Arousal increases neural gain via the locus coeruleus-norepinephrine system in younger adults but not in older adults

Article

Accepted Version

Arousal increases neural gain via the locus coeruleus-norepinephrine system in younger adults but not in older adults

Tae-Ho Lee[1,2,3], Steven G. Greening[1,2,4], Taiji Ueno[5], David Clewett[6,7], Allison Ponzio[2], Michiko Sakaki[8], and Mara Mather*[1,2,6]

[1] Department of Psychology, University of Southern California, USA
[2] Davis School of Gerontology, University of Southern California, USA
[3] Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, USA
[4] Department of Psychology, Louisiana State University, USA
[5] School of Human Sciences, Takachiho University, Japan
[6] Neuroscience Graduate Program, University of Southern California, USA
[7] Department of Psychology, New York University, USA
[8] School of Psychology and Clinical Language Sciences, University of Reading, UK

April, 2018, in press, *Nature Human Behavior*

Correspondence. Correspondence and requests for materials should be addressed to Mara Mather (mara.mather@usc.edu).

Acknowledgements. This work was supported by grants from the National Institute on Aging RO1AG025340 awarded to MM, JSPS KAKENHI 16H03750 and 15K21062 awarded to TU, JSPS KAKENHI 16H05959, 16KT0002, 16H02053 and European Commission CIG618600 awarded to MS. The funders had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Author Contributions. All the authors contributed to the preparation of the manuscript. THL and MM designed the study. THL, SG, AP acquired the data. Data were analyzed by THL with SG, DC and MM. Modeling was conducted by TU and MS. We thank Christine Cho for assistance with Figures 1 and 7.

Competing Interests. The authors declare no competing financial nor non-financial interests.

ABSTRACT

In younger adults, arousal amplifies attentional focus to the most salient or goal-relevant information while suppressing other information. A computational model of how the **locus coeruleus-norepinephrine (LC-NE)** system can implement this increased selectivity under arousal and an fMRI study comparing how arousal affects younger and older adults' processing indicate that the amplification of salient stimuli and the suppression of non-salient stimuli are separate processes, with aging affecting suppression without impacting amplification under arousal. In the fMRI study, arousal increased processing of salient stimuli and decreased processing of non-salient stimuli for younger adults. In contrast, for older adults, arousal increased processing of both low and high salience stimuli, generally increasing excitatory responses to visual stimuli. Older adults also showed decline in LC functional connectivity with frontoparietal networks that coordinate attentional selectivity. Thus, among older adults, arousal increases the potential for distraction from non-salient stimuli.

INTRODUCTION

The arousal system helps the brain and body coordinate action during threatening situations. Physiological arousal fluctuates moment by moment in response to events such as thoughts, loud noises, effort, and emotions. During an arousal response, the locus coeruleus (LC), a small nucleus in the brainstem, releases norepinephrine (NE) throughout most of the brain via its extensive network of axons. NE increases the gain on neural activity, so that highly active neurons become more excited while less active neurons get suppressed [1; 2]. Consistent with this, people notice and encode perceptually salient or goal-relevant stimuli even more under arousal while neglecting stimuli that do not stand out [3]. For instance, if people hear an emotional sound like a baby crying or a tone previously associated with getting a shock, in the next few seconds they notice salient visual stimuli even more and non-salient stimuli even less than they would otherwise [4; 5].

Although these behavioral findings suggest that NE released during arousal affects neural representations differently depending on their priority or salience, it is not yet known how this interaction of arousal and salience occurs. The Glutamate Amplifies Noradrenergic Effects (GANE) model posits that phasic LC activity leads to selective cortical sites of amplified activity [2]. These hotspots emerge when, somewhere in the cortex, strongly active synapses “leak” glutamate into the extrasynaptic space at the same time that the LC is activated (Figure 1). The hotspots are triggered because glutamate stimulates NE release from nearby LC varicosities if the LC neurons happen to be activated (depolarized). The locally released NE in turn stimulates glutamate release via beta receptors on glutamatergic neurons, leading to a glutamate-NE feedback loop that promotes even higher excitation in the most highly active areas.

In addition to these hotspots of amplified activity under arousal, GANE also outlines several mechanisms that suppress less active representations under arousal. First, the low levels of NE released at regions where no hotspots emerge cause suppression of activity in non-hotspot regions. This is due to the differential actions of alpha2A and beta-adrenergic receptors. The beta-adrenergic receptors involved in the excitatory hotspot feedback loop have a low affinity for NE and so are activated only with the high levels of NE that are triggered when local high levels of glutamate interact with nearby LC varicosities under phasic arousal. In contrast, alpha2A noradrenergic receptors have a high affinity for NE and so are activated at relatively low levels of NE. Furthermore, whereas beta-adrenergic receptors tend to be excitatory, alpha2A-adrenergic receptors typically have inhibitory effects. Alpha2A receptors are

highly prevalent both as autoreceptors at LC varicosities and as heteroreceptors on other neurons, leading to broad-scale inhibitory effects of arousal and NE on neural activity [6].

In addition, GABA receptors could contribute to greater suppression of less salient representations via a couple of mechanisms. First, high glutamatergic activity at local hotspots should activate nearby GABAergic interneurons that suppress competing weaker representations in the same local network. Second, attention networks in frontoparietal regions [7] appear to coordinate activity across disparate cortical representations via long-range glutamatergic projections to other brain regions that stimulate local GABAergic neurons [8] and via long-range GABAergic projections [7]. Frontoparietal attention networks help coordinate selectivity across the cortex [9]. Because LC-NE activity stimulates these brain regions [10-12], the GANE model proposed that frontoparietal brain regions contribute to the increased inhibition of low priority information under arousal.

The GANE model thus posits that the downstream inhibitory and excitatory effects of arousal on perception and attention have distinct mechanisms. In the current study, we tested this hypothesis by comparing younger and older adults, as there are reasons to believe that the inhibitory effects of arousal will decline more in aging than the excitatory effects. Aging is associated with more decline in alpha2A receptor function than in beta receptor function, as reflected in decreased alpha2-adrenergic receptor density in contrast with increased beta-adrenergic receptor density in older rhesus monkeys [13; 14] and decreased gene expression differences in the alpha2A receptor gene but not beta receptor genes in older humans [15; 16]. Furthermore, GABA function declines with age [17]. Fast-spiking interneurons use more energy than most other neurons, leaving them especially vulnerable to metabolic and oxidative stress in aging [18]. In animals, age-related loss of GABAergic interneurons is greater than loss of other neurons [19; 20; see also 21 for consistent findings in humans] and GABA function also declines more than glutamate function [22]. In addition, the frontoparietal networks activated by the LC-NE system [for review see 2] that help implement inhibition and selective processing across disparate cortical regions show age-related changes in functional connectivity that are associated with age-related declines in cognitive performance [23-28]. Based on these age-related vulnerabilities of the inhibitory mechanisms of GANE, we predict that arousal suppresses processing of less salient information less effectively in older adults than in younger adults.

We used functional magnetic resonance imaging (fMRI) and computational modeling to test this prediction. We adapted a paradigm we previously used with younger adults [4] to compare activation of salient and non-salient visual stimuli under arousal in younger adults

versus older adults. We measured parahippocampal place area (PPA) activity while participants viewed a pair of images: one scene image that was either high or low priority compared to a simultaneously displayed object (Figure 2). The high priority options were both perceptually salient and goal relevant (i.e., participants had to indicate the location of the perceptually salient object). We focused on scene-associated activation in the PPA because it exhibits greater category specificity than most other category-selective cortical regions [29]. Before each pair of images was presented, we manipulated arousal by playing a tone that was conditioned to predict a shock (CS+) or no shock (CS-). We measured skin conductance and pupil dilation to assess arousal. After confirming our hypothesis of age-related differences in how salience and arousal influence PPA activity, we evaluated whether the neurochemical mechanisms associated with the GANE model could explain the pattern of observed fMRI effects. For this we implemented GANE in a neural network model and then examined how age-related declines in inhibitory mechanisms influence attention under arousal in this model. We then examined how arousal and place image salience on each trial influenced functional connectivity dynamics among the LC, PPA, and frontoparietal network for younger versus older adults.

RESULTS

fMRI Study

Fear conditioning effectiveness. In the fMRI experiment, younger adults (n=28) and older adults (n=24) first completed a fear-conditioning task in which they learned associations between a CS+ tone and shock, and associations between a CS- tone and lack of shock during functional imaging. (See 'Methods and Materials' for more task details.) During the fear conditioning task, the CS+ tone increased arousal, as indicated by skin conductance, pupil diameter, and brain activation patterns (see Supplementary Results and Supplementary Figures 1 and 2). CS+ tones continued to increase arousal during the subsequent spatial detection task involving the conditioned tones (see Supplementary Results and Supplementary Figure 3).

PPA ROI results during spatial detection task. After fear conditioning, participants completed the main task, a spatial detection task with each trial starting with a CS+ or CS- tone, followed by a place-object image pair (Figure 2). Participants' task was to quickly indicate whether the high-salience image was on the right or left via a button press. Based on previous studies [3; 4] and our model, we expected that arousal would enhance processing of salient stimuli. We examined the effects of picture saliency on stimulus-specific brain activation by tracking

activation in individually determined PPA regions-of-interest (ROI; Figure 3A) in response to the place images when they were salient vs. non-salient. These ROI results are the critical result we use to assess activation levels of the scene representation when it is salient vs. non-salient. A mixed-effects ANOVA on the extracted PPA percent signal changes for the target processing with *Arousal Condition* (2: CS+, CS-) X *Place Saliency Type* (2: salient place target, non-salient place target) X *Hemisphere* (2: left, right) X *Age Group* (2: younger, older) as factors yielded no main effects, but an *Arousal Condition* X *Place Saliency Type* X *Age Group* interaction, $F(1, 50) = 6.12$, $p = .017$, $\eta_p^2 = .109$, indicated that arousal and saliency interacted differently for younger adults versus older adults.

To examine these different arousal-by-salience interactions for each age group, we conducted separate repeated-measures ANOVAs for younger adults and older adults. For the younger group, there was a significant cross-over *Arousal Condition* X *Place Saliency Type* interaction, $F(1, 27) = 6.35$, $p = .018$, $\eta_p^2 = .19$. Compared with CS- tones, CS+ tones amplified PPA activation when a place image was salient ($M_{CS+} = .325$ vs. $M_{CS-} = .294$; planned comparison $t[27] = 1.84$, $p = .038$; one-tailed) but not when the place image was non-salient ($M_{CS+} = .268$ vs. $M_{CS-} = .283$; planned comparison $t[27] = -1.02$, $p = .159$; one-tailed; Figure 3B). There was no main effect of *Arousal Condition,* $F(1, 27) = 0.35$, $p = .557$, $\eta_p^2 = .013$, thus in younger adults the impact of arousal depended on the saliency of the place image.

For the older group, in contrast, there was only a main effect of *Arousal Condition,* $F(1, 23) = 4.99$, $p = .036$, $\eta_p^2 = .178$, indicating that CS+ trials generally increased PPA activity ($M_{CS+} = .174$ vs. $M_{CS-} = .151$) regardless of saliency type (Figure 3C). There was no arousal-by-salience interaction, $F(1, 23) = 1.11$, $p = .303$, $\eta_p^2 = .046$. In addition, there were no significant effects of hemisphere in any of these analyses.

Thus, as expected for younger adults, arousal interacted with saliency to increase the gain on perceptual processing during high arousal moments. In contrast, older adults showed no selectivity in the impact of arousal. For older adults, arousal increased activation associated with the presented place images regardless of their salience.

GANE model simulation

While the fMRI results confirm our primary hypothesis regarding age-related changes to arousal's impact on perceptual processing (as reflected in the PPA results) and provide evidence for the involvement of the LC-NE system, they cannot directly evaluate whether neurochemicals specified in the GANE model could have produced the observed effects. To address this, an auto-encoder neural network was used to instantiate GANE while considering

all behavioral elements in the task (Figure 4A). Its input, intermediary, and output layers each has 80 processing units and they are connected by links (see Supplementary Methods for more detail). Each unit in each layer represents a unique stimulus within that layer. A processing unit in a neural network simulation is a neuron-like object intended to represent a small population of neurons. The activation strength of these processing units in the intermediary layer during the task was used as an approximate measure of brain activation and compared with PPA fMRI ROI results.

As described above, during the behavioral task, participants were required to indicate which of two presented stimuli were more salient. To enable the model to complete the same task, the model was first trained and values of connection weights linking units were determined to generate a stronger signal for a salient stimulus and a weaker signal for a non-salient stimulus in the output units when it received two inputs with different activation strengths in the input layer. Next the model completed the main task, during which it received a stronger value for one input unit (i.e., a salient stimulus) and a weaker value for another input unit (i.e., a non-salient stimulus). The activation of these units propagated to the intermediary layer units, whose activation strengths were determined not only by these incoming inputs but also by current arousal and NE levels. The resultant activations from the intermediary layer propagated to the output layer units. Stronger signals in the output units are considered as stronger attention to the corresponding input stimulus. As the fMRI study probed the brain activity during such a behavior, we also investigated the activity of the intermediary layer units during the time when the model achieved such an input-output mapping. The effect of arousal induced by CS+ were also modelled. To incorporate the local NE effects GANE posits, we assigned a unique NE parameter to each unit. On each trial, this NE parameter starts with the low baseline value of 1.0 X 10^{-9} mol/liter NE (based on the baseline NE level observed in previous physiological studies of approx 1nM in the cortex [30]). Immediately after an arousing event, there is unit-specific NE release-depending on the unit's activation level. If the unit's NE value exceeds a threshold high enough to activate beta-adrenergic receptors (7 x 10-6 [31; 32]), this leads to an excitatory feedback loop to allow for additional glutamate and NE release [33], resulting in our hypothesized NE hotspots. Activation of beta-adrenergic receptors also leads to the activation of GABAergic signals and suppresses other competing units [34]. The unit-specific value of NE then becomes smaller and smaller as time elapses after the event, simulating the NE reuptake process [35]. This model simulates the arousal-by-salience interaction (Figure 4B) seen both in the current study (Figure 3B) and in our previous research with younger adults [4].

Modeling GANE changes in older adults

We examined several ways to simulate effects of age-related declines in inhibitory mechanisms in the model (Figure 4C, panels 1-4). First, we modified the reuptake rate to be lower (based on less alpha2A inhibition of NE release). This change had no effect on the greater excitation of high salience units under arousal but abolished the inhibitory effect of arousal on low salience units. Moderate GABA impairment also eliminated the inhibition of low salience units under arousal. Combining both of these impairments in one model or making the GABA impairment more extreme led to indiscriminate excitation of units regardless of their salience (Figure 4C, panels 3-4). In summary, these models indicate that impairment of basic inhibitory mechanisms, whether due to decreased function in either GABA or alpha2A receptors or both, could reduce how much arousal inhibits low salience items without affecting how much arousal excites high salience items, as shown in our fMRI data (Figure 3C).

Effects of Arousal on Frontoparietal Network and LC Functional Connectivity

Returning to the fMRI analyses, the remaining results shed further light on how arousal affects network dynamics and locus coeruleus functional connectivity.

Whole-brain voxelwise analysis. We examined overall brain activity differences on arousal vs. non-arousing trials during the main detection task to see if arousal amplified activity in frontoparietal network regions associated with attentional selectivity. When the interaction between *Arousal Condition* and *Age Group* was examined in a whole-brain analysis, significant differences in the right frontoparietal network region including the DLPFC, IFG, inferior parietal lobule (IPL), and dorsal premotor cortex extending to the frontal eye field (FEF) were identified (Figure 5A, Supplementary Figure 4, and Supplementary Table 2). These regions are involved in attentional inhibition, selection and control [9; 36; 37]. The significant interaction arose because, in younger adults, arousal during the task increased activation of these attentional selection regions, whereas in older adults, arousal did not significantly affect these frontoparietal regions (Figure 5B and Supplementary Figure 5). Furthermore, we found that the mean activation in these regions was significantly correlated with pupil diameter changes (CS+ minus CS- during the post-tone period) in younger adults, r (25) = .615, p = .001, $95\%\ CI^{\,n\,=\,5{,}000\ \text{bootstrap}}$ = [0.214, 0.828], but not in older adults, r(15) = .231, p = .371, $95\%\ CI^{\,n\,=\,5{,}000\ \text{bootstrap}}$ = [-0.182, 0.692]s (Figure 5C). There was no statistical difference in correlation coefficients between aging

groups. In sum, the results suggest that arousal changes indexed by pupil size modulate frontoparietal attentional processes more for younger than for older adults.

PPA functional connectivity analysis. In addition to PPA activation levels examined in the earlier ROI analyses, we also examined PPA-LC functional connectivity. In the GANE model, local cortical NE hotspots can only emerge both where there is high glutamatergic activity and when the LC is active. This is because the NMDA receptors on the LC varicosities in cortex are only activated by glutamate when the LC is simultaneously depolarized. Thus, GANE predicts increased BOLD coupling between the LC and the PPA when the participant is in a high arousal state and viewing a salient place stimulus. For these analyses, one important question is whether the BOLD coupling seen in fMRI occurs at a similar timescale as release of NE. LC-NE axons are slower than the typical axon conduction rate, conducting impulse activity on the order of 0.20-0.86 m/s [38]. Although this is slow for neural transmission, this is fast enough to act on a trial-by-trial basis in our study where trials lasted for a few seconds. Furthermore, a rat study shows a relatively tight timing relationship between LC and cortical BOLD activity [39]. When right or left LC was phasically stimulated (1s on/1 s off) for 20 s, frontoparietal cortex cerebral blood flow (CBF) started increasing within the first 3 s of the stimulation and continued to increase during the stimulation duration. When the LC stimulation period ended, CBF immediately started declining on the contralateral side, whereas there was a few-second delay in CBF decline on the ipsilateral side. Thus, current evidence suggests BOLD responses to LC activation can occur quickly enough to be detected in a trial-by-trial design.

We examined the functional connectivity of PPA seed regions (individually located for each participant), comparing CS+ and CS- trials for salient place condition and non-salient place condition for each age group. Given our a-priori prediction of LC involvement in arousal-salience interactions based on our GANE model simulation and the small size of the LC (see Figure 6A for LC location), we focused our investigation on the brainstem region aligned using a brainstem-weighted registration process [40]. Both younger and older adults showed greater PPA-LC functional connectivity during arousing trials than during non-arousing trials (Figure 6B, left panel), a main effect that was seen during trials with salient places but not during trials with non-salient places (Figure 6B, middle panel). This led to significant arousal-by-salience interactions in clusters overlapping the LC for both groups (Figure 6B, right panel). There were no significant clusters within the LC for the 3-way interaction of arousal, saliency, and age.

According to the GANE model, the PPA should have high levels of glutamatergic activity during viewing salient stimuli, and those high levels of glutamate should allow for stimulation of

more local NE release (which in turn stimulates more glutamate release) if the LC is phasically activated (Figure 1). Thus, it is during conditions of high glutamate in the PPA and high phasic activity in the LC that coordinated bursts in activity should occur in the two regions. Thus, the arousal-by-salience interactions in functional connectivity between these regions support the GANE model hotspot mechanism, indicating that LC activity during arousal is more coordinated with activity in a cortical representational area when that cortical area is representing something salient than non-salient.

In addition, the finding that the arousal-by-salience interaction was significant for PPA-LC functional connectivity not only for younger adults who showed the behavioral arousal-by-salience effect but also for older adults who did not show behavioral selectivity is quite interesting and suggests that the hot spot excitatory mechanism in which highly activated representations become even more active under arousal will fail to yield selectivity without intact inhibitory contributions. This scenario of intact NE-glutamate interactions that fail to lead to selective enhancement of salient stimuli is represented by our modeling, as depicted in Figure 4C, with the strong GABA impairment model in the rightmost panel. That modeling scenario indicates that an increase in activation under arousal for salient representations will not yield a selective benefit for salient representations in the presence of an impairment in inhibitory mechanisms.

Using the same individually defined PPA ROIs, we also examined PPA functional connectivity with cortical regions in a whole-brain analysis. This allowed us to see if arousal influenced the strength of functional connectivity between the PPA and frontoparietal regions. There was an age-by-arousal interaction of functional connectivity within parietal regions (Figure 6C, lower left). When examined independently, younger adults had an arousal-by-salience interaction in functional connectivity with the PPA in frontoparietal network regions. This arousal-by-salience interaction reflected greater PPA-frontoparietal functional connectivity during CS+ than CS- trials only when the displayed place stimulus was salient. In contrast, older adults showed no differential cortical functional connectivity with PPA depending on salience or arousal. These findings suggest that arousal had a bigger impact on how frontoparietal network modulated activity in the place area for younger adults than for older adults.

Frontoparietal network functional connectivity. To see if there was also an age-by-arousal interaction in how the LC interacted with the frontoparietal network, we used a bilateral mask of the frontoparietal network (Figure 6A from [41]) as the seed region, applied to activity within the brainstem mask (with brainstem-optimized alignment, as detailed above). The frontoparietal

seed region had significantly more functional connectivity with the LC during CS+ trials than during CS- trials for both younger and older adults, but this effect was significantly stronger in younger adults, as indicated by significant age-by-arousal interaction effect clusters overlapping the LC (Figure 6D). Thus, in summary, significant age differences were seen in the functional connectivity pathways between LC and frontoparietal network regions and between frontoparietal network regions and the PPA (Figure 7).

Analyses to check for potential age-related confounds. Older adults may respond less specifically to places in the PPA due to age-related dedifferentiation. Representational similarity analyses (see Supplementary Figure 6 and Supplementary Results) indicate this was not the case in our dataset. Another possible account of our findings is that younger adults were more likely than older adults to shift their gaze to salient items, especially under arousal. Analyses of gaze biases indicated this was not the case (see Supplementary Figure 7 and Supplementary Results).

DISCUSSION

Under emotionally intense or cognitively demanding situations that elevate arousal, it can be beneficial to focus on whatever is most salient or important at that moment and ignore everything else. In this study, we tested a theoretical model of how arousal influences cortical processing (GANE [2]) and how these processes differ in older adults. We predicted that arousal would amplify salient stimuli similarly in younger and older adults but that arousal would suppress non-salient stimuli only in younger adults. To test this, we adapted an fMRI paradigm we had previously used with younger adults [4], in which one of two competing categorical stimuli had greater perceptual salience. We found that younger adults showed the expected increased gain under arousal, as indicated by greater activation of highly salient representations and less activation of competing less salient representations. In contrast, older adults showed no increase in selectivity under arousal. Instead, they showed greater activation of both salient and non-salient stimuli under arousal. Thus, our findings suggest that, for older adults, arousal is less effective at highlighting only stimuli that stand out most and instead increases distractibility from multiple strongly activated representations.

We used neural network simulation to test whether these findings are consistent with GANE. The neural network model of GANE we outline in this paper provides a computational model of how the LC-NE system can simultaneously up-regulate and down-regulate processing of different stimuli depending on their salience. In this model, in younger adults, activation of the

LC under arousal increases the gain on cortical neural activity by increasing activation of highly active representations while also increasing suppression of not-very-active representations. Activation of highly active representations is amplified as depolarization of LC neurons allows NMDA receptors on the LC axons passing through cortical regions to respond to high levels of glutamate in a particular cortical milieu and release more NE in that local region (Figure 1). At these sites where highly active representations release high levels of glutamate, glutamate-NE interactions create hotspots of even further amplified glutamatergic activity. At the same time, LC-NE activity amplifies inhibitory mechanisms via increased alpha-2A and GABAergic inhibition during LC activation.

Within our model, we simulated several different scenarios involving age-related decline in alpha-2A receptor activity and GABAergic processing inhibitory mechanisms. These simulations yielded intact excitatory components of the LC-NE effects in older adults, but a lack of the countervailing inhibitory components seen in younger adults. Two scenarios (Figure 4C, panels 3 and 4) not only eliminated inhibition of low salience representations but reversed it to yield excitation of low salience representations under arousal. Thus, the modeling indicated that age-related impairments in basic neural inhibitory mechanisms could lead to age differences in processing non-salient information while not affecting processing of salient information, supporting the notion that the excitatory and inhibitory effects of arousal are dissociable.

Furthermore, our fMRI functional connectivity analyses help discriminate between potential mechanisms underlying the age-related changes. The GANE hot spot mechanism predicts that activity in the LC should be most coordinated with a particular cortical region when two factors coincide: 1) that cortical region is strongly activated and 2) the LC is activated. Using individually defined parahippocampal place area (PPA) as seed regions confirmed this prediction; the LC was significantly more functionally connected to the PPA on trials when the place stimulus was salient and there was an arousing CS+ tone. This arousal-by-salience interaction in LC-PPA functional connectivity was significant for both younger and older adults. Thus, the direct interactions between the LC and the cortical representation were similarly modulated by arousal and salience for younger and older adults, suggesting that this pathway was responsible for the increased excitation of the salient stimulus representation under arousal seen in both younger and older adults. In contrast, age-by-arousal interactions were found in the interactions of the frontoparietal network with both the LC and the PPA. Arousal activated the frontoparietal network less in older adults than in younger adults and the frontoparietal network was less involved in modulating activity in the PPA under arousal. Frontoparietal network regions engage in long-range communication across cortical networks to activate local GABA

activity [e.g., 7; 8], thus, a reduction in frontoparietal activation under arousal would decrease the ability of arousal to amplify reactivity of GABA (as in Figure 4C, panel 4).

These findings raise the question of why, during brief bursts of arousal, LC increases its coordination with frontoparietal network less among older adults than younger adults. Previous findings reveal age differences in the frontoparietal network activity and functional connectivity that are associated with age-related declines in cognitive performance [23-28]. Thus, it is possible that at least part of the reduced impact of arousal on this network lies in declines in the frontoparietal network itself that make it less sensitive to modulatory influences such as NE release. But contrary to this notion are findings that LC-frontoparietal functional connectivity is greater during rest among older than younger participants (although the sample only included ages 18-49 [42]). This suggests another possibility: tonically elevated baseline cortical levels of NE among older adults [43] make arousal inductions less able to increase global levels of NE in ways that stimulate the frontoparietal network. Noradrenaline transporter blockade increases frontoparietal functional connectivity [11] suggesting that increasing general cortical NE levels increases frontoparietal activity. If the alpha-adrenergic receptors in the frontoparietal network are already activated by higher circulating levels of NE in older adults, small global increases in NE levels may not have much impact. In contrast, high NE levels still seem to have an impact on beta-adrenergic excitatory processes in older adults, as indicated by intact arousal-by-saliency LC-PPA functional connectivity interactions in older adults (Figure 6B), which based on GANE, depend on beta-adrenergic activity.

Our findings not only advance understanding the basic mechanisms of selectivity under arousal but also those underlying age-related decline in selectivity. The GANE computational model outlined here provides a framework for thinking about how local cortical interactions of NE and glutamate can lead to hot spots of increased neural activation under arousal. The functional connectivity analyses from the fMRI study help provide information about the broader context of which brain regions beyond the local site representing the stimulus are involved. In particular, the functional connectivity findings point to an important role of the frontoparietal network in coordinating suppression of competing representations across disparate regions. In the original presentation of GANE [2], a potential role of frontoparietal cortex was suggested based on the strong noradrenergic influences over this network but it was not the main focus. The findings here suggest that the LC interactions with frontoparietal cortex are an important component of the phenomenon of increased selectivity under arousal. Furthermore, our findings of arousal-by-salience interactions in LC-PPA functional connectivity support the GANE hotspot model in which cortical regions with high glutamatergic activity show further amplified activity

when the LC is simultaneously activated. These findings replicated in older adults and there were no age differences in the strength of this direct LC-PPA functional connectivity, indicating this aspect of LC function is still intact in late life, allowing for greater excitation of high salience stimuli under arousal.

In general, older adults are worse at inhibiting irrelevant information [44]. For instance, older adults activate representations of whatever is the focus of their attention as much as do younger adults, but fail to suppress the representations they should be ignoring [45; 46]. Our findings indicate that age differences in the likelihood of suppressing less salient competing information are particularly pronounced under arousal. This raises the interesting question of whether arousal-induced activation of the LC-NE system contributes to laboratory findings of age differences under arousal. Our model and findings suggests that the more engaged (and therefore the more LC is likely to be activated) participants are during a task, the more marked the age differences in the ability to inhibit irrelevant information should be. The LC is activated by a wide range of circumstances, including threatening or exciting situations, cognitive load, and novelty. Focusing on what is most salient during these moments may often be advantageous even if it means neglecting some less salient information. Our findings indicate that, due to age-related changes in inhibitory mechanisms, older adults cannot rely on increases in selective attention during these potentially high-stake moments.

METHODS AND MATERIALS

GANE fMRI experiment

***Participants*.** Twenty-eight healthy younger adults (M_{age} = 24.39 years, age range = 18 – 34; 9 females) and 24 healthy older adults (M_{age} = 66.95 years, age range = 55 – 75; 9 females) participated in the current study. There were no significant differences between groups in terms of intellectual level ($M_{education}$: younger adults = 16.85 vs. older adults = 16.38 years; $M_{\text{Wechsler Test of Adult Reading}}$: younger adults = 43.96 / 50 vs. older adults = 39.75 / 50). Participants had normal or corrected-to-normal visual acuity. Participants provided informed consent approved by the University of Southern California Institutional Review Board and were paid for their participation. Procedures conformed to human-subject ethical guidelines.

***MRI data acquisition and preprocessing*.** MRI data were acquired on a Siemens 3T Magnetom Trio with a liquid crystal display projector (1024 × 768 pixels at 60 Hz) onto a rear project screen behind the head of participants and viewed using a mirror attached to a 32-

channel matrix head coil. High resolution structural images (MPRAGE) were acquired first; repetition time (TR) = 1950 ms; echo time (TE) = 2.26 ms; flip angle (FA) = 7°; 1-mm isotropic voxel; field of view (FOV) = 256 mm. Next, functional images were acquired with gradient-echo echo-planar T2*-weighted imaging. Each functional volume consisted of 41 interleaved (no skip) 4 mm axial T2*-weighted slices; TR = 2000 ms; TE = 25 ms; FA = 90°; matrix size = 64 X 64; FOV = 256 mm. The fear conditioning run, each run of the spatial detection task, and the PPA localizer run were acquired with 180, 160 and 256 EPI volumes respectively. An additional T1-weighted fast-spin echo (FSE) sequence was administered (repetition time = 750 ms, echo time = 12 ms, flip angle = 120, 1 average, 11 axial slices, field of view = 220 mm, bandwidth = 220 Hz/Px, slice-thickness = 2.5 mm, slice gap = 3.5 mm, in-plane resolution = 0.43 mm^2, scan duration = 1 minute and 53 seconds).

During preprocessing, we discarded the first three volumes to account for equilibration effects. FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL [FMRIB's Software Library; 47]. The following preprocessing steps were applied; motion correction using MCFLIRT [48]; slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET [49]; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; ICA denoising using MELODIC ICA2 [50] and an automated toolbox [51] (an average of 15.54 components were removed from each participant); registration to high resolution structural and standard Montreal Neurological Institute (MNI) 2-mm brain using FLIRT [48]. For brainstem-targeted connectivity analysis, we performed an additional registration step to optimize brainstem alignment (please see section on functional connectivity with brainstem regions for more details).

***Stimuli and apparatus*.** Two tones (500 Hz and 800 Hz) served as conditioned stimuli (i.e., CSs). We used 270 house/ building place images obtained from several websites, and 240 color photographs of various real-world objects obtained from a previously published set of object stimuli [52]. All stimuli were gray-scaled and normalized to the mean luminance of all images. In the main spatial detection task, one object and one place image were randomly selected from the stimuli pool (each participant saw 160 object and 160 place stimuli from the larger pool of stimuli). The mild electric shock used as an unconditioned stimulus (US) was delivered to the third and fourth fingers of the left hand via a shock stimulator (E13-22; Coulbourn Instruments, Allentown, PA), which included a grounded RF filter. The PsychToolbox extension [53; 54] of

Matlab 2010b (The MathWorks Corp. Natrick, MA) controlled stimuli presentation and data collection.

Spatial detection task. After the fear-conditioning task (see Supplementary Methods for details), participants performed a simple spatial detection task (Figure 2). A trial began with simultaneous onset of a fixation cross and either the CS+ or CS- tone. The tone played for 0.7 s, then the fixation cross remained on the screen for 2 s after the tone ended. Then a place-object image pair was presented in two placeholder frames simultaneously for 0.6 s (4.3° X 4.3°; 11.5° eccentricity). The salient image had a higher contrast level (80%) than the paired non-salient image (20%), and to further increase its salience, it was framed by yellow for 0.1s. Participants were asked to identify the location of the salient image by pressing a left or right button. The ITI was randomly jittered (2.5, 3.5, 4.5 and 5.5 s). Each place image was randomly paired with one of the object images with unique pictures shown on each trial; with locations also randomly determined. Across five runs, 160 trials were presented. During each run, 16 CS+ trials (eight place salient and eight place nonsalient trials) and 16 CS- trials appeared in a random order. To minimize extinction, three additional CS+ shock trials were presented randomly in each run with the constraint that shocks did not occur on consecutive trials. Other than the shock and a subsequent 10-s blank interval, these booster trials were identical to the main trials, and were excluded from further analysis.

We asked participants to fixate their eyes on the fixation point that was always in the middle of the screen during the task. We took into account stimulus size and eccentricity when choosing the two cue image locations, so that participants could see both sides simultaneously even when their gaze was directed at the fixation point. Both younger and older adults successfully maintained gaze on the fixation point (see Supplementary Figure 7). Details on skin conductance and pupil dilation measures during the tasks are in the Supplemental Methods (see associated Supplementary Figure 7).

Parahippocampal place area (PPA) ROI analysis for spatial detection task. We first estimated stimulus-dependent changes in BOLD signal for each participant using a GLM with regressors for target stimulus and their temporal derivatives for each saliency condition (i.e., when place image was salient vs. non-salient) as a function of arousal condition (i.e., CS+ and CS-). Motion parameters, booster shock trials, error trials and tone onset timing were included in the design matrix as covariates of no interest. The effects of each regressor were estimated

over five functional runs (fixed-effects; one younger and one older adult completed four runs, and one older adult finished three runs due to time issues).

We conducted a region of interest (ROI) analysis using FSL Featquery (fmrib.ox.ac.uk/fsl/feat5/featquery.html) to probe how emotional arousal interacted with stimulus saliency for each Age Group, focusing on the parahippocampal place area (PPA) response, with PPA delineated for each participant based on a localizer scan (see Supplementary Methods). The PPA is selective for place/scene images [55] and responds to gross spatial properties more than to object identity, showing little modulation by object properties [56]. Although object images used in the current study induce selective brain response in the lateral occipital complex [LOC; 57], the response of the LOC and its sub-regions is mediated not only by object shape property itself, but also by various factors such as spatial information of the presented images [33], simultaneous presentation with task-irrelevant information [i.e., clutter; 58] and other contextual factors such as bottom-up saliency [59]. Consistent with previous findings, we found that neural activity in the LOC did not adequately discriminate between our object and place images (Figure 8). Hence, the LOC was a sub-optimal region for measuring visual competition between places and objects, however objects served as useful control stimuli for examining the effects of scene salience on PPA response.

Whole-brain voxelwise analysis for spatial detection task*.* In this analysis, we focused on whether emotional arousal had different effects on brain activity in younger versus older adults (i.e., the interaction *Arousal Condition* X *Age Group).* To do so, a standard GLM was performed to estimate the BOLD signal for the tone onset and their temporal derivatives as a function of arousal condition (CS+, CS-) regardless of saliency conditions. Motion parameters, booster shock trials, and target onset timing were included in the design matrix as covariates of no interest. A group-level analysis (random-effects) was also performed (random-effects with FLAME1+2 model; $Z > 2.3$ with corrected cluster $p = .05$, one-tailed).

PPA-whole brain functional connectivity analysis. To characterize dynamic interregional interactions, a beta series correlation analysis [60] was performed using least squares estimation [see LS-S model; 61] where each single-level general linear model (GLM) included regressors for the current trial, all other remaining events, and all other non-interest events (i.e., nuisance regressor; motion parameters, booster shock trials, error trials and tone onset timing). Finally, extracted mean activation (i.e., mean parameter estimates) of each trial from the individual ROI masks were used to compute correlations between the seed's signal and signal

of all other voxels in the whole brain, thus generating condition-specific seed correlation maps. Correlation magnitudes were converted into *z* scores using the Fisher's *r*-to- *z* transformation. Condition-dependent changes in functional connectivity were assessed using random effects analyses, which were thresholded at the whole-brain level using clusters determined by $Z > 2.3$ and a cluster significance threshold of $p = .05$ (*corrected*; one-tailed). Since our interest was how the PPA interacted with frontoparietal networks as a function of place salience, arousal level and age, we examined the 3-way Arousal (CS+, CS-) X Saliency (place salient, place non-salient) X Age Group (younger, older) interaction.

PPA and frontoparietal network functional connectivity with brainstem regions. To optimize brainstem signal measures for analyses examining functional connectivity between cortical seed regions and the LC, we conducted a separate registration process for the target brainstem region. Images were registered to a 2-mm standard-space MNI image using the following steps: 1) Registering each participant's functional scan to his/her high-resolution anatomical scan using an affine transformation with 6 DOF; 2) Registering each participant's high-resolution anatomical scan to the MNI standard-space 2mm brain template using an affine transformation with 12 DOF; 3) Performing a follow-up anatomical-to-standard affine registration with 12 DOF and applying a binarized brainstem mask (Harvard-Oxford atlas at 50% probability) as a reference weight [40]. Then we used the same beta series correlation analysis method as outlined above, with the mean parameter estimates extracted from the PPA and the frontoparietal network from data processed using the standard whole-brain alignment process. Condition-specific seed correlation maps were produced for the relationship between these cortical seeds' signals and signals in voxels within the brainstem mask. Given our a-priori prediction of LC involvement in arousal-salience interactions based on our GANE model simulation and the small size of the LC, we applied voxel-based thresholding combined with false recovery rate (FDR) correction ($q = .01$) based on the statistical map within the brainstem mask (from Harvard-Oxford atlas).

Code Availability

The code associated with the neural network simulation and with the experimental tasks are publicly available at https://osf.io/zw8aj/.

Data Availability

The behavioral and summarized data from the current study are available at https://osf.io/zw8aj/. The MRI data are available at the OpenNeuro repository at https://openneuro.org/datasets/ds001242.

References

1. Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience, 28*, 403-450.
2. Mather, M., Clewett, D., Sakaki, M., & Harley, C. W. (2016). Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory. *Behavioral and Brain Sciences, 39*, e200.
3. Mather, M., & Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspectives on Psychological Science, 6*, 114-133.
4. Lee, T. H., Sakaki, M., Cheng, R., Velasco, R., & Mather, M. (2014). Emotional arousal amplifies the effects of biased competition in the brain. *Social Cognitive and Affective Neuroscience, 9*(12), 2067-2077.
5. Sutherland, M. R., & Mather, M. (2012). Negative arousal amplifies the effects of saliency in short-term memory. *Emotion, 12*, 1367-1372.
6. Samuels, E. R., & Szabadi, E. (2008). Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. *Current Neuropharmacology, 6*(3), 235-253.
7. Womelsdorf, T., & Everling, S. (2015). Long-range attention networks: circuit motifs underlying endogenously controlled stimulus selection. *Trends in Neurosciences, 38*(11), 682-700.
8. Zhang, S., Xu, M., Kamigaki, T., Do, J. P. H., Chang, W.-C., Jenvay, S., . . . Dan, Y. (2014). Long-range and local circuits for top-down modulation of visual cortex processing. *Science, 345*(6197), 660-665.
9. Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201-215.
10. Guedj, C., Meunier, D., Meunier, M., & Hadj-Bouziane, F. (2017). Could LC-NE-dependent adjustment of neural gain drive functional brain network reorganization? *Neural Plasticity, 2017*.
11. Hernaus, D., Casales Santa, M. M., Offermann, J. S., & Van Amelsvoort, T. (2017). Noradrenaline transporter blockade increases fronto-parietal functional connectivity relevant for working memory. *European Neuropsychopharmacology, 27*(4), 399-410.
12. Strange, B. A., & Dolan, R. J. (2007). Beta-adrenergic modulation of oddball responses in humans. *Behav Brain Funct, 3*, 29.
13. Bigham, M. H., & Lidow, M. S. (1995). Adrenergic and serotonergic receptors in aged monkey neocortex. *Neurobiology of Aging, 16*(1), 91-104.
14. Moore, T. L., Schettler, S. P., Killiany, R. J., Herndon, J. G., Luebke, J. I., Moss, M. B., & Rosene, D. L. (2005). Cognitive impairment in aged rhesus monkeys associated with monoamine receptors in the prefrontal cortex. *Behavioural Brain Research, 160*(2), 208-221.
15. Berchtold, N. C., Coleman, P. D., Cribbs, D. H., Rogers, J., Gillen, D. L., & Cotman, C. W. (2013). Synaptic genes are extensively downregulated across multiple brain regions in normal human aging and Alzheimer's disease. *Neurobiology of Aging, 34*(6), 1653-1661.
16. Erraji-Benchekroun, L., Underwood, M. D., Arango, V., Galfalvy, H., Pavlidis, P., Smyrniotopoulos, P., . . . Sibille, E. (2005). Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. *Biological Psychiatry, 57*(5), 549-558.
17. Rozycka, A., & Liguz-Lecznar, M. (2017). The space where aging acts: focus on the GABAergic synapse. *Aging cell, 16*, 634-643.

18. Kann, O., Papageorgiou, I. E., & Draguhn, A. (2014). Highly energized inhibitory interneurons are a central element for information processing in cortical networks. *Journal of Cerebral Blood Flow and Metabolism, 34*(8), 1270-1282.
19. Hua, T., Kao, C., Sun, Q., Li, X., & Zhou, Y. (2008). Decreased proportion of GABA neurons accompanies age-related degradation of neuronal function in cat striate cortex. *Brain Research Bulletin, 75*(1), 119-125.
20. Spiegel, A. M., Koh, M. T., Vogt, N. M., Rapp, P. R., & Gallagher, M. (2013). Hilar interneuron vulnerability distinguishes aged rats with memory impairment. *Journal of Comparative Neurology, 521*(15), 3508-3523.
21. Braak, H., & Braak, E. (1986). Ratio of pyramidal cells versus non-pyramidal cells in the human frontal isocortex and changes in ratio with ageing and Alzheimer's disease. *Progress in Brain Research, 70*, 185-212.
22. Stanley, E. M., Fadel, J. R., & Mott, D. D. (2012). Interneuron loss reduces dendritic inhibition and GABA release in hippocampus of aged rats. *Neurobiology of Aging, 33*(2), 431. e431-431. e413.
23. Avelar-Pereira, B., Bäckman, L., Wåhlin, A., Nyberg, L., & Salami, A. (2017). Age-related differences in dynamic interactions among default mode, frontoparietal control, and dorsal attention networks during resting-state and interference resolution. *Frontiers in Aging Neuroscience, 9*, 152.
24. DuPre, E., & Spreng, R. N. (2017). Structural covariance networks across the life span, from 6 to 94 years of age. *Network Neuroscience, 1*(3), 302-323.
25. Grady, C., Sarraf, S., Saverino, C., & Campbell, K. (2016). Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiology of Aging, 41*, 159-172.
26. Mitchell, K. J., Ankudowich, E., Durbin, K. A., Greene, E. J., & Johnson, M. K. (2013). Age-related differences in agenda-driven monitoring of format and task information. *Neuropsychologia, 51*(12), 2427-2441.
27. Nashiro, K., Sakaki, M., Braskie, M. N., & Mather, M. (2017). Resting-state networks associated with cognitive processing show more age-related decline than those associated with emotional processing. *Neurobiology of Aging, 54*(Supplement C), 152-162.
28. Siman-Tov, T., Bosak, N., Sprecher, E., Paz, R., Eran, A., Aharon-Peretz, J., & Kahn, I. (2017). Early Age-Related Functional Connectivity Decline in High-Order Cognitive Networks. *Frontiers in Aging Neuroscience, 8*(330).
29. Downing, P. E., Chan, A. W. Y., Peelen, M. V., Dodds, C. M., & Kanwisher, N. (2006). Domain specificity in visual cortex. *Cerebral Cortex, 16*(10), 1453-1461.
30. Slaney, T. R., Mabrouk, O. S., Porter-Stransky, K. A., Aragona, B. J., & Kennedy, R. T. (2013). Chemical gradients within brain extracellular space measured using low flow push–pull perfusion sampling in vivo. *ACS Chemical Neuroscience, 4*(2), 321-329.
31. Harley, C. W., Lalies, M. D., & Nutt, D. J. (1996). Estimating the synaptic concentration of norepinephrine in dentate gyrus which produces β-receptor mediated long-lasting potentiation in vivo using microdialysis and intracerebroventricular norepinephrine. *Brain Research, 710*(1), 293-298.
32. Salgado, H., Kohr, G., & Trevino, M. (2012). Noradrenergic 'tone' determines dichotomous control of cortical spike-timing-dependent plasticity. *Scientific Reports, 2*, 7.
33. Ferrero, J. J., Alvarez, A. M., Ramirez-Franco, J., Godino, M. C., Bartolome-Martin, D., Aguado, C., . . . Sanchez-Prieto, J. (2013). β-adrenergic receptors activate Epac, translocate Munc13-1 and

enhance the Rab3A-Rim1α interaction to potentiate glutamate release at cerebrocortical nerve terminals. *Journal of Biological Chemistry*, jbc. M113. 463877.

34. Nai, Q., Dong, H.-W., Hayar, A., Linster, C., & Ennis, M. (2009). Noradrenergic regulation of GABAergic inhibition of main olfactory bulb mitral cells varies as a function of concentration and receptor subtype. *Journal of Neurophysiology, 101*(5), 2472-2484.
35. Amara, S. G., & Kuhar, M. J. (1993). Neurotransmitter transporters: recent progress. *Annual Review of Neuroscience, 16*(1), 73-93.
36. Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective, & Behavioral Neuroscience, 7*(1), 1-17.
37. Scolari, M., Seidl-Rathkopf, K. N., & Kastner, S. (2015). Functions of the human frontoparietal attention network: Evidence from neuroimaging. *Current Opinion in Behavioral Sciences, 1*, 32-39.
38. Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews, 42*(1), 33-84.
39. Toussay, X., Basu, K., Lacoste, B., & Hamel, E. (2013). Locus coeruleus stimulation recruits a broad cortical neuronal network and increases cortical perfusion. *The Journal of Neuroscience, 33*(8), 3390-3401.
40. Napadow, V., Dhond, R., Kennedy, D., Hui, K. K., & Makris, N. (2006). Automated brainstem co-registration (ABC) for MRI. *Neuroimage, 32*(3), 1113-1119.
41. Laird, A. R., Fox, P. M., Eickhoff, S. B., Turner, J. A., Ray, K. L., McKay, D. R., . . . Fox, P. T. (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of Cognitive Neuroscience, 23*(12), 4022-4037.
42. Zhang, S., Hu, S., Chao, H. H., & Li, C.-S. R. (2015). Resting-State Functional Connectivity of the Locus Coeruleus in Humans: In Comparison with the Ventral Tegmental Area/Substantia Nigra Pars Compacta and the Effects of Age. *Cerebral Cortex*, bhv172.
43. Gannon, M., & Wang, Q. (2018). Complex noradrenergic dysfunction in Alzheimer's disease: Low norepinephrine input is not always to blame. *Brain Research*.
44. Healey, M. K., Hasher, L., & Campbell, K. L. (2013). The role of suppression in resolving interference: Evidence for an age-related deficit. *Psychology and Aging, 28*(3), 721.
45. Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience, 8*(10), 1298-1300.
46. Mitchell, K. J., Johnson, M. R., Higgins, J. A., & Johnson, M. K. (2010). Age differences in brain activity during perceptual versus reflective attention. *NeuroReport, 21*(4), 293-297.
47. Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*, S208-S219.
48. Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.
49. Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155.
50. Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging, 23*, 137-152.
51. Tohka, J., Foerde, K., Aron, A. R., Tom, S. M., Toga, A. W., & Poldrack, R. A. (2008). Automatic independent component labeling for artifact removal in fMRI. *Neuroimage, 39*(3), 1227-1245.

52. Brady, T. F., Konkle, T., Alvarez, G. A., & Oliva, A. (2008). Visual long-term memory has a massive storage capacity for object details. *Proceedings of the National Academy of Sciences, 105*(38), 14325-14329.
53. Brainard, D. H. (1997). The psychophysics toolbox. *Spatial Vision, 10*(4), 433-436.
54. Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spatial Vision, 10*(4), 437-442.
55. Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392*(6676), 598-601.
56. Epstein, R. (2005). The cortical basis of visual scene processing. *Visual Cognition, 12*(6), 954-978.
57. Grill-Spector, K., & Malach, R. (2001). fMR-adaptation: a tool for studying the functional properties of human cortical neurons. *Acta Psychologica, 107*(1-3), 293-321.
58. Erez, Y., & Yovel, G. (2014). Clutter modulates the representation of target objects in the human occipitotemporal cortex. *Journal of Cognitive Neuroscience, 26*(3), 490-500.
59. Altmann, C. F., Deubelius, A., & Kourtzi, Z. (2004). Shape saliency modulates contextual processing in the human lateral occipital complex. *Journal of Cognitive Neuroscience, 16*(5), 794-804.
60. Gazzaley, A., Rissman, J., Cooney, J., Rutman, A., Seibert, T., Clapp, W., & D'Esposito, M. (2007). Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. *Cerebral Cortex, 17*, I125-I135.
61. Mumford, J. A., Turner, B. O., Ashby, F. G., & Poldrack, R. A. (2012). Deconvolving BOLD activation in event-related designs for multivoxel pattern classification analyses. *Neuroimage, 59*(3), 2636-2643.
62. Okubo, Y., Sekiya, H., Namiki, S., Sakamoto, H., Iinuma, S., Yamasaki, M., . . . Iino, M. (2010). Imaging extrasynaptic glutamate dynamics in the brain. *Proceedings of the National Academy of Sciences, 107*(14), 6526-6531.
63. Keren, N. I., Lozar, C. T., Harris, K. C., Morgan, P. S., & Eckert, M. A. (2009). In vivo mapping of the human locus coeruleus. *Neuroimage, 47*(4), 1261-1267.

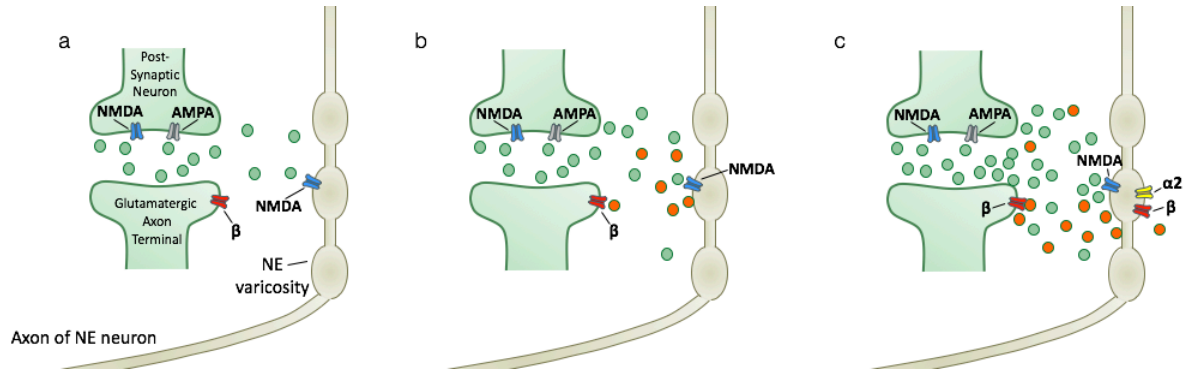

Figure 1. A graphical depiction of the proposed mechanism. (A) Glutamate spills over from glutamatergic synapses at the sites of excited representations [62] (e.g., neurons responding to the salient building depicted in Figure 2B). (B) If the LC happens to be activated (i.e., depolarized) at the same time that glutamate reaches NMDA receptors on LC axons, this triggers more local release of NE from those LC varicosities. (C) Elevated local levels of NE activate beta-adrenergic receptors that further stimulate glutamate release, leading to a local hot spot of high excitation. Autoreceptors at LC varicosities also contribute to increasing neural gain by inhibiting NE release when low levels of NE activate alpha-adrenergic receptors but increasing NE release when high levels of NE activate beta-adrenergic receptors [for details see 2].

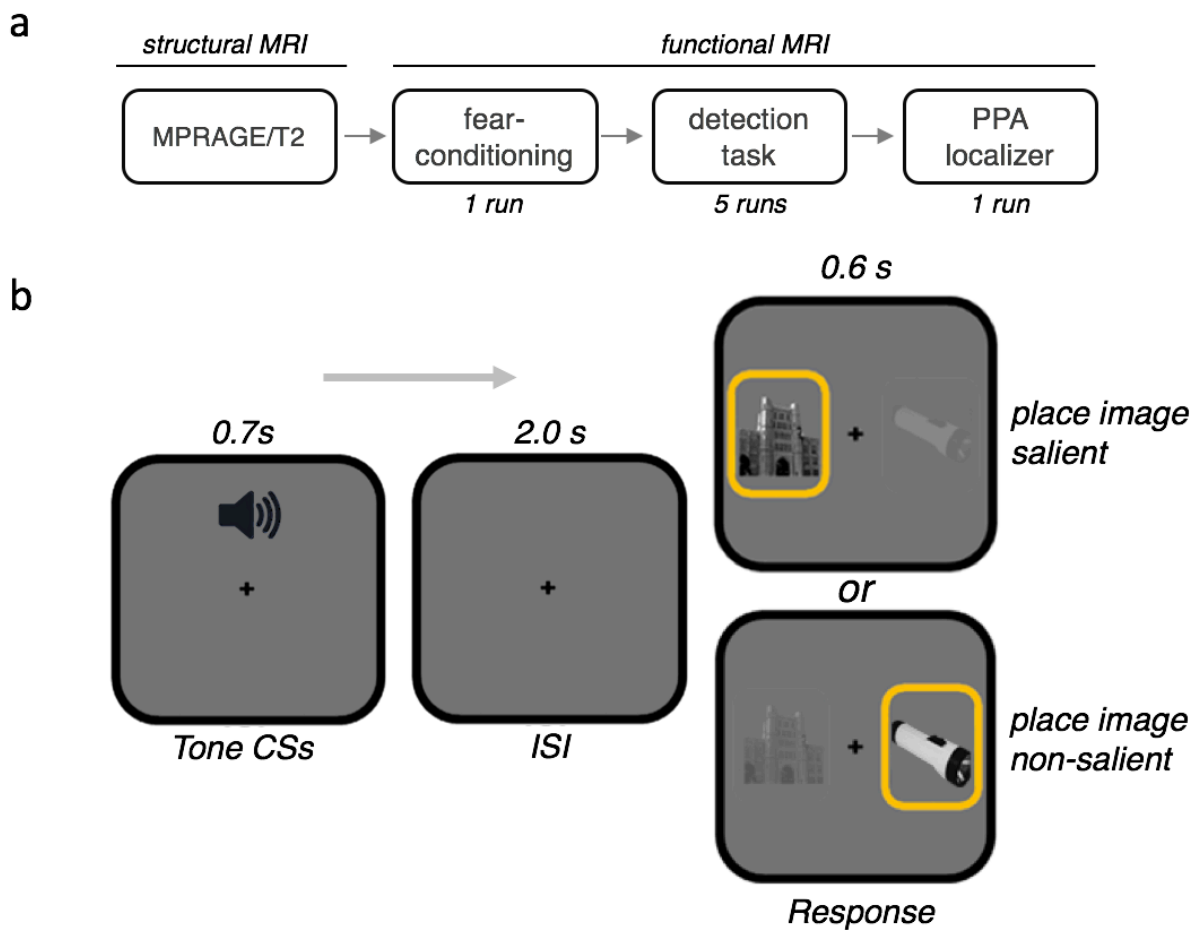

Figure 2. A) MRI session sequence. B) Schematic illustration of one trial for the detection task. Participants heard a tone for .7s, then after a 2-s interstimulus interval (ISI), were shown one salient image and one non-salient image and pressed a button to indicate whether the salient image was on the right or left. Salience was manipulated both by varying the contrast between the two images and by having the more salient image have a yellow border.

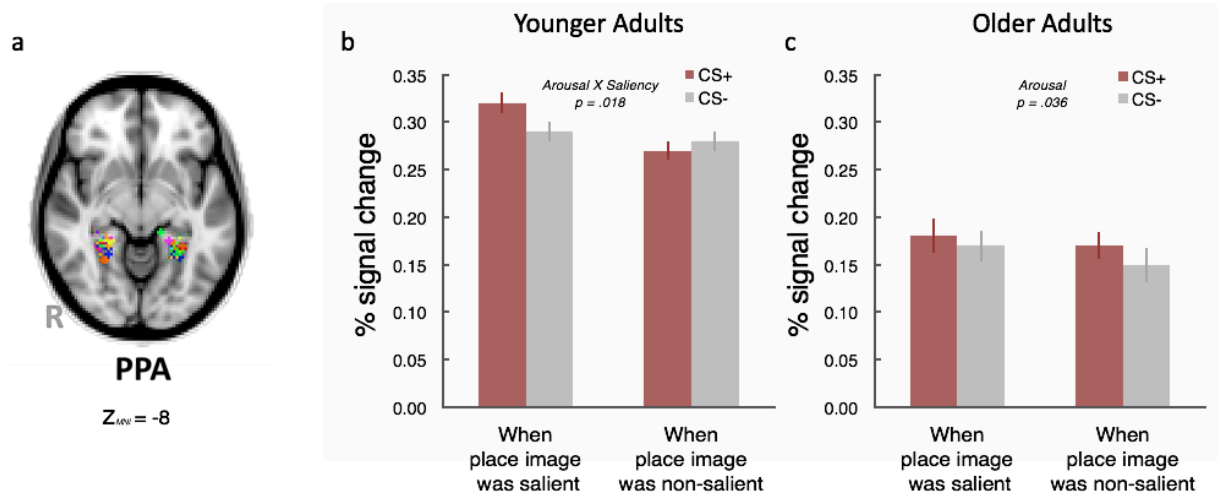

Figure 3. Place area activity during the spatial detection task. (A) Location of individual PPAs (B) Averaged % signal changes in the PPA region as a function of trial type and arousal in younger adults (N=28) and (C) in older adults (N=24). For distributions of individual data points, please see Supplementary Figure 3.

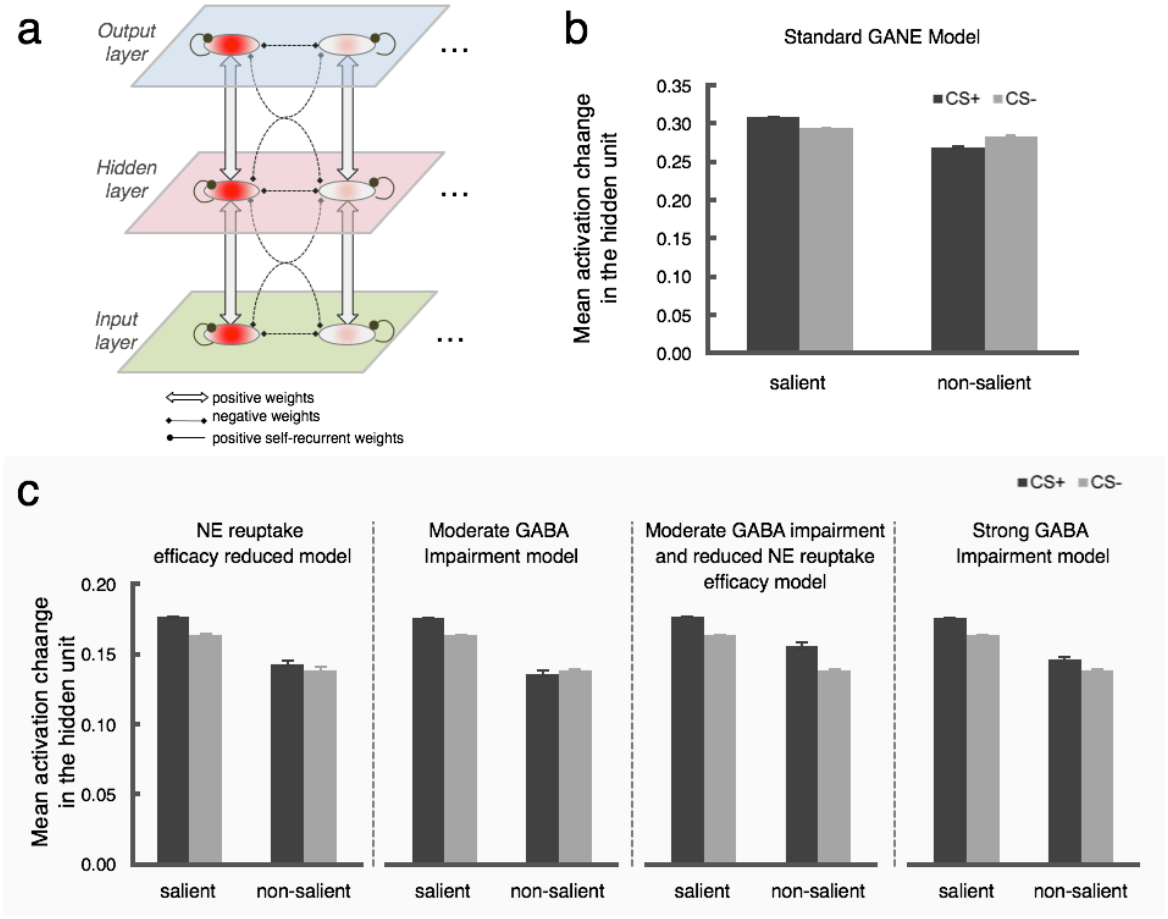

Figure 4. Computational modelling. (A) Schematic illustration of the model architecture. Only two units in each layer are displayed. (B) Simulated values for activation in the GANE model hidden unit representing the place area when arousal is high or low and the place stimuli representation is salient or nonsalient. (C) Examining effects of impaired inhibitory mechanisms in the model to simulate older adults. 1st panel: reduced NE reuptake efficacy based on impaired alpha2a function. 2nd panel: moderately impaired GABA function. 3rd panel: reduced NE reuptake efficacy and moderately impaired GABA function. 4th panel: Strong GABA impairment. Notes: The sample size in each simulation was 50; y-axis error bars indicate standard error of the mean.

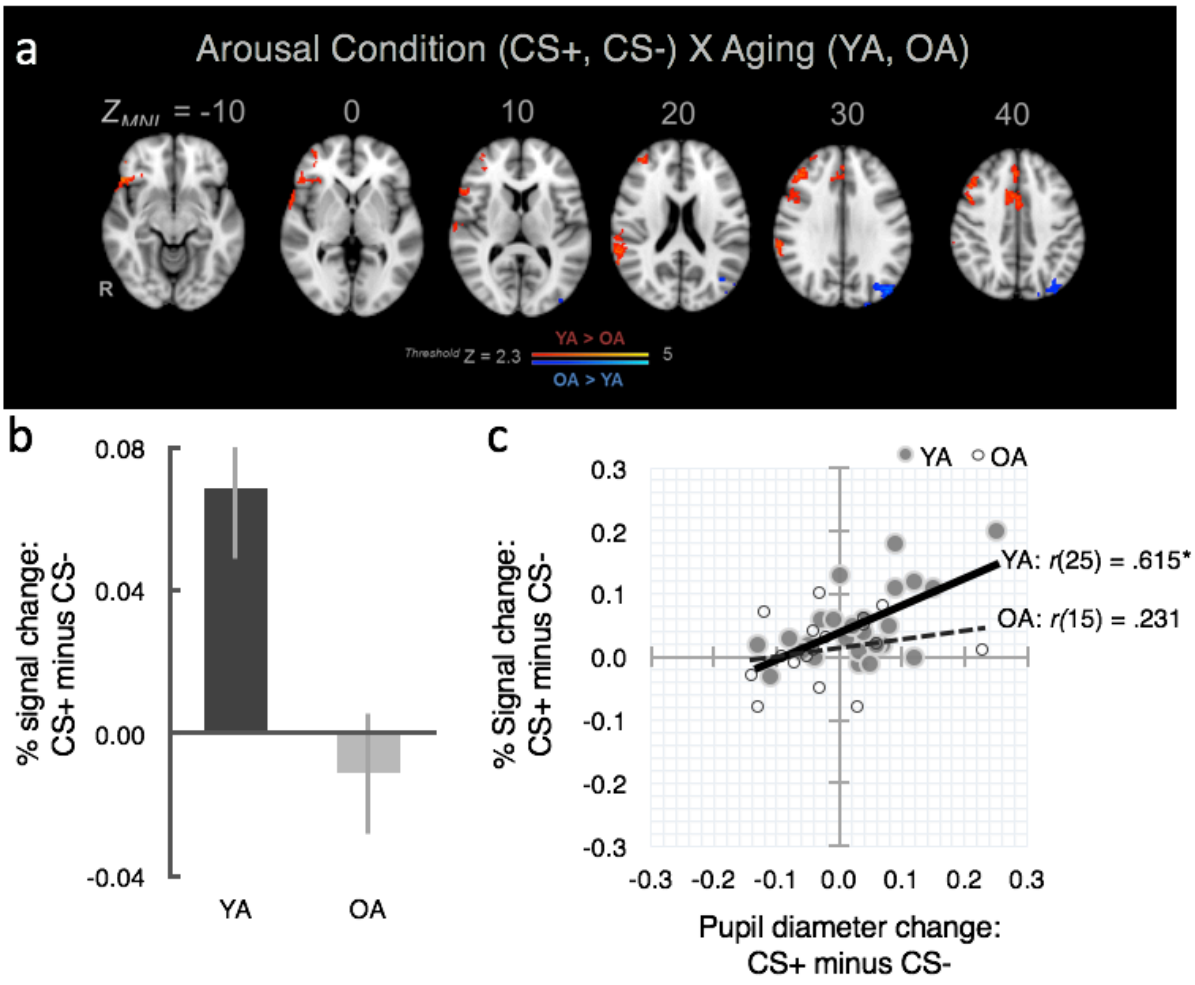

Figure 5. (A) Whole-brain analysis results of the Arousal X Age Group interaction and (B) extracted percentage signal change (CS+ minus CS-) within the frontoparietal network clusters for younger adults (YA, N =28) and for older adults (OA, N = 24). Although error bars are included for the graph, it should not be interpreted inferentially. (C) Scatter plot illustrating the relationship between percentage signal change in the frontoparietal network region during the detection phase and pupil diameter changes during the post-tone period for each age group. *p = .001, 95% CI from non-parametric testing with 5,000 bootstrapped samples, (YA N =27 and OA N = 17). To see distributions of individual data points for (B), please see Supplementary Figure 5.

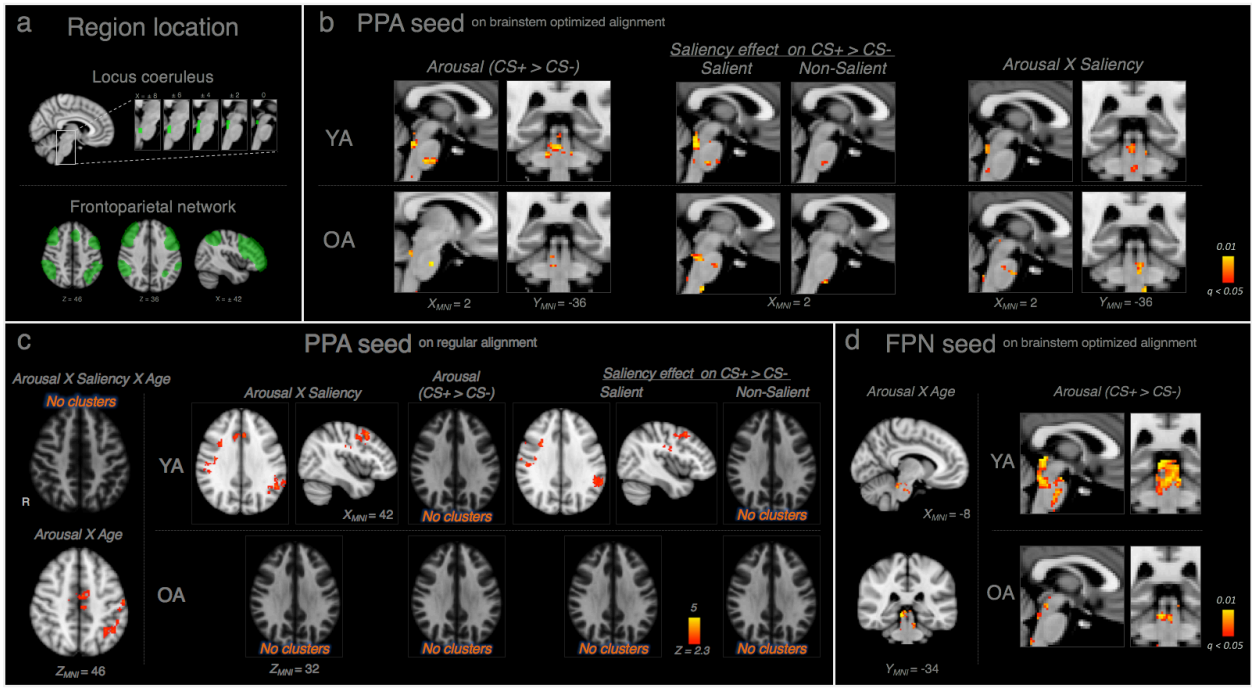

Figure 6. (A) For reference for the connectivity analyses, we provide images of the target regions of interest; the locus coeruleus (LC) mask is from Keren et al. [63], and the bilateral frontoparietal network (FPN) mask is from Laird et al. [41]. (B) Parahippocampal place area (PPA; individually localized for each participant) served as the seed region with brainstem as the target; both younger and older adults had greater LC activity for arousing than non-arousing trials (left panel), with this arousal effect significant in the salient condition but not in the non-salient condition (middle panel), leading to an arousal-by-saliency interaction within the LC (left panel). (C) The same PPA seed with cortex as the target revealed regions in the FPN that showed age differences in how much arousal modulates functional connectivity. (D) Using the Laird et al. (2011) FPN mask shown in panel A as the seed region and the brainstem as the target region revealed greater increases in LC-FPN functional connectivity under arousal for younger than for older adults. Note: YA, younger adult (N=28); OA, older adult (N=24).

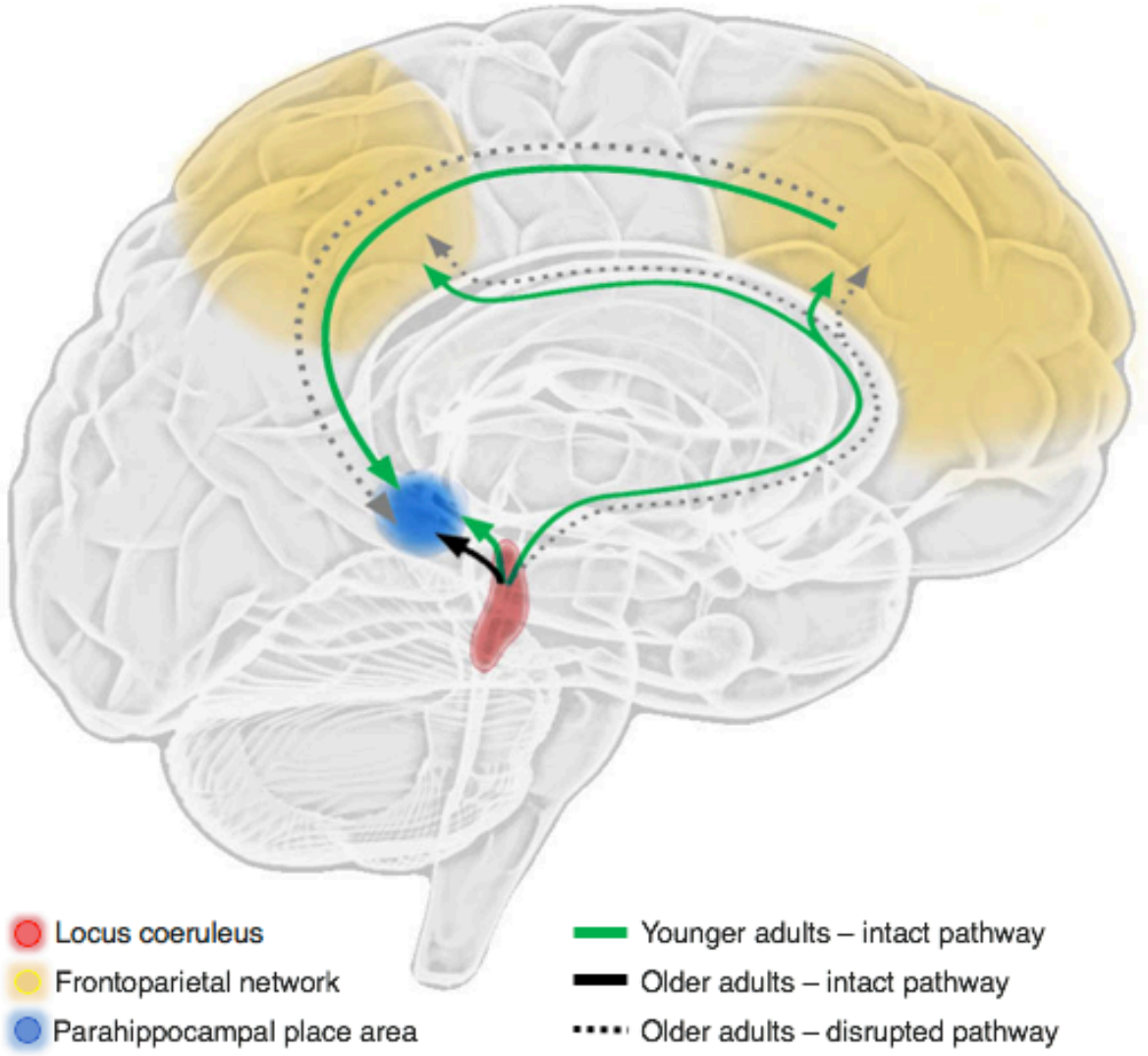

Figure 7. The arrows summarize the increased functional connectivity observed under arousal. For younger adults, there were increases in functional connectivity under arousal in all three pathways represented here. For older adults, arousal increased functional connectivity between the locus coeruleus (LC) and local cortical representations (here the parahippocampal place area or PPA) especially when that cortical representation was of a salient stimulus, just as seen for younger adults. However, older adults showed smaller increases in LC-frontoparietal functional connectivity than younger adults did, and older adults showed no detectable increases under arousal in functional connectivity between the frontoparietal network and the PPA. This pattern of results suggests that older adults had intact LC direct modulation of salient cortical representations of place stimuli under arousal, but the frontoparietal network no longer responded effectively to LC and so frontoparietal contributions to attentional selectivity did not increase under arousal.