The locus coeruleus-norepinephrine system role in cognition and how it changes with aging

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Abstract

With its extensive projections that release norepinephrine (NE), the locus coeruleus (LC) has a major influence on the rest of the brain and influences cognitive processes. It aggregates signals regarding arousal from various other brain systems and modulates neural processing to become more focused under arousal. Because of challenges in measuring its structure and function in living humans, there has historically been little focus on the LC's role in determining the fate of cognition in aging. However, in the past few years, a growing number of animal and human findings suggest that the integrity of the LC-NE system plays a key role in maintaining late life cognition. In particular, age declines in selective attention, episodic memory, working memory and cognitive flexibility have been linked to the LC. Furthermore, LC degeneration can accelerate progression of Alzheimer's disease whereas an intact LC may contribute to cognitive reserve.

The locus coeruleus (LC) consists of two bilateral small brainstem nuclei that are the source of most of the brain's norepinephrine (NE; Berridge & Waterhouse, 2003). Although small, LC neurons have axons that project through much of the rest of the brain (Schwarz et al., 2015), typically releasing norepinephrine into the extrasynaptic space rather than at specific synapses (Vizi, Fekete, Karoly, & Mike, 2010). Given this anatomy and its central role in arousal, the LC has been considered ideal for broadcasting the message to pay extra attention to goal-relevant or emotionally salient information under arousing circumstances, such as when under pressure or threat. However, findings that arousal affects representations differently depending on their salience or priority, suggests that the LC does something more sophisticated than simply providing a one-size-fits-all broadcast message (Mather, Clewett, Sakaki, & Harley, 2016). As reviewed in this chapter, local cortical conditions help control how NE release modulates attention and cognition, allowing LC activity to increase cognitive selectivity and attentional focus. This chapter also covers emerging evidence that LC integrity plays a more important role in late life cognition than previously appreciated and that the LC is one of the earliest sites of Alzheimer's-related tau pathology in the brain. In particular, changes in the LC-NE system in aging appear to contribute to declines in attention and memory.

The LC integrates information about brain arousal state

Although the LC projects widely to much of the rest of the brain, in most cases, this communication is not reciprocated (Figure 1). Instead, inputs to the LC come from a select group of brain regions that provide information about a wide array of types of arousal, allowing the LC to be a hub region for integrating information about arousal (for review see Samuels & Szabadi, 2008). This information includes signals regarding stress from the amygdala and paraventricular nucleus of the hypothalamus, movement and motivation from dopaminergic nuclei, wakefulness and sleep from serotonergic, cholinergic, and dopaminergic nuclei as well

as the hypothalamus and medulla, and additional arousal signals from histamine and orexin neurons. There is little cortical input to the LC, but a notable exception comes from prefrontal cortex, which provides signals regarding effort-related arousal. This prefrontal influence is reflected in increased pupil dilation during working memory (Huang & Mather, 2018; Figure 2), as LC activity increases pupil dilation (Joshi, Li, Kalwani, & Gold, 2015).

Local fluctuations in glutamate signal priority to the LC-NE system

Having one brain region that integrates all these disparate signals about arousal provides the foundation to organize neural processing during many different types of arousal in a similar way. A common need during high arousal situations that involve high effort, threat, stress or motivation is to focus resources on what really matters at that moment and not be distracted by low priority information. But without direct input from most of the cortex how can the LC 'know' which neural representations are currently high priority?

Behaviorally, it is clear that arousal makes attention more selective. In particular, whatever already would stand out due to its bottom-up or top-down priority (i.e., perceptual salience or goal relevance) stands out even more, whereas lower priority stimuli receive even less attention than they would otherwise (Mather & Sutherland, 2011). For instance, when letters are flashed quickly on a white screen and people are asked to report which letters they saw, they are more likely to report letters that are more perceptually salient than the other letters. However, if they had just heard an arousing sound seconds before seeing the letters, they are even more likely to report the more salient letters and less likely to report the less salient letters (Sutherland & Mather, 2012).

Given that NE is typically released into the extrasynaptic space, how can specific synaptic networks that are currently high priority be targeted for enhancement while currently low priority networks are suppressed? One potential solution to this problem of the 'priority-blind' LC is to have some local cortical signal of priority that modulates the effect of NE within the

neural network generating the signal. In the brain, a simple signal of the current priority of a particular stimulus (for instance, the letter “P” that just flashed on the screen) is the level of excitatory activity at the neurons representing that stimulus. As outlined in the ‘Glutamate Amplifies Noradrenergic Effects’ (GANE) model (Mather et al., 2016), glutamate (the brain’s primary excitatory neurotransmitter) spills over from synapses allowing it to stimulate receptors on nearby LC axons (Figure 3a). These glutamatergic receptors stimulate more local release of NE (Figure 3b), which in turn activates excitatory β-adrenergic receptors that lead to more glutamate release (Figure 3c). This feedback mechanism stimulates hot spots of even higher activity among strongly activated neurons.

Having different types of noradrenergic receptors with different thresholds for activation plays a key role in allowing this increase in cortical gain. There are three classes of noradrenergic receptors: α2-, α1-, and β-adrenergic receptors, listed in order of their affinity for NE, as α2-adrenergic receptors require the lowest levels of NE to be activated, whereas β-adrenergic receptors require many times more NE to be activated (Ramos & Arnsten, 2007; Salgado, Kohr, & Trevino, 2012). α2a-adrenergic receptors generally have inhibitory effects, serving as autoreceptors on LC neurons or on glutamatergic or other neurons that reduce neurotransmitter release (Starke, 2001). In contrast, β-adrenergic receptors typically have excitatory effects (Berridge, 2008; McCormick, Pape, & Williamson, 1991) and promote synaptic plasticity (O'Dell, Connor, Gelinas, & Nguyen, 2010).

In rodents, stimulating LC and then measuring NE levels via microdialysis indicate that stimulating LC activity can increase NE release in cortex or hippocampus between 1-5 times baseline NE levels (Berridge & Abercrombie, 1999; Fernández-Pastor & Meana, 2002; Florin-Lechner, Druhan, Aston-Jones, & Valentino, 1996; Pudovkina, Kawahara, de Vries, & Westerink, 2001). This is a much smaller range than the difference in NE levels needed to activate α2-adrenergic vs. β-adrenergic receptors (see Mather et al., 2016), suggesting that

differences in LC activity are not in themselves enough to account for the full range of NE levels that occur elsewhere in the brain. Thus, local cortical conditions such as glutamate levels likely play a key role in allowing for a greater range of NE levels, as well as levels that are high enough to activate β-adrenergic receptors that stimulate synaptic change.

In summary, the LC-NE system integrates many signals related to the brain's arousal state and has a wide network of afferent projections where it typically releases NE into extrasynaptic space. Yet despite relying on volume transmission, it can interact with local cortical excitation levels to modulate its impact on neural activity to promote even more selective processing during states of arousal.

The nature of the LC-NE system makes it especially vulnerable in aging

The features that allow the LC to be a centralized aggregator of arousal signals that can broadcast messages throughout the brain yet have quite specific targeted effects make it more vulnerable in aging (Mather & Harley, 2016). In particular, the LC faces a uniquely high set of risk factors for tau pathology. One consists of the long, thin, and only sparsely myelinated nature of LC axons. Tau pathology tends to occur in neurons with long and thin-caliber axons with little or no myelin (Braak & Del Tredici, 2015). In contrast, short-axoned or highly myelinated projection neurons resist tau pathology. Highly myelinated neurons also transmit signals faster. So why would the LC-NE system, a key system involved in arousal and therefore involved in responding to threat, have slow axonal transmission, instead of being optimized for speed?

In general, cells involved in sensing internal states and maintaining homeostasis are mostly unmyelinated, which in turn may enhance axons' ability to gather information about their mileau, via exchange of ions or extracellular current flow (Damasio & Carvalho, 2013). This is consistent with GANE model's postulate that the LC is sensitive to local cortical excitation levels, releasing more NE where there are already high levels of excitation, allowing highly

active mental representations to get even more highly activated under arousal (Mather et al., 2016). To calibrate local NE release levels to local cortical conditions requires extensive two-way communication along the far-reaching LC axons. The cost of this may come in vulnerability to toxin exposure.

Furthermore, no other neuronal system has as extensive an exposure to circulating blood as the LC (Braak & Del Tredici, 2015; Pamphlett, 2014). Locus coeruleus neurons regulate the majority of the brain's microvasculature, with each LC neuron (with a tiny diameter of 45 μm) estimated to innervate nearly a tennis court length worth of capillaries (20 meters; Pamphlett, 2014). Thus, a small amount of blood-borne toxic material could pose a relatively high burden for LC neurons.

In addition to blood, cranial nerves such as the trigeminal and vagal nerves provide another route for toxic substances to enter the brain. For instance, in mice, avian flu virus travels from the gut and peripheral nervous system to the brainstem solitary nucleus and from there to LC, substantia nigra and other brainstem nuclei, where the virus causes protein phosphorylation and aggregation that persists long after infection (Jang et al., 2009). Particulate matter in air also leads to vagal nerve inflammation (Villarreal-Calderon et al., 2010) and post-mortem examination of Mexico City residents with high exposures to air pollution show accelerated rates of Alzheimer's pathology in infants' and children's brainstems (Calderón-Garcidueñas et al., 2018).

Another risk factor for the LC is its high energy need. LC axons' sparse myelination increases the energy needed to transmit signals (Braak & Del Tredici, 2015), making the neurons vulnerable to activity-dependent oxidant stress (Matschke et al., 2015). In addition, LC neurons have intrinsic pacemaker mechanisms that maintain firing even when glutamate and GABA inputs are blocked, and are modulated by calcium channels (Matschke et al., 2015). A comparison across neurogenerative disorders suggests that the types of neurons that are most vulnerable are those that exhibit highly regulated firing properties that rely heavily on calcium

regulation, which in turns depends on proper cellular homeostasis (Roselli & Caroni, 2015). Thus, there are a number of features that make the LC more vulnerable than most brain regions to degeneration over time.

Alzheimer's-related tau pathology is found in the LC early in adulthood

Recent findings suggest that Alzheimer's-related tau pathology first occurs in brainstem nuclei, in particular, in the LC, in most people by early adulthood. In a sample of 2332 autopsied brains of people ranging from 1 to 100 years old at death (with a diverse set of precipitating causes of death), only 10 brains (all younger than 24 years old) had no indication of abnormal tau anywhere in the brain (Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Another 58 brains had no abnormal cortical tau in the cortex but did have abnormal tau in the brainstem, predominantly in the locus coeruleus. From the LC, the path of tau pathology appeared to spread to the transentorhinal cortex and then to hippocampus and other cortical regions, with cortical amyloid β-peptide (Aβ) plaques emerging only after brainstem tau pathology. In samples with cognitive test data, neocortical tau pathology is more strongly associated with cognitive decline than amyloid pathology (Giannakopoulos, Gold, von Gunten, Hof, & Bouras, 2009; Nelson et al., 2012; Suemoto et al., 2017). In addition, in older adults, greater post-mortem LC neuronal density and higher LC neuron number are associated with better cognitive performance before death (Kelly et al., 2017; Wilson et al., 2013). Thus, understanding the LC's role in cognition in aging and how it relates to the spread of tau pathology throughout the brain is relevant even for "normal" aging.

LC-NE role in various cognitive functions in aging and Alzheimer's disease

Selective attention. As already outlined, the LC integrates information about arousal states and, as arousal increases, release of NE modulates cortical activity to increase the gain on processing and make it more selective (Mather et al., 2016). A recent study that manipulated

arousal via fear conditioned sounds and the salience of place vs. object images seen on each trial revealed a number of interesting findings about how arousal and LC activity affects attention differently in older than in younger adults (Lee et al., 2018). For younger adults, playing a tone that predicted a shock increased parahippocampal place area (PPA) activity when the place image was the more salient image on a trial but decreased PPA activity when the place was the less salient image (see also Lee, Sakaki, Cheng, Velasco, & Mather, 2014). In contrast, for older adults, arousal increased PPA activity in response to place images regardless of whether they were more or less salient than the competing object images. Thus, arousal increased the selectivity of attention for younger but not older adults.

The Glutamate Amplifies Noradrenergic Effects (GANE) model posits that greater excitation associated with processing salient stimuli under arousal is driven by local cortical control over how much NE is released when the LC is activated (Mather et al., 2016). Regions that are highly active and therefore have high levels of glutamate stimulate greater local release of NE, which in turns activates β-adrenergic receptors that stimulate more glutamate release, increasing excitation in that region. This model predicts that the LC and any particular region of cortex should be most coordinated in their activation levels when arousal is high (activating the LC) and that cortical region is highly active (for instance, the PPA during viewing of a highly salient picture of a place). Consistent with this prediction, both younger and older adults showed the greatest functional connectivity between LC and PPA on trials that were arousing and included a salient place image (Lee et al., 2018). Thus, the role of the LC in increasing excitation of highly active representations seems to be intact in older adults.

But then what can explain the failure of arousal to suppress non-salient stimuli in older adults? The coordination of stimuli salience or priority across different cortical regions relies on the frontoparietal network, which provides a priority map of the environment (Ptak, 2012). Lee et al. (2018) found that whereas, for younger adults, arousal increased activation levels within this frontoparietal network and increased its functional connectivity with the LC, arousal had a

significantly diminished impact on older adults' frontoparietal activation levels and frontoparietal-LC functional connectivity.

Perhaps the most obvious interpretation of these findings is that the LC is less effective at modulating frontoparietal activity in older adults. But findings that older adults show significantly **more** LC-frontoparietal functional connectivity at rest than do younger adults (Jacobs, Müller-Ehrenberg, Priovoulos, & Roebroeck, 2018; Min et al., under review; Zhang, Hu, Chao, & Li, 2016) raise the possibility that LC-NE system activity may be upregulated to compensate for age-related decline within the system (Mather, in press), leading to a higher tonic level of NE activity within frontoparietal regions, making it more difficult to further upregulate activity in these regions. The issue of potential upregulated tonic NE activity is addressed more fully in a later section. In any case, there are clear age-related changes in how the LC interacts with frontoparietal brain regions involved in attentional selectivity.

Episodic memory. NE plays an important role in episodic memory, especially for memory of highly salient arousing events and stimuli (Harley, 1987; McGaugh, 2004; Tully & Bolshakov, 2010). These beneficial effects of NE on episodic memory are typically driven by β-adrenergic receptors that can be activated by the glutamate-NE hot spot mechanism (Mather et al., 2016). Some have even argued that neuromodulators such as NE and dopamine are necessary for spike-timing-dependent long-term potentiation supporting memory consolidation (Huang et al., 2014; Johansen et al., 2014). Rodent research in which infusion of NE into the hippocampus or hippocampal slices eliminates age-related memory deficits suggest that decreased basal extracellular NE levels in the hippocampus in older rodents accounts for a substantial component of their impaired spatial and emotional memory (Luo et al., 2015; Mei et al., 2015).

Because extracellular NE levels cannot be measured without invasive techniques, we have less information regarding LC-NE function and its role in memory in humans. However, MRI sequences have been developed that indicate the location of the LC (Betts, Cardenas-

Blanco, Kanowski, Jessen, & Düzel, 2017; Chen et al., 2014; Keren et al., 2015; Keren, Lozar, Harris, Morgan, & Eckert, 2009; Hämmerer et al., 2018; Langley, Huddleston, Liu, & Hu, 2017; Priovoulos et al., 2017; Sasaki et al., 2006). In humans, a dark pigment called neuromelanin accumulates in LC and substantia nigra neurons during catecholamine metabolism and sequesters potentially toxic chemicals such as iron. Neuromelanin combined with iron shortens the longitudinal (T1) relaxation of the tissue's net magnetization vector, more than iron alone (Trujillo et al., 2017). Thus, T1-weighted imaging sequences show hyperintensities in the locations corresponding with LC neuromelanin-containing neurons (Keren et al., 2015). As neuromelanin tends to accumulate slowly and be maintained within organelles within neurons until the neurons die (Zucca et al., 2017), among older adults LC degeneration should decrease LC T1-weighted MRI contrast in comparison with other control regions.

Consistent with this, older adults with greater LC contrast ratios tend to have better episodic memory. Among 22 older adults, MRI LC contrast ratios were positively associated with memory for pictures appearing before losses (Hämmerer et al., 2018). Furthermore, among 233 older adults, LC contrast ratios positively associated with a verbal learning task (Dahl et al., under review). These findings suggest that structural integrity of the LC in late life helps predict episodic memory performance.

Working memory. Animal research indicates that activation of α2a receptors in dorsolateral prefrontal cortex enhances working memory processes (Arnsten & Goldman-Rakic, 1985; Franowicz et al., 2002). In humans, links between LC and working memory function have been identified using pupil dilation as a window into LC-NE function (Granholm et al., 2017). Typically, on a digit-span task, pupil dilation increases as people hear and try to maintain each additional digit in working memory (Kahneman & Beatty, 1966; Figure 2). Older adults with memory deficits show greater pupil dilation at low loads and reduced pupil dilation at high loads

than non-impaired older adults (Granholm et al., 2017), which may relate to impairments in LC function.

Cognitive flexibility. Rodent studies indicate a key role for the LC in cognitive flexibility. For instance, reversibly silencing the LC using optogenetic techniques selectively impaired learning that was dependent on cognitive flexibility, such as reversal learning and extra-dimensional set-shifting (Janitzky et al., 2015). Furthermore, a transgenic rat model of Alzheimer's disease (expressing disease-causing mutant amyloid precursor protein and presenilin-1) showed hyperphosphorylated tau in the LC before it spread to entorhinal cortex and were worse at reversal learning compared to their wild-type littermates (Rorabaugh et al., 2017). This reversal learning impairment was eliminated by activating the LC via designer receptors.

Is the LC-NE system the neural mechanism of cognitive reserve?

Education and working in more cognitively challenging professions are associated with reduced risk of being diagnosed with Alzheimer's disease, but a faster decline once diagnosed (Stern, 2012). One possibility is that the LC-NE system is a key neural mechanism underlying this phenomenon known as 'cognitive reserve' (Mather & Harley, 2016; Robertson, 2014, 2013). Experiencing mental challenges and novel situations stimulate the LC and, in turn, should increase the protective effects of NE release outlined earlier. In particular, the anti-inflammatory effects of NE rely on β-adrenergic receptor activation. Based on the GANE model outlined earlier, the high levels of NE required to activate β-adrenergic receptors are most likely to occur at cortical sites processing salient or high priority stimuli during phasic LC activation. This combination is especially likely to occur during the sort of mentally stimulating situations encountered during learning new things or navigating challenging social situations.

This fits with education delaying onset of Alzheimer's disease, but how can it be reconciled with decline once diagnosed being faster among the higher educated? Stern (2012) argued that those with higher cognitive reserve due to education or high professional attainment are at later stages of the disease at the point that it is detected, because they are better able to compensate for the pathology. In addition, by the time someone is in the symptomatic phases of Alzheimer's disease, the anti-inflammatory benefits of β-adrenergic receptor activity may be outweighed by the fact that β-adrenergic activity also stimulates Aβ production (Ni et al., 2006). Aβ is a by-product of mental activity that is typically flushed out during sleep (Shokri-Kojori et al., 2018), but it becomes toxic in Alzheimer's disease when it is no longer cleared out as effectively and aggregates into Aβ plaques.

Do aging and AD increase or deplete NE?

To assess NE levels in living Alzheimer's disease patients, researchers typically rely on cerebral spinal fluid and blood samples. These samples reveal Alzheimer's disease patients have normal or elevated levels of NE. The other standard approach to quantify NE is from homogenized tissue from postmortem brains. In these studies, brain samples from Alzheimer's disease patients have depleted NE levels (for review see Mather & Harley, 2016).

How can these opposite findings be reconciled? One possibility is that, in Alzheimer's disease, overall NE levels may be lower due to fewer NE-containing LC neurons but circulating levels of NE in extracellular space remain constant or even increase (Gannon & Wang, 2018). Indeed, measurements of NE levels and dynamics in fresh brain tissue from patients who had diagnostic craniotomy indicated maintained ability of neurons to release NE but decreased varicosity uptake of NE and decreased tissue levels of NE in Alzheimer's patients compared with controls (Palmer et al., 1987).

As Alzheimer's disease slowly diminishes the number of functioning LC neurons, surviving neurons may upregulate their NE release (Gannon & Wang, 2018). Consistent with this possibility, Alzheimer's disease patients have greater mRNA expression per remaining LC neuron of tyrosine hydroxylase, the rate limiting enzyme in the synthesis of NE or NE transporter (NET) (Szot et al., 2000; Szot et al., 2006). As elevated levels of this enzyme can increase NE production, this suggests an upregulation in the capacity of each LC neuron to produce more NE. Alzheimer's patients also show increased sprouting of remaining LC neurons in the region right around the LC and in the hippocampus (Booze, Mactutus, Gutman, & Davis, 1993; Nelson, Kolasa, & McMahon, 2014; Szot et al., 2006), as well as in prefrontal cortex (Szot et al., 2007). Also contributing to greater extracellular levels of NE, NET levels in the LC decrease in AD (Gulyás et al., 2010; Szot et al., 2006). NET is a presynaptic pump that returns NE to the neuron to be metabolized, so decreases in NET leave more NE in the synapse.

Does the LC-NE system protect against Alzheimer's disease?

Animal research suggests that LC degeneration is not simply associated with Alzheimer's disease pathology elsewhere in the brain but in fact exacerbates progression of the disease. Using a neurotoxin to selectively lesion LC in rodent transgenic models of Alzheimer's disease accelerates Alzheimer's-like pathology and cognitive deficits (Chalermpalanupap et al., 2018; Heneka et al., 2010; Heneka et al., 2006; Jardanhazi-Kurutz et al., 2010; Rey et al., 2012).

An intact LC may protect against Alzheimer's-related neuropathology and cognitive decline in a variety of ways. For instance, extracellular NE has protective effects due to its free radical scavenging that reduces oxidative stress (Feinstein, Kalinin, & Braun, 2016). NE also reduces glial cell inflammatory responses via β-adrenergic receptor activation (Frohman, Vayuvegula, Gupta, & Van Den Noort, 1988; Galea, Heneka, Russo, & Feinstein, 2003; Hetier, Ayala, Bousseau, & Prochiantz, 1991; Minghetti et al., 1997). Also via β-adrenergic receptors

and not α-adrenergic receptors, NE reduces the cytokine-dependent induction of type 2 nitric oxide synthase in astrocytes (Feinstein, Galea, & Reis, 1993). β-adrenergic receptors require high concentrations of NE (i.e., about 25 times higher than for alpha1-adrenergic receptors Salgado et al., 2012). LC activation does not lead to enough NE release at most downstream sites to activate these high threshold receptors but high levels of local activity--as might occur when a set of neurons representing a particular object are highly active because that object is the focus of attention-- stimulate greater NE release at those sites (Mather et al., 2016). These specific mechanisms through which NE diminishes inflammation may contribute to the 'cognitive reserve' that results from education and mental stimulation.

Conclusions

The LC is a small brain nucleus that has not been considered in most theories of cognitive aging. In part, the LC was ignored because its small size, lack of clear borders, and pulsatile motion make its structure and activity hard to measure, especially in living humans. However, growing evidence suggests that it plays an important role in memory and cognition, and that its large network of axons that are tuned to local cortical conditions are especially vulnerable to toxins and viruses that lead to pathology. Initial LC tau pathology typically appears in early adulthood and slowly spreads to the entorhinal cortex and beyond. LC contributions to cognitive aging have likely been underappreciated due to lack of ability to measure LC structure or activity in living humans. However, recent advances in neuroimaging have begun to make it possible to assess LC integrity and functioning and have confirmed what postmortem findings suggested as well as yielding new insights.

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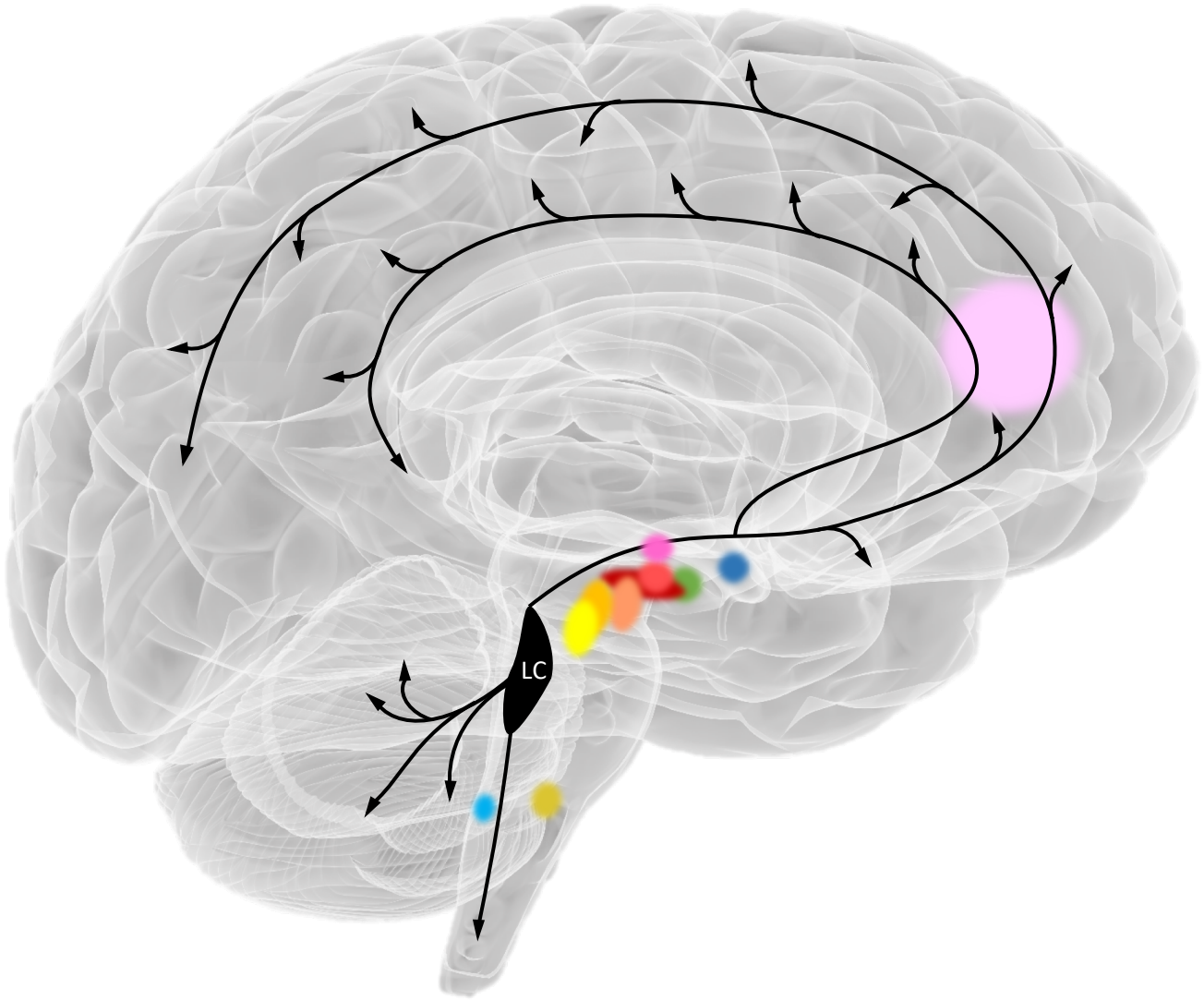
Figure Captions

Figure 1. Locus coeruleus (LC) axons project to much of the rest of the brain but the LC receives direct input from only a subset of these regions. These regions provide information about different aspects of arousal states and include excitatory input from amygdala, paraventricular nucleus of the hypothalamus, lateral hypothalamus/perifornical area, ventral tegmental area, dorsal raphe, pedunculopontine and laterodorsal tegmental nuclei, and rostroventrolateral medulla, and inhibitory input from ventrolateral preoptic area of the hypothalamus, nucleus prepositus hypoglossi, and tuberomammillary nucleus (for review see Samuels & Szabadi, 2008).

Figure 2. Participants heard one digit each 1.5 s, and heard either 3, 5, or 7 digits in a row that they retained for an immediate test. The '0' point on the right is the end of auditory list presentation. After three digits were heard, pupil diameter increased for each additional digit added to their working memory load.

Figure 3. A graphical depiction of the proposed mechanisms of the GANE model. **A**. Glutamate (grey circles) spills over from glutamatergic synapses at the sites of excited representations. **B**. If the LC happens to be activated (that is, depolarized) at the same time as glutamate reaches the NMDA receptors on LC axons, this triggers more local release of norepinephrine (NE; black circles) from those LC varicosities. **C.** Elevated local levels of NE activate *β*-adrenergic receptors that further stimulate glutamate release, leading to a local hotspot of high excitation. Autoreceptors at LC varicosities also contribute to increasing neural gain by inhibiting the release of noradrenaline when low levels of noradrenaline activate *α*-adrenergic receptors but increase the release of noradrenaline when high levels of noradrenaline activate *β*-adrenergic receptors. Reprinted from Lee et al., (2018).

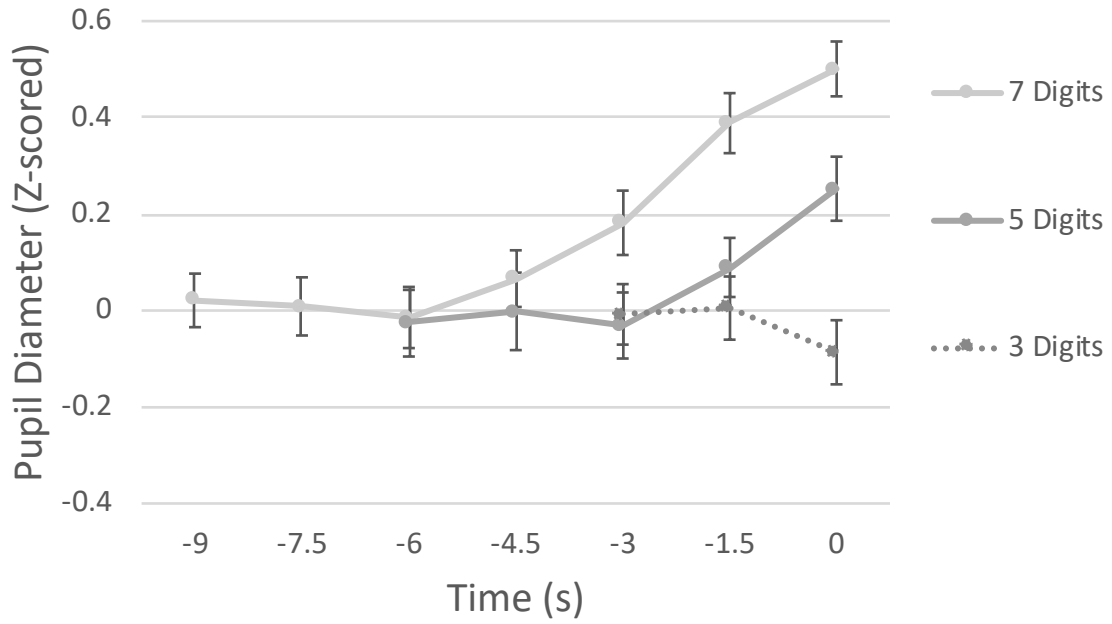


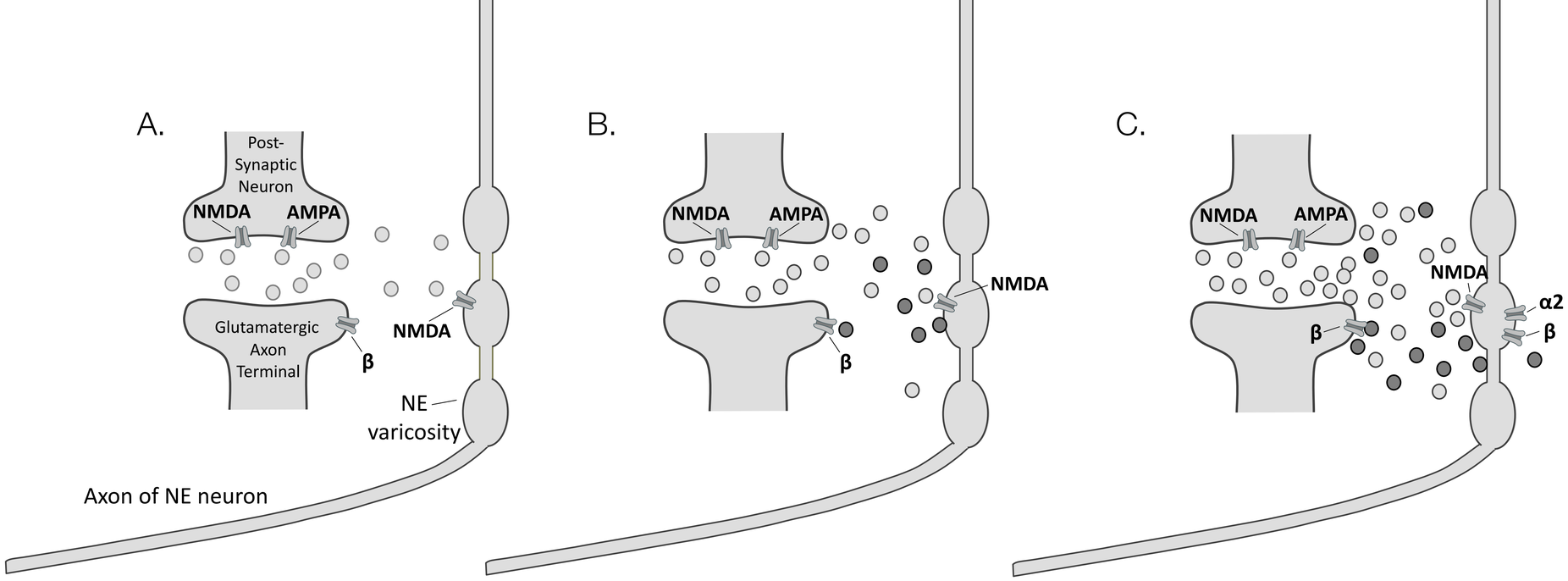
EXCITATORY INPUTS

- Prefrontal Cortex
- Paraventricular nucleus of hypothalamus
- Amygdala
- Lateral hypothalamic/perifornical area
- Ventral tegmental area
- Pedunculopontine and laterodorsal tegmental nuclei
- Dorsal raphe
- Rostroventrolateral medulla

INHIBITORY INPUTS

- Ventrolateral preoptic area of hypothalamus
- Nucleus prepositus hypoglossi
- Tuberomamillary nucleus


0.6
0.4
0.2
0
-0.2
-0.4
Pupil Diameter (Z-scored)
-9
-7.5
-6
-4.5
-3
-1.5
0
Time (s)
7 Digits
5 Digits
3 Digits


A.
Post-
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varicosity
Axon of NE neuron
B.
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AMPA
β
NMDA
C.
NMDA
AMPA
β
NMDA
α2
β