0.24$, $p = 0.013$) but not in arousal ratings ($R^2 = 0.01$, $r = -0.11$, $p = 0.23$). Ventral salience connectivity did not predict arousal ratings for high arousal positive images ($R^2 = 0.006$, $r = -0.07$, $p = 0.42$). As sex and education did not appear to be a confound based on non-significant bivariate correlations with either the independent or dependent variables ($p > 0.05$), these demographic factors were left out of the mediation analysis.

Aging Effects on Salience Subsystems Connectivity

We found that intrinsic connectivity within the ventral salience subsystem was not only preserved as we predicted but it was actually increased with age whereas within the dorsal salience subsystem decreased with age (see **Figure 3**). The ventral salience subsystem connectivity between the vAI and amygdala was increased with age ($R^2 = 0.09$, $r = 0.30$, $p = 0.002$). In contrast, the connectivity within the dorsal salience subsystem connectivity between the dAI and MCC was reduced with age ($R^2 = 0.12$, $r = -0.34$, $p = 0.0001$). Age was also positively correlated with arousal ratings in response to arousing negative images ($R^2 = 0.09$, $r = 0.31$, $p = 0.001$), such that elderly people expressed more negative arousal than the young, but negatively correlated with executive function ($R^2 = 0.05$, $r = -0.23$, $p = 0.017$), such that the elderly showed reduced executive function (see **Figure 3**). No significant correlation was found between age and arousal ratings in response to arousing positive images ($R^2 = 0.007$, $r = 0.08$, $p = 0.37$). As sex and education did not appear to be a confound based on non-significant bivariate correlations with either the independent or dependent variables, these demographic factors were left out of the mediation analysis.

Salience Subsystems Connectivity Mediates the Relationship Between Age and Behavior

Using mediation analysis (Baron and Kenny, 1986; Preacher and Hayes, 2008), we found support for our prediction that age-related changes behavior is mediated by salience network connectivity changes. We found that arousal ratings were partially mediated by altered connectivity within the ventral salience subsystem (see **Figure 4A**). In Step 1 of the mediation model, the regression of arousal ratings on age was significant, $b = 0.007$, $\beta = 0.31$, $t_{(106)} = 3.34$, $p = 0.001$ (total effect, path a). Step 2 showed that the regression of ventral subsystem connectivity on age was also significant, $b = 0.004$, $\beta = 0.30$, $t_{(106)} = 3.21$, $p = 0.002$ (path b). Step 3 of the mediation showed that the mediator (vAI-amygdala connectivity within the ventral salience subsystem) controlling for age, marginally predicted affect, $b = 0.291$, $\beta = 0.18$, $t_{(105)} = 1.833$, $p = 0.07$ (path c). Step 4 of the analyses (direct effect, path a') revealed that, controlling for the mediator (vAI-amygdala connectivity within the ventral salience subsystem), age was still a significant predictor of arousal ratings, $b = 0.005$, $\beta = 0.26$, $t_{(105)} = 2.68$, $p < 0.008$. The Sobel test was statistically significant, indicating the indirect effect (path bc, indirect effect) was statistically significant, as was the reduction in path a, indicating significant partial mediation ($z = 1.66$, $p = 0.048$).

As predicted, we found that age-related declines in executive function were mediated by decreased connectivity within the dorsal salience subsystem connectivity (see **Figure 4B**). **Figure 4B** shows the standardized beta coefficients for the total as well as the direct and indirect effects. In Step 1 of the mediation model (total effect, path a), the regression of Trails B performance on age, ignoring the mediator, was significant, $b = -0.002$, $\beta = -0.23$, $t_{(109)} = -2.43$, $p = 0.017$. Step 2 showed that the regression of dorsal subsystem connectivity on age was also significant, $b = -0.006$, $\beta = -0.34$, $t_{(109)} = -3.77$, $p = 0.0001$ (path b). Step 3 of the mediation showed that the mediator (dAI-MCC connectivity within the dorsal salience subsystem) controlling for age, was closely approaching significance, $b = 0.097$, $\beta = 0.19$, $t_{(108)} = 1.95$, $p = 0.053$ (path c). Step 4 of the analyses revealed that, controlling for the mediator (dAI-MCC connectivity within dorsal salience subsystem), age was no longer a significant predictor of Trails B performance, $b = -0.001$, $\beta = -0.16$, $t_{(108)} = -1.65$, $p = 0.102$ (direct effect, path a'). The Sobel test was statistically significant, indicating the indirect effect (path bc, indirect effect) was significant, showing significant mediation ($z = 1.62$, $p = 0.05$).

DISCUSSION

The results of this study are consistent with our hypothesis that age differentially affects the intrinsic connectivity of the two subsystems of the salience network, and that these differences mediate dissociable age-related influences on the abilities that those networks support. We predicted relative preservation of the circuitry for identifying evocative and affectively important

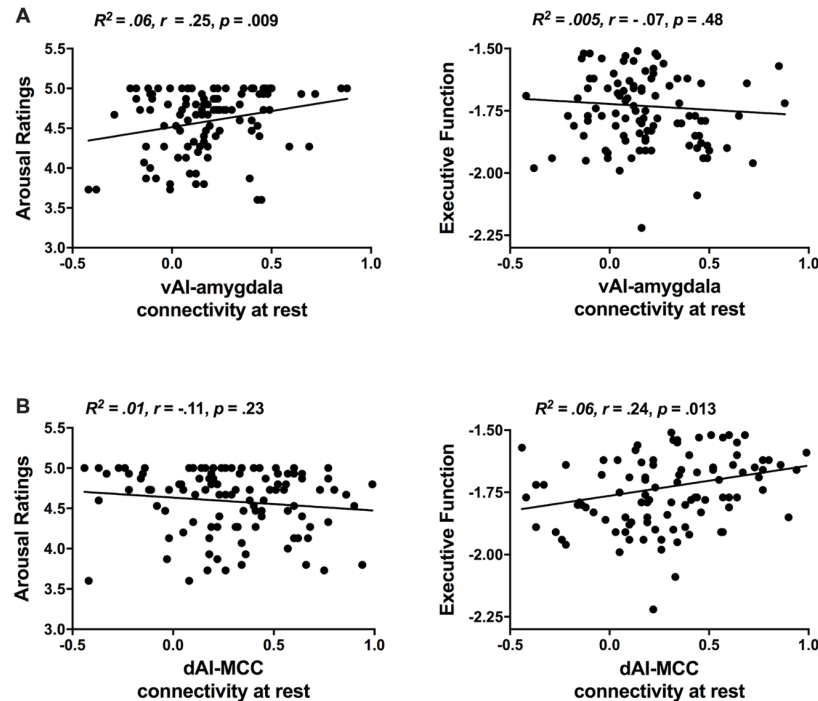


FIGURE 2 | Replication of the dissociable relationships between salience subsystems and behavior previously demonstrated in Touroutoglou et al. (2012).

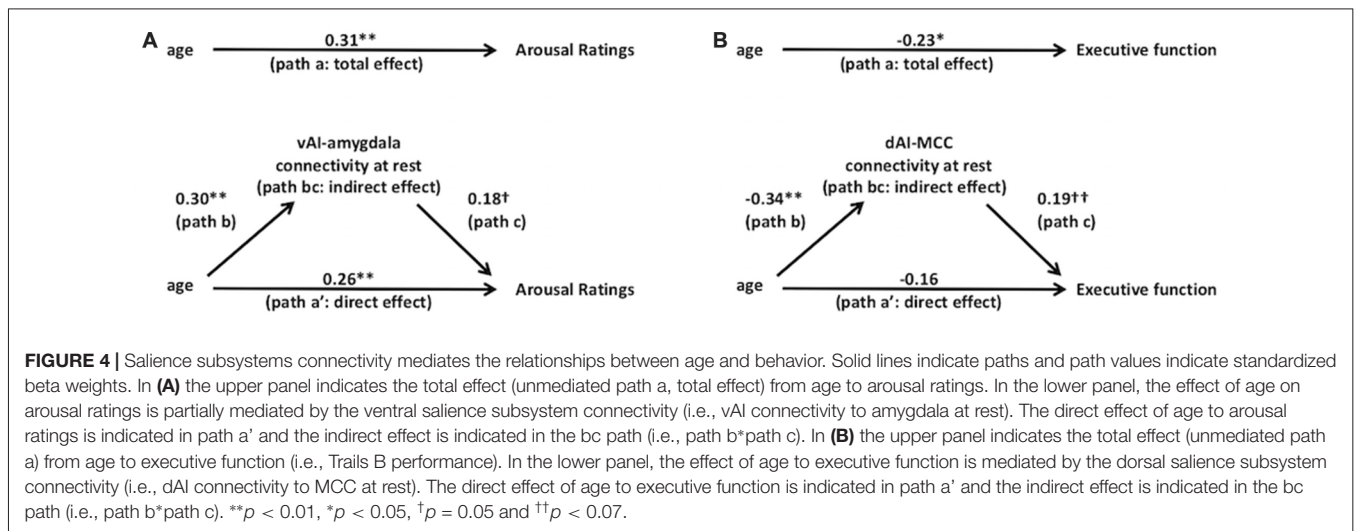
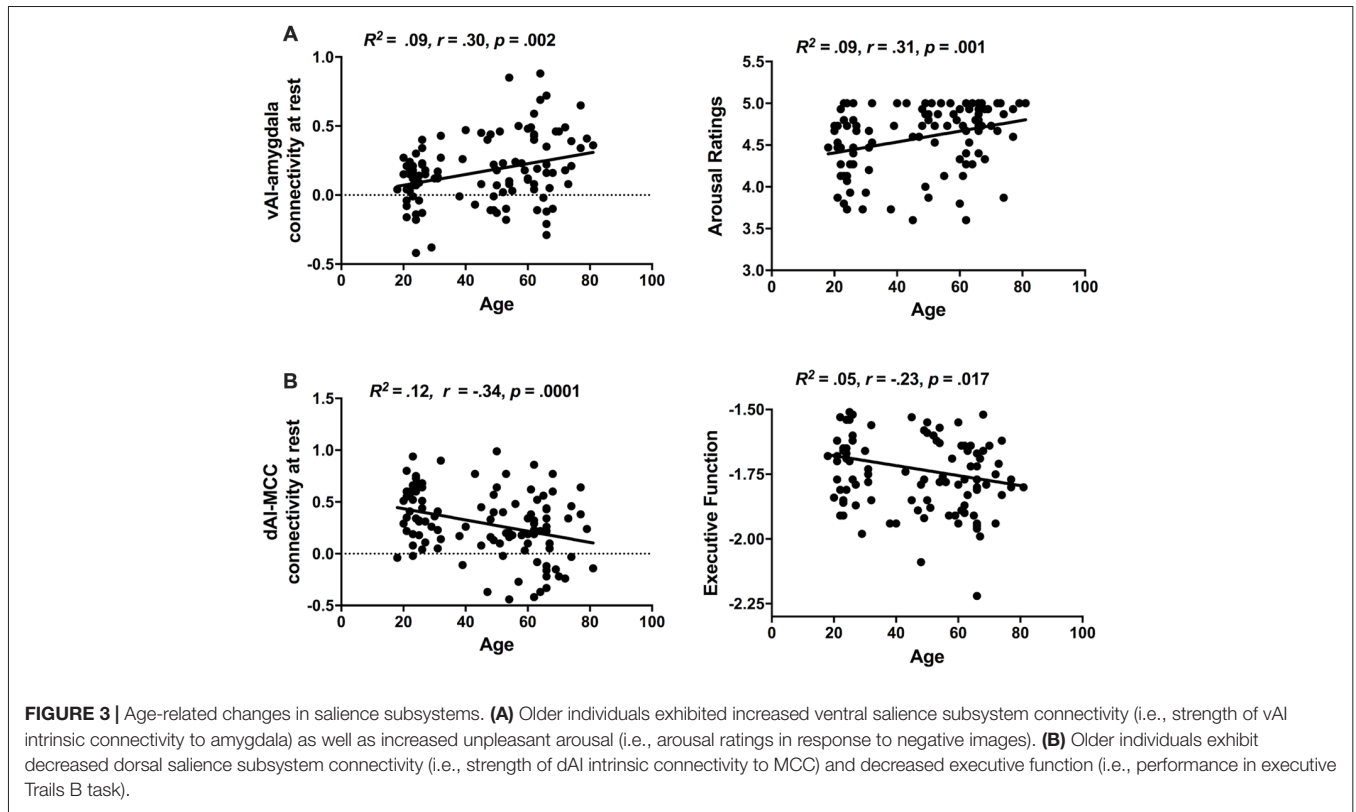
(A) Individual differences in ventral salience subsystem connectivity (i.e., strength of vAI intrinsic connectivity to amygdala) are associated with variation in unpleasant arousal (i.e., arousal ratings in response to negative images), but not in executive function performance. **(B)** Individual differences in dorsal salience subsystem connectivity [i.e., strength of dAI intrinsic connectivity to mid-cingulate cortex (MCC)] are associated with variation in performance in executive Trails B task, but not in arousal ratings.

stimuli with age. The results suggest not only preservation but actual increased connectivity between major nodes of the ventral salience subsystem in the aging brain, leading to increased affective reactivity. In contrast, the circuitry for performing a cognitive task requiring set shifting degrades with age, leading to impaired executive function. As we predicted, connectivity in the dorsal salience subsystem declined with age. This result may explain the diverse results reported in previous studies of aging and salience network connectivity (Allen et al., 2011; Onoda et al., 2012; Wang et al., 2012; He et al., 2013, 2014; Roski et al., 2013; Cao et al., 2014; Langner et al., 2015; Sakaki et al., 2016; Xiao et al., 2018). These findings are consistent with age-related atrophy gradients in the human brain (Salat et al., 2004; Fjell et al., 2009, 2014; McGinnis et al., 2011). Studies reporting decreased connectivity of the salience network have not considered connectivity to the amygdala (Allen et al., 2011; Onoda et al., 2012; He et al., 2013; Roski et al., 2013; Langner et al., 2015), which is a node of the ventral, but not dorsal, salience subsystem (Touroutoglou et al., 2012). In contrast, studies reporting preserved salience connectivity have included the amygdala (Wang et al., 2012; Cao et al., 2014). Similarly, increased task-related connectivity between the amygdala and ACC during the presentation of negative stimuli has been reported in the elderly relative to the young (St Jacques et al., 2009, 2010). These findings add to literature suggesting an important protective role of limbic circuitry in successful aging

(Harrison et al., 2012, 2018; Rogalski et al., 2013; Sun et al., 2016).

Our brain-behavior relationships replicated the findings of our previous analysis of salience subsystem function (Touroutoglou et al., 2012), suggesting that dorsal salience subsystem connectivity predicts executive function, while ventral salience subsystem connectivity predicts unpleasant arousal in a sample of young, healthy adults. Thus, the functional dissociation of the salience network persists with aging. This finding is consistent with several lines of research showing preserved or enhanced arousal processing in the elderly. Greater ratings of arousal in the elderly relative to the young have been reported for all material, irrespective of valence (Smith et al., 2005; Gavazzoni et al., 2008; Gruhn and Scheibe, 2008; Moriguchi et al., 2011; Sands and Isaacowitz, 2017). Similarly, the tendency to direct attention towards salient arousing stimuli is preserved in aging; both young and elderly people show equivalently enhanced detection speed of high vs. low arousal targets (Mather and Knight, 2006; Leclerc and Kensinger, 2008). Brain imaging studies focused on arousal have also shown equivalent responses for the young and elderly in the amygdala and throughout the salience network (Moriguchi et al., 2011; Kehoe et al., 2013; Dolcos et al., 2014).

Mediation analysis further demonstrated that age-related changes in arousal ratings were partially mediated by increased



connectivity within the ventral salience subsystem, such that age-related increases in ventral salience connectivity led to the increased experience of arousal in response to negative evocative images. This suggests that the age-related changes in arousal observed in previous studies may be attributable to age-related increases in ventral salience network connectivity. However, as this mediation was only partial, it seems likely that the experience of arousal is influenced by other brain systems, such as midbrain and brainstem nuclei within the default mode network (Bar et al., 2016), which are important for interoception that serves

as the sensory basis for feelings of arousal (Barrett, 2004; Barrett and Bliss-Moreau, 2009; Kleckner et al., 2017). In addition to central nervous systems, the experience of arousal may also be influenced by the peripheral autonomic nervous system (Xia et al., 2017). Furthermore, our participants demonstrated a ceiling effect in their arousal ratings, reducing the available variance for mediation.

While our results showed that arousal experience was positively associated with age, executive function declined in the older members of our sample. This finding is consistent

with substantial previous research (Park et al., 2002; Hedden and Gabrieli, 2004; Reuter-Lorenz and Park, 2010). Previous studies, however, have typically related this decline to changes in the connectivity in other brain networks, such as the default mode network (Andrews-Hanna et al., 2007) or fronto-parietal network (Geerligs et al., 2014). The present findings indicate that reduced executive function in older age is also mediated by reduced integrity of the dorsal salience subsystem, possibly through reduced attentional function and speed of processing.

One limitation of this study is that the present analytic approach employed only resting state fMRI. Future research should investigate both the resting state and dynamic coupling of the two salience subsystems to better understand how distinct aspects of salience processing are changed in aging. Additionally, as the strength of brain-behavior correlations reported here are of only moderate strength, further research will be needed to assess the reliability and replicability of these findings. Furthermore, this study used a cross-sectional design to examine mediation models and thus cannot speak to the temporal ordering and causal relationship between brain salience network connectivity and behavior. Future longitudinal studies are needed to elucidate causal models of longitudinal changes in aging (Raz and Lindenberger, 2011). In addition, this study used *a priori* seeds defined in an independent data set of young adults. Most studies of aging have focused on changes in hub connectivity strength with aging, as we did here. It is nonetheless possible that the network topology may also change with aging (Meunier et al., 2009). Future studies should explore this question as well as replicate these findings using an exploratory whole brain approach.

Attention and affective experience are two important psychological phenomena that change with age, but the brain basis underlying these changes remains unclear due to conflicting results across published studies. Here, we show that the brain's intrinsic salience network has two subsystems that are not affected by aging in a uniform way. The dorsal components

of the salience network lose coherence with age, and this decreased connectivity fully mediates an age-related reduction in executive function. The ventral components of the salience network increase their coherence with age, and this increased connectivity partially mediates an age-related increase in arousal-based affective reactivity. These findings resolve conflicting results in prior studies of salience processing in elderly, and enhance our understanding of salience network functions. These findings may also help to resolve conflicting results in clinical studies of disease. Some studies report differences in salience connectivity in age-related diseases such as Alzheimer's disease (Chand et al., 2017) and minimal hepatic encephalopathy (Chen et al., 2016) while others show no significant differences in Alzheimer's disease or Mild Cognitive Impairment (Wang et al., 2015). It may be that the dual model of salience network organization suggested here could provide a framework to understand disparate findings on brain network connectivity and disease.

AUTHOR CONTRIBUTIONS

AT, JA, BD and LB designed the research. AT, JZ, JA, BD and LB performed the research, analyzed the data and wrote the manuscript.

FUNDING

This work was supported by a National Institute on Aging grant (R01 AG030311-06A1) to LB and BD.

ACKNOWLEDGMENTS

We thank Trey Hedden for his helpful comments on an earlier draft of this manuscript and Michael Stepanovic, Morenikeji Adebayo and Felicia Sun for their assistance in data acquisition and preprocessing.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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