

Trends in Cognitive Sciences

The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain --Manuscript Draft--

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Abstract:	Research on cognitive aging has focused on how decline in various cortical and hippocampal regions influence cognition. However, brainstem regions play essential modulatory roles, and new evidence suggests that among these, the integrity of the locus coeruleus-norepinephrine system plays a key role in determining late life cognitive abilities. The locus coeruleus is especially vulnerable to toxins and infection and is often the first place Alzheimer's related pathology appears, with most people showing at least some tau pathology by their mid-twenties. On the other hand, norepinephrine released from the locus coeruleus during arousing, mentally challenging or novel situations helps protect neurons from damage, which may help explain how education and engaging careers prevent cognitive decline in later years.

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Trends Box

- In late life, lower LC neural density is associated with cognitive decline.
- Because of its neurons' long unmyelinated axons, high exposure to blood flow and location adjacent to the 4th ventricle, the LC is especially vulnerable to toxins.
- The tau pathology precursor of Alzheimer's disease emerges in the LC by early adulthood in most people. However, the pathology typically spreads slowly and only some end up with clinically evident Alzheimer's disease.
- Norepinephrine helps protect neurons from factors that accelerate Alzheimer's disease, such as inflammation and excitotoxicity.
- Education and engaging careers produce late-life "cognitive reserve" or effective brain performance despite encroaching pathology. Activation of the LC-NE system by novelty and mental challenge throughout one's life may contribute to cognitive reserve.

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12 The Locus Coeruleus:
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14 Essential for Maintaining Cognitive Function and the Aging Brain
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5 **Abstract**
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8 Research on cognitive aging has focused on how decline in various cortical and
9 hippocampal regions influence cognition. However, brainstem regions play essential
10 modulatory roles, and new evidence suggests that among these, the integrity of the
11 locus coeruleus-norepinephrine system plays a key role in determining late life cognitive
12 abilities. The locus coeruleus is especially vulnerable to toxins and infection and is often
13 the first place Alzheimer's related pathology appears, with most people showing at least
14 some tau pathology by their mid-twenties. On the other hand, norepinephrine released
15 from the locus coeruleus during arousing, mentally challenging or novel situations helps
16 protect neurons from damage, which may help explain how education and engaging
17 careers prevent cognitive decline in later years.
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Relevance of the locus coeruleus to cognitive aging

Neuromodulators transform the firing patterns of neurons, reconfiguring neuronal circuits in ways that can dramatically change their output [1, 2]. In this review, we focus on how age-related changes in the function of norepinephrine (NE), one of the main neuromodulators, can help explain cognitive change in aging. NE is best known for its roles in behavioral arousal and in the control of heart rate and blood pressure, but it also regulates attention, memory and cognition [3]. Most NE in the brain comes from the locus coeruleus (LC), a small nucleus in the pons on the lateral edge of the 4th ventricle. The LC appears to be the first brain region where Alzheimer’s disease pathology emerges [4, 5]. Recent evidence suggests that maintaining the neural density of the LC-NE nuclei prevents cognitive decline in aging [6].

As we discuss in more detail later in this review, maintaining LC integrity in aging may help cognition in two ways. First, NE modulates cognitive processes such as episodic memory, working memory, and inhibiting irrelevant information. Thus impairments in the LC-NE system should disrupt these cognitive processes. In addition, the LC-NE may contribute indirectly to cognitive function. It has long been observed that factors such as social engagement and education seem to protect against cognitive impairment even when Alzheimer’s disease neuropathology is present in the brain [7]. The emerging findings regarding the LC-NE system in aging and dementia suggest that this system supports these “cognitive reserve” effects [8]. NE released when the LC is activated by novelty, interest, excitement, or effort can protect against some of the threats to aging brains, such as inflammation and aggregated β -amyloid (see Glossary [5, 9, 10]). Thus, the arousal, effort and novelty exposure associated with engaging in

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4 social interactions and learning may lead to NE release that prevents age-related
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6 damage elsewhere in the brain, thereby helping non-LC regions maintain effective
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8 cognitive function for longer.
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10 11 **LC neuropathology in aging** 12 13

14 Most studies examining how LC neuron counts change with age suggest an age-
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16 related decline in LC neuron number by ~ 20-40% (e.g., [11-15]), with selective cell loss
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18 in the rostral LC compartment [16, 17]. However, it should be noted that some of these
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20 studies made lifespan comparisons on the basis of brain samples ranging from N = 5 to
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22 13 [11, 12, 16] and did not exclude cases with pathology elsewhere in the brain. More
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24 recent studies either excluding cases with neurofibrillary tangles elsewhere in the brain
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26 [18, 19] and/or using unbiased estimation procedures [19, 20] have found no age
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28 differences. Despite uncertainty about whether LC neuron counts change in aging, there
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30 is clear evidence that LC tau pathology increases with age [21], as outlined in the next
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32 section.
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38 *Alzheimer's disease pathology originates in the LC* 39 40

41 A recent theory of sporadic (late onset) Alzheimer's disease development, based
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43 on an extensive analysis of normal and diseased brains over the human lifespan,
44
45 proposes that the earliest pathology associated with Alzheimer's disease is the
46
47 occurrence of abnormal (hyperphosphorylated) tau in a few neurons of the LC [4, 21]. In
48
49 healthy neurons, tau protein stabilizes the hollow tubes (microtubules) that provide a
50
51 transport mechanism within neurons. But when hyperphosphorylated, tau loses its
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53 function and can eventually aggregate into neurofibrillary tangles.
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4 Although hyperphosphorylated tau in the LC has been documented as early as
5 age 6, the majority of children younger than 10 did not show any pathology [21]. But of
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9 61 brains from age 21-30 examined, 59 (96.7%) had some tau pathology in the LC, and
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12 of 100 brains from age 31-40 examined, 100% had LC tau pathology (as did all 2139
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14 cases over the age of 40) [21]. As people age, abnormal tau expression eventually
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16 extends along LC axons and reaches other memory-related neurons (usually the
17
18 transentorhinal region first) [21]. By late stages of the disease tau pathology extends
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20 through much of the neocortex [21]. Postmortem presence of neocortical neurofibrillary
21
22 tangles correlates strongly with cognitive impairment before death (and more strongly
23
24 than do β -amyloid plaques) [22]. Furthermore, in postmortems of patients with
25
26 diagnosed Alzheimer's disease, loss of LC cells reaches 50% in the rostral nucleus [23].
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31 These findings suggest not only that the LC is central to the development and
32
33 expression of Alzheimer's disease [5], but also that, while age increases the likelihood
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35 of reaching a symptom threshold, the underlying process of slowly spreading tau
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37 pathology via LC projection pathways is common to us all and starts in early adulthood.
38
39 (See Box 1 for some current ideas about why the LC is so vulnerable.) Furthermore,
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41 one current speculation is that this tau pathology eventually leads to the plaque-like β -
42
43 amyloid deposits found in brains with Alzheimer's disease, via release of β -amyloid by
44
45 the LC projection neurons with abnormal tau [24]. (For more information about β -
46
47 amyloid, see Box 2).
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53 The lack of techniques to directly assess subtle LC abnormalities in living young
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55 adults (but see Box 3) means that nothing is known about the functional consequences
56
57 of early tau pathology in the LC. However, one study raises the intriguing possibility that
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4 even early LC tau pathology may be associated with cognitive abilities. In this study,
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7 nuns with lower idea density in autobiographies they had written at around age 22
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9 showed significantly more clumps of abnormal tau (neurofibrillary tangles) in cortex and
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11 hippocampus when they died than those who previously had high idea density [25].
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14 Given that tau pathology typically starts in the LC in early adulthood before slowly
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16 spreading to neocortical regions [21], the nuns with higher levels of cortical abnormal
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18 tau later in life likely also had higher LC tau pathology in their 20's. Future development
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20 of techniques to detect tau pathology in the LC while people are still alive could make it
21
22 feasible to examine whether even subtle levels of LC damage affect cognition or
23
24 whether the damage must be more extensive to see impairment.
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28 *LC integrity associated with late-life cognitive ability*

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31 There is growing evidence that, in later life, individual differences in LC integrity
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33 relate to cognitive abilities (e.g., [26, 27]). In the Rush Memory and Aging Project, older
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35 participants without diagnosed dementia upon enrollment completed on average about
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37 six years of annual cognitive testing before they died [6]. An autopsy examination of the
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39 density of monoaminergic neurons in the LC, dorsal raphe nucleus, substantial nigra,
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41 and ventral tegmental area revealed that, when measures from these sampled regions
42
43 were modeled together, only LC neuronal density had a significant relationship with
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45 cognitive decline in the years preceding death (based on a composite score of tests of
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47 episodic, semantic and working memory, perceptual speed and visuospatial ability).
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50 These findings are striking and suggest a central role for the LC in late-life cognitive
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52 function.
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57 *LC neuromelanin increases in early and middle adulthood*

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4 Neuromelanin is a pigmented polymer that results from the oxidation of
5
6 catecholamines, including norepinephrine in the LC and dopamine in the substantia
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8 nigra [28, 29]. As people age, neuromelanin accumulates in the LC and the substantia
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10 nigra [17, 30]. Neuromelanin may play both neuroprotective and neurotoxic roles [29]. It
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12 chelates environmental toxins including heavy metals such as iron, cadmium, mercury
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14 and lead, thus reducing their toxicity. It also removes excess catecholamines within
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16 cells. But when neuromelanin-containing neurons die, the neuromelanin released into
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18 extracellular space may instigate chronic inflammation via slow release of the metals
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20 and toxic components it previously accumulated [29].
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26 The fact that LC neurons are marked by neuromelanin is useful not only in
27
28 postmortem identification of LC neurons, but also in neuroimaging. With the use of
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30 magnetic resonance imaging sequences optimized to detect neuromelanin, the LC can
31
32 now be reliably located (Fig. 1B; [26, 30, 31]). Among older adults, greater signal
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34 contrast in the LC is associated with higher verbal knowledge [26], whereas lower signal
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36 intensity is associated with mild cognitive impairment and Alzheimer's disease [27].
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41 *NE protects neurons*

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43 Animal research indicates that NE helps protect neurons from primary insults that
44
45 can lead to neurodegeneration in aging, such as inflammation or excitotoxicity [5, 9, 10,
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47 32]. Supplying NE to the hippocampus can reverse age-related long-term potentiation
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49 deficits in older rats [33]. Increasing NE levels improved cognition in aging rats [34] and
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51 in transgenic mice models of Alzheimer's disease [35, 36]. In vitro, NE administration
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53 promoted growth factors and provided protection against β -amyloid toxicity by an
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55 adrenergic-receptor-independent route [37]. Consistent with this protective role of NE,
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4 damaging the LC in transgenic Alzheimer's disease model mice increased cortical and
5 hippocampal neuroinflammation and β -amyloid deposition [38].
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9 NE protects against amyloid-induced toxicity via beta-adrenergic receptors
10 activating the cAMP/PKA cellular signaling pathway [39-41]. NE also inhibits
11 inflammatory activity via beta receptor binding and activation of cAMP-signaling
12 pathways [9, 32]. The involvement of low affinity beta-adrenergic receptors suggests
13 that at least some of the benefits of NE do not depend on the average brain levels of NE
14 (as these do not tend to be high enough to stimulate beta receptors [42]), but instead
15 the more transient phasic spikes in LC activity that are hypothesized to produce highly
16 localized spikes in NE release where there are high levels of neural activity under
17 arousal (see Box 4).
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30 *NE decline in Alzheimer's disease may accelerate impact of disease*

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33 Based on how Alzheimer's disease pathology targets the LC (see Box 1), functions
34 regulated by NE should show marked dysregulation in Alzheimer's disease. This is
35 indeed the case for many NE-related functions [5], such as memory, which depends on
36 synaptic plasticity modulated by NE and declines in Alzheimer's disease, and blood
37 pressure, which declines around the time of disease diagnosis [43]. Along with these
38 more obvious symptoms, loss of LC-NE function impairs cellular-level protective
39 mechanisms and increases inflammation [5, 44]. These changes likely accelerate the
40 course of Alzheimer's disease [5, 44].
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53 Interactions between β -amyloid and NE are an important component of how the
54 LC-NE system can influence the course of Alzheimer's disease [44]. NE inhibits
55 amyloid-induced oxidative stress, mitochondrial depolarization and caspase activation
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4 [39]. NE also stimulates microglial cells that help clear out β -amyloid [10]. Thus, by
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6 impairing NE function, Alzheimer's disease removes an important defense against
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8 accumulation of β -amyloid, accelerating the likelihood that damaging β -amyloid
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10 oligomers will form. These findings suggest that Alzheimer's disease involves the
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12 spread of neuropathology while simultaneously reducing the brain's ability to combat
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14 these threats.
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19 NE levels change in opposing ways in the brain and periphery in Alzheimer's
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21 disease. In brain tissue [45-49] as well as in ventricular fluid [50], patients with
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23 Alzheimer disease have less NE than do age-matched controls. Indeed, in the brain, NE
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25 was the most depleted among 31 metabolites examined and the one with the strongest
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27 correlation with the degree of the Alzheimer's disease pathology [50]. These lower
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29 cortical NE concentrations at death were associated with more cognitive impairment for
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31 Alzheimer's disease patients in their last months of life [23, 45].
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36 In contrast, in lumbar cerebrospinal fluid (CSF) and plasma, Alzheimer's disease
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38 patients have higher NE levels [51-53], and higher CSF concentrations of NE are
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40 associated with poorer cognitive performance both among adults without clinical levels
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42 of cognitive impairment and among Alzheimer's disease patients [54, 55]. Why might
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44 there be such a discrepancy between brain and lumbar levels of NE? In general, lumbar
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46 CSF contents can diverge dramatically from brain CSF contents [56]. With aging, CSF
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48 flow rate decreases which may increase the influence of plasma NE on lumbar CSF
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50 measures (as seen with blood-derived proteins in CSF [57]).
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55 *LC-NE roles in cognition and how they correspond with age-related changes*
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4 As reviewed above, declines in the LC-NE system are associated with lower
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6 cognitive function among older adults. However, previous research has focused on
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8 aggregate measures of cognition and not on which specific cognitive functions might be
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10 most influenced by LC-NE changes in aging.
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14 Nevertheless, it is striking to observe how the cognitive functions generally most
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16 affected in aging depend on NE. For instance, with age, people get worse at inhibiting
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18 irrelevant information [58]. This age differences is especially pronounced in the
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20 afternoon, older adults' "off-peak" time of day [58], which may reflect circadian rhythms
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22 in NE. Unfortunately little is known about age differences in circadian rhythms of brain
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24 NE levels, but plasma levels show age differences [59]. As outlined in Box 4, NE (or
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26 arousal) enhances the selectivity of cortical processing by enhancing activity where
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28 activation levels are high and suppressing activity where they are lower. This enhances
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30 processing of perceptually salient or behaviorally important stimuli while suppressing
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32 processing of less salient information. Impairment in these processes promoting
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34 cognitive selectivity may contribute to older adults' high distractibility.
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41 Working memory is another weakness for older adults [60]. In monkeys,
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43 dorsolateral prefrontal working memory processes are enhanced by α_2 noradrenergic
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45 agonists [61, 62], and so impaired adrenergic function in aging may contribute to
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47 working memory decline. Older adults also have difficulty switching tasks [63] or get
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49 stuck in a particular mindset when problem solving [64]. A burst of NE release seems to
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51 facilitate dynamic reorganization of neural networks [65], so impaired NE function could
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53 reduce cognitive flexibility.
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4 Furthermore, aging impairs episodic memory in many ways, some of which may
5 relate to NE function. For instance, older adults are less effective at “pattern separation”
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7 or the ability to distinguish among similar experiences [66], a function that depends on
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9 the dentate gyrus of the hippocampus, a region heavily modulated by NE. Pattern
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11 separation performance is higher in those with higher levels of salivary alpha amylase
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13 (a biomarker of NE) [67]. Thus, age-related decreases in hippocampal NE may be one
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15 factor leading to poorer pattern separation among older adults.
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21 Thus, NE plays a role in the cognitive functions most affected in aging and
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23 examining whether LC-NE system declines play a role in the specific attention and
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25 memory deficits seen in aging is a promising direction for future research.
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28 *Implications and potential interventions*

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30 The evidence we have reviewed so far indicates that the LC-NE system plays a
31
32 key role in how well cognitive function is maintained in late life. A natural next question
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34 is whether there are LC-NE targeted interventions that could help maintain cognitive
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36 function during aging.
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40 **Does activating the LC-NE system throughout life create cognitive reserve?**

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42 One fascinating cultural phenomena is the Flynn effect, in which successive
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44 generations have been getting smarter, at least as assessed by IQ tests [68]. There is
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46 no definitive answer as to why this has been occurring, but researchers believe that
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48 environments have gradually become more stimulating, promoting learning. One
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50 possibility is that stimulating environments enhance cognition in part via their activation
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52 of the LC-NE pathway (e.g., [69]).
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4 Certainly, evidence from animals indicates that environmental stimulation
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6 increases cortical NE levels. For instance, giving mice a few hours a day of an enriched
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8 environment for most of their lives increased levels of NE in a broad swath of cortex
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10 characterized as parietal-temporo-occipital cortex, whereas there were no significant
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12 increases in dopamine or serotonin [70]. In rat hippocampus, long-term environmental
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14 enrichment increased NE levels by 68% [71]. An enriched olfactory environment
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16 increased noradrenergic neurons in the LC in young and middle-aged mice but not in
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18 older mice [72], suggesting that the effect of enriched environments might be most
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20 potent in early and mid-life.
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26 The benefits of environmental enrichment (including enhanced long-term
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28 potentiation and protection against β -amyloid oligomers) seem to depend on beta-
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30 adrenergic and NMDA pathways [40, 73]. Given the high levels of NE needed for beta-
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32 adrenergic activation [74], this suggests that low or moderate levels of NE are not
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34 sufficient to yield long-term benefits. Instead, to get NE levels high enough to activate
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36 low affinity beta receptors, phasic spikes in LC activity may be necessary. As outlined in
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38 Box 4, these brief bursts of LC activity induced by arousing situations and mental
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40 stimulation should lead to hot spots of high NE release in the brain regions that are
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42 currently most active. These hot spots may then not only target brain resources to what
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44 matters most at that moment, but also have beneficial long-term effects via synaptic
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46 plasticity processes initiated by beta-adrenergic receptors.
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53 In older humans, engagement in intellectually stimulating activities enhances
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55 memory recall and cognitive flexibility [75, 76]. Over a lifetime, repeated activation of the
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57 LC-NE system could be the mechanism through which education, intelligence and
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4 mental stimulation lead to “cognitive reserve” or “neural reserve” in which cognitive
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6 function can be maintained despite encroaching late-life brain pathology [8]. Consistent
7
8 with this, in healthy older adults, LC neuromelanin contrast intensity is associated with a
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10 composite measure of cognitive reserve including education level and verbal
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12 intelligence [26]. Likewise, in the Rush Memory and Aging Project results described
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14 previously [6], individuals who had greater LC neuronal density and showed less
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16 cognitive decline might be exhibiting “neural reserve,” rather than those with less
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18 neuronal density showing pathological decline. Consistent with this, within that mostly
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20 dementia-free sample, measures of neuronal density and neurofibrillary tangles were
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22 not correlated within the LC. This lack of relationship is not too surprising, as neurons
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24 producing tau pretangle and tangle material often survive as long as the individual lives
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26 [4]. Both neuronal density and overall tangle level in the brainstem were independently
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28 associated with cognitive decline before death. Thus, individuals with greater LC
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30 neuronal density had an advantage that could potentially keep them functioning at a
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32 higher level despite encroaching tau pathology.
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41 The Flynn effect on IQ scores of young adults suggests that our increasingly
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43 complex global societies are enhancing cognitive function. Presumably, this societal-
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45 level enriched environment should have not only affected younger adults, but also
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47 decreased rates of Alzheimer’s disease. Indeed, population rates of Alzheimer’s
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49 disease have been on the decline across different countries [77, 78]. However, current
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51 studies do not indicate how much such effects are due to greater rates of education and
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53 other types of environmental enrichment, in contrast with other factors such as better
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55 control of cardiovascular disease.
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Can increasing NE levels help older adults' cognition?

Given the associations between lower brain levels of NE and impaired cognition, as well as the impaired cellular protection discussed in previous sections, one plausible intervention could be to increase NE levels in the brains of older adults. In rat brains, long-term cardiovascular training increases NE levels [79] and NE synthesis increases during exercise [80]. Several days or weeks of exercise enhances learning and memory for the next few days, and this enhancement is blocked by beta adrenergic blockers during the exercise [81, 82]. These findings suggest that exercise may enhance memory in older adults via stimulation of LC-NE pathways. Consistent with this, older adults who rated pictures and then rode a stationary bicycle later remembered those pictures better than those who just continued sitting after viewing the pictures [83]. These enhancing effects of exercise were seen for both healthy older adults and those with amnesic mild cognitive impairment, and in both groups the enhancement was correlated with a measure of endogenous NE (salivary alpha amylase). Longer-term exercise interventions also enhance cognition in older adults [84], although the role of NE has not yet been examined in human studies of exercise effects on cognition.

To date, there has been little research in humans investigating whether pharmacologically increasing NE levels could benefit cognition. One 6-month double-blind study of patients with mild-to-moderate Alzheimer's disease found that adding atomoxetine, an NE reuptake inhibitor, to ongoing cholinesterase-inhibitor therapy, did not significantly improve cognitive function [85]. The lack of effectiveness may relate to the patients' Alzheimer's disease, as animal research suggests that NE reuptake inhibitors lack effectiveness when NE levels are already reduced due to disease [32].

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4 As already mentioned, evidence from monkeys indicates that an individual dose of
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6 an α 2a adrenergic agonist (guanfacine) improves dorsolateral prefrontal working
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8 memory processes shortly afterwards [61, 62]. However, in the LC and elsewhere in the
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10 brain, activation of α 2a receptors decreases release of NE [86], and rodent research
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12 indicates that α 2 antagonists have neuroprotective effects (for review see [32]). In one
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14 such study relevant for questions about cognitive effects, an α 2 antagonist administered
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16 for several months prevented age-related spatial working memory deficits in a
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18 transgenic mouse model of Alzheimer's disease [87]. Thus, it seems unlikely that long-
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20 term administration of α 2a agonists that reduce brain levels of NE would have beneficial
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22 effects. Consistent with this, a double-blind 12-week clinical trial of an α 2 adrenergic
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24 agonist (guanfacine) in healthy adults age 75 or older [88] yielded no improvement in
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26 executive function but instead a trend in the opposite direction, suggesting that any
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28 positive effects of the agonist in prefrontal working memory circuits were outweighed by
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30 its negative effects.
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38 **Long-term effects of beta-blockers**

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40 Given the evidence already discussed that NE release can protect against amyloid
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42 toxicity and that many of the protective effects of NE are mediated by beta-adrenergic
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44 receptor pathways, it seems that long-term use of beta-adrenergic antagonists could
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46 accelerate Alzheimer's disease. This has major public health relevance as many older
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48 adults are prescribed beta-blockers to help manage cardiovascular disease [89].
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50 However, epidemiological studies find contradictory relationships between taking beta-
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52 blockers and cognitive decline (e.g., [90, 91]) and a randomized trial of the beta-blocker
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54 propranolol found no effect on cognition [92]. These inconsistent findings across studies
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4 may be due to the multifaceted effects of beta-blockers. Insofar as they improve
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6 cardiovascular health, they should also improve brain health and cognition. But insofar
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8 as they diminish defenses against Alzheimer's-related damage, they should impair
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10 cognition. Furthermore, it seems likely that the effects of beta-blockers will depend on
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12 whether there are significant levels of β -amyloid-related pathology in the brain. In
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14 people without β -amyloid load, the cardiovascular benefits of beta-blockers may
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16 outweigh the disadvantages for cognition, whereas the reverse may be true for those
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18 already diagnosed with Alzheimer's disease [93].
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23 **Concluding remarks**

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26 In the current review, we outlined evidence suggesting that age-related change in
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28 the LC structure and NE function plays more of a role in cognitive aging than has been
29
30 previously appreciated. LC structural integrity in late life is associated with cognitive
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32 function [6, 26], as are NE levels in the brain [23, 45]. Furthermore, many of the
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34 cognitive functions that have been identified as especially vulnerable in aging are
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36 strongly influenced by NE.
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41 Understanding the role of the LC in cognitive aging is not just of theoretical
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43 importance. The LC is especially vulnerable to damage and is usually the first site
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45 exhibiting Alzheimer's disease pathology [21]. It is likely to be via the LC's network of
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47 connections that late-onset Alzheimer's disease pathology spreads [94], and so
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49 interventions targeting these early indications of disease should be the focus of future
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51 research (see Outstanding Questions box).
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56 One exciting prospect is that, by stimulating the LC and NE release, cognitive
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58 challenges and physical exercise may be effective interventions throughout life that
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harness the anti-inflammatory and cell-protective qualities of NE to help forestall
cognitive decline and dementia [8].

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5 **Box 1: Why are LC neurons especially vulnerable?**
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8 LC neurons are implicated not only in Alzheimer disease pathology, but also in
9
10 other neurodegenerative diseases, such as Parkinson's disease and Down's syndrome
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12 [95-97]. Why might LC neurons be especially vulnerable? One factor is their high
13
14 bioenergetic need. Perhaps as part of mechanisms that insure maintained operation
15
16 during essential physiological functions, LC neurons maintain their spiking rate even
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18 when glutamate and GABA inputs are blocked [98]. L-type Ca^{2+} channels enhance the
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20 reliability of this autonomous spiking, but at the cost of increased mitochondrial oxidant
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22 stress [98].
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28 In addition to high energetic demands, LC neurons have extensive exposure to
29
30 central nervous system capillaries, as NE released by the LC is critical for maintaining
31
32 the blood-brain barrier and increasing levels of blood flow selectively in the most active
33
34 brain areas under arousal [99]. In the normal human brain, each LC neuron innervates
35
36 an estimated 20 meters of capillaries [100], and each LC cell body tends to have two or
37
38 more capillaries wrapped around it, an arrangement that is unusual in the brain (see
39
40 Figure I; [101]). Because of this high exposure to blood circulation, LC neurons are
41
42 likely to take up toxicants [100]. In addition, the LC's close proximity to the fourth
43
44 ventricle (see Figure 1) may also expose it to toxins in cerebrospinal fluid [5].
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50 Alternatively, tau pathology may be triggered by a virus, for instance the common
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52 herpes simplex type 1 virus [102]. After someone recovers from a herpes infection, the
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54 virus lies dormant in the trigeminal ganglion, which projects to the LC, potentially
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56 allowing the spread of the reactivated virus along that pathway. Thus, there are a
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4 number of ways in which the LC is vulnerable to damage but more research is needed
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7 to uncover the triggering events for the initial tau pathology.
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10 11 **Box 2: β -amyloid is a by-product of mental activity**

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14 Challenging cognitive tasks require mental activity and resources. The depletion of
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16 mental resources can be behaviorally measured. For example, exerting willpower to
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18 abstain from tempting snacks can lead a dieter to binge more on ice cream later [103].
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20 Depletion of resources also occurs for other challenging cognitive tasks such as those
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22 involving sustained vigilance or interference [104]. Engaging in one type of challenging
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24 task depletes performance only for that specific cognitive function and not for others that
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26 rely on non-overlapping brain regions [105]. Thus, the brain mechanisms underlying
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28 cognitive depletion must target a particular region. One potential mechanism meeting
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30 this criterion is that synaptic activity triggers neurons to release β -amyloid peptide [106,
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32 107], which in turn suppresses local neuronal activity [108]. The released β -amyloid can
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34 linger for a while, but is usually cleared during sleep when the fluid volume surrounding
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36 cells is dramatically increased (by 60% in mice) allowing waste products to be removed
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38 by circulation in the newly discovered glymphatic system [109]. One interesting
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40 speculation is that β -amyloid suppression of neuronal activity in the vicinity of previously
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42 highly active neurons explains how people can experience cognitive depletion for
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44 specific challenging tasks, and why that depletion might last until they next sleep [110].
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53 Clearing β -amyloid is critical for healthy aging. If the β -amyloid peptides
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55 accumulate too much, they start to clump together and form toxic oligomers and then
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57 eventually the classic Alzheimer's disease marker, amyloid plaques [111]. Factors that
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impair β -amyloid clearance put the most active brain regions at risk for plaque build-up, and indeed, the most active brain regions tend to show the most β -amyloid plaque build up in Alzheimer's disease [111].

NE has multiple (and opposing) roles in this process. On the one hand, NE promotes wakefulness—and the primary accumulation of β -amyloid occurs during wakefulness [109]. Indeed, more wakefulness relates to more amyloid plaques in mouse models [112]. NE constricts the fluid volume surrounding brain cells during wakeful arousal (working against β -amyloid clearance), whereas NE antagonists (or low levels of NE during sleep) increase fluid volume [109]. In addition, local hot spots of high glutamate-NE activity (see Box 4) may stimulate β -amyloid release via greater synaptic activity (and via greater beta-adrenergic receptor activation [44]) in that region. Thus, phasic increases in NE are likely to promote local release of β -amyloid while higher tonic levels of NE during wakefulness are likely to prevent β -amyloid clearance.

On the other hand, beta-adrenergic receptor activation also promotes exchange of the fluid surrounding brain cells by enhancing the strength of arterial pulsatility [113]. In addition, via beta-adrenergic receptors, NE stimulates glial cells to clear β -amyloid [114]. Thus, local hot spots of high glutamate-NE activity should stimulate clearance of the β -amyloid they accumulate.

Box 3: Pupil dilation provides a window into LC activity

NE inhibits pupil constriction [115, 116] and pupils dilate more when NE levels increase, such as during aerobic exercise [118], muscular exertion [119, 120], viewing emotionally or sexually arousing pictures [121], or wakefulness compared with sleep

[122, 123]. In monkeys, LC stimulation prompts pupil dilation [117], and in humans, pupil dilation correlates with LC activity seen using functional neuroimaging [124].

During waking hours, people's average pupil size decreases linearly with age [125, 126] and is even smaller in patients with Alzheimer's disease [127]. This age-related decrease is not due to impaired mechanics, as eye drops consisting of the alpha noradrenergic alpha1-agonist phenylephrine dilated both younger and older adults' pupils to about the same diameter [128]. The success of this NE intervention among older adults suggests that low tonic NE levels lead to their lower baseline pupil dilation.

Box 4: Local cortical regions self-regulate (GANE)

From the level of individual neurons to whole brain coordination of blood flow, NE shapes brain activity in ways that enhance selectivity. At first, this is a surprising notion to grasp, because the LC-NE system is set up to broadcast messages broadly. LC neurons have long axons with many varicosities that release NE along their paths [129]. NE is released into extrasynaptic gaps, which allows for a broader influence than targeting specific neurons. But despite this broad spatial scope, it has long been known that NE has selective effects, quieting most neurons but allowing those with the most intense firing response to continue their activity unabated [129]. The Glutamate Amplifies Noradrenergic Effects (GANE) model [42] proposes that NE selectively enhances the most activated representations because of positive feedback loops between NE and glutamate, the brain's primary excitatory neurotransmitter. In the brain, activation of a particular representation (such as the image of someone's face) depends on glutamate release spreading excitation among the neurons in a network representing

that information. Glutamate spills over from these synapses and binds to NMDA receptors on nearby projections from LC neurons (Figure IIA). When the glutamate stimulation occurs at the same time as LC neuron activation, this stimulates local release of norepinephrine (Figure IIB).

When sufficient NE is released in the vicinity of glutamatergic neurons, it activates beta-adrenergic receptors on those neurons that stimulate more glutamate release. This glutamate, in turn, stimulates more local NE release at the NE varicosity. This feedback cycle creates a hot spot where local NE levels increase (by an order of magnitude) more than when the LC neuron is stimulated without the concomitant local excitation (for supporting evidence see [42]). Importantly, in addition to creating a positive feedback loop, beta-adrenergic receptors engaged at NE hotspots amplify excitatory glutamatergic activity and memory supporting plasticity for neurons in the vicinity of the hotspot.

These hot spots of activity occur in the context of general suppression of neural activity in part via α_1 and α_2 -adrenergic receptors that require lower levels of NE for activation (in contrast with excitatory beta-adrenoceptors that require high levels of NE). This local modulation of NE release based on current excitation levels explains how arousal can enhance noticing and remembering of things that were perceptually salient or goal relevant at the moment a surge of arousal occurred while simultaneously impairing processing of less salient or important things [130-132].

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Figure Captions

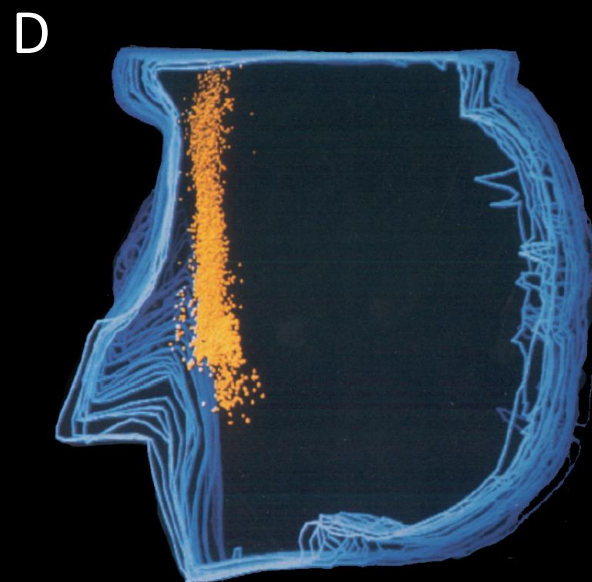
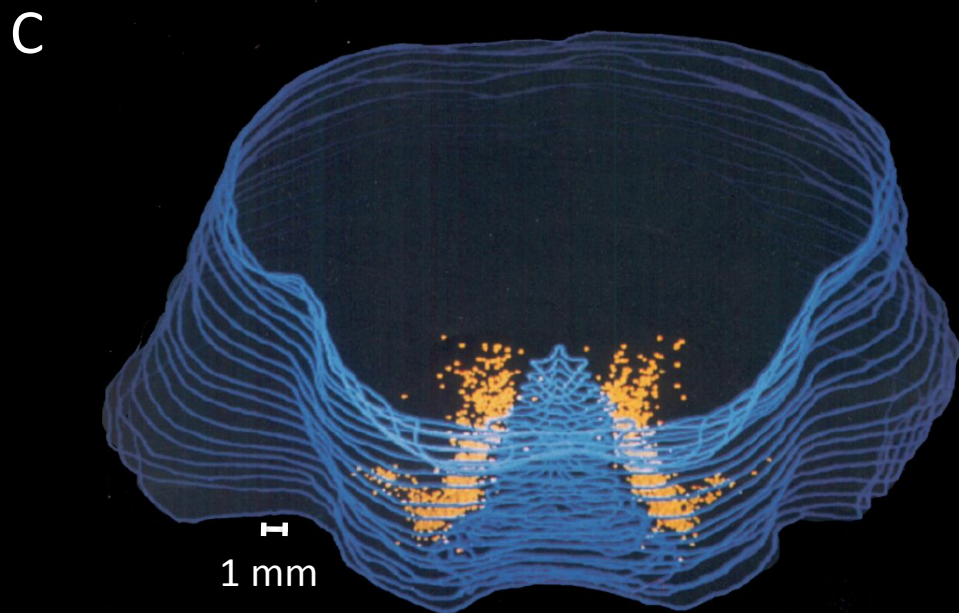
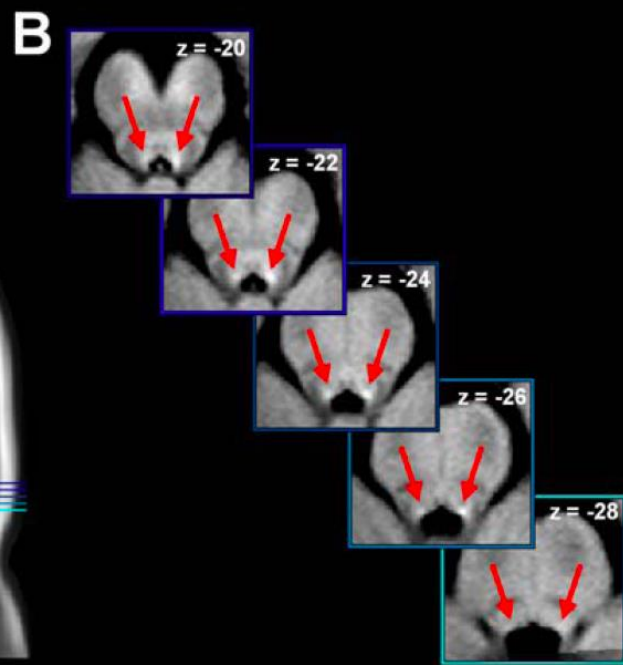
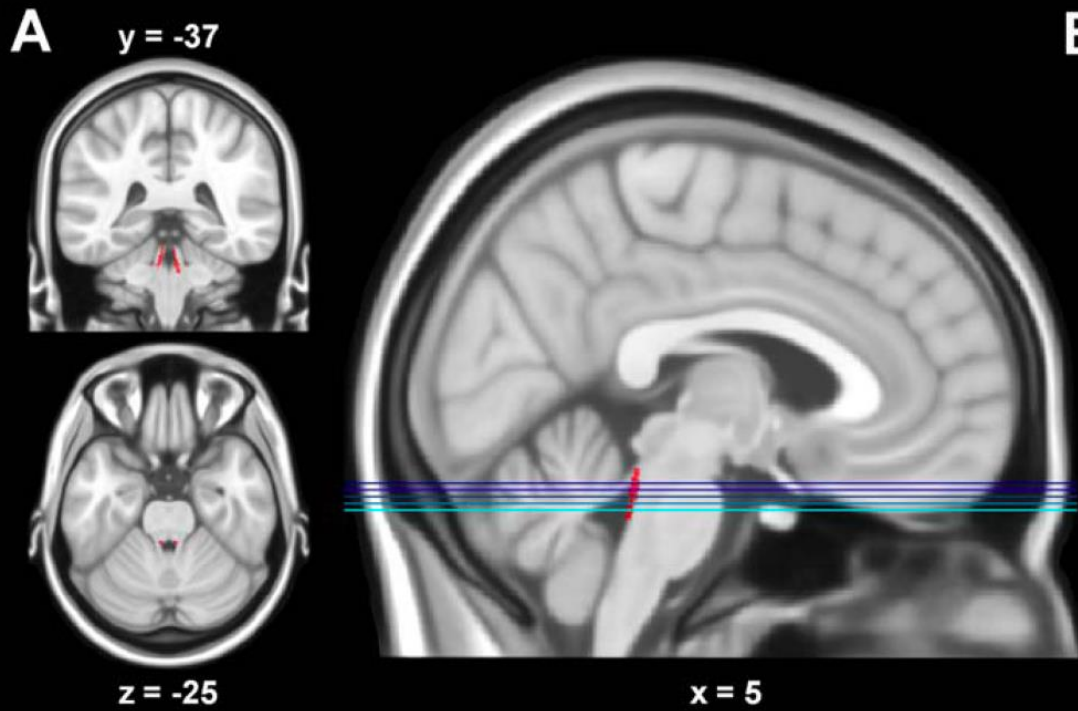
Figure 1. Images of the locus coeruleus (LC). A) The LC is shown in red. B) Axial slices corresponding to the lines indicated on the whole brain sagittal image, with red arrows pointing to the LC visible as white spots where higher levels of neuromelanin led to greater contrast. C) Computer reconstruction of post-mortem distribution of LC neurons in an adult aged 64, with slices cut 45° above the horizontal plane. As cells descend caudally, they are displaced laterally by the fourth ventricle. D) A reconstruction from a sagittally sectioned brain aged 60. The dorsal part of the LC starts at the level of the inferior colliculus (IC) and extends to about the level of the superior medullary velum. Figures 1A and B reprinted from [124], C and D modified from [11].

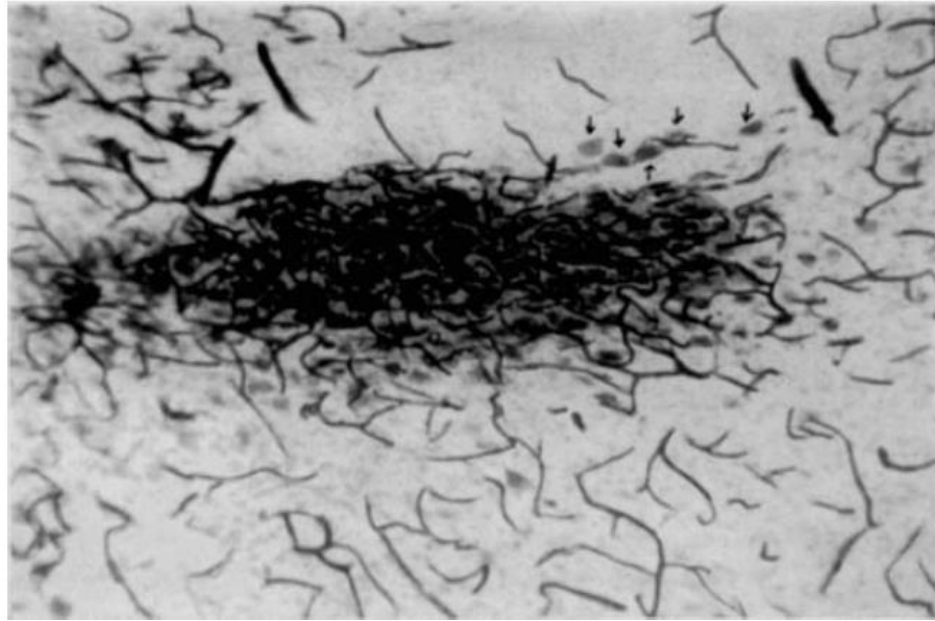
Figure I. Horizontal section through the locus coeruleus showing that two or more capillaries tend to be wrapped around each cell. The small arrows indicate cells of the nucleus of the mesencephalic root of the Vth that have a lower capillary supply and a different appearance than the locus coeruleus cells. Figure reprinted from [101].

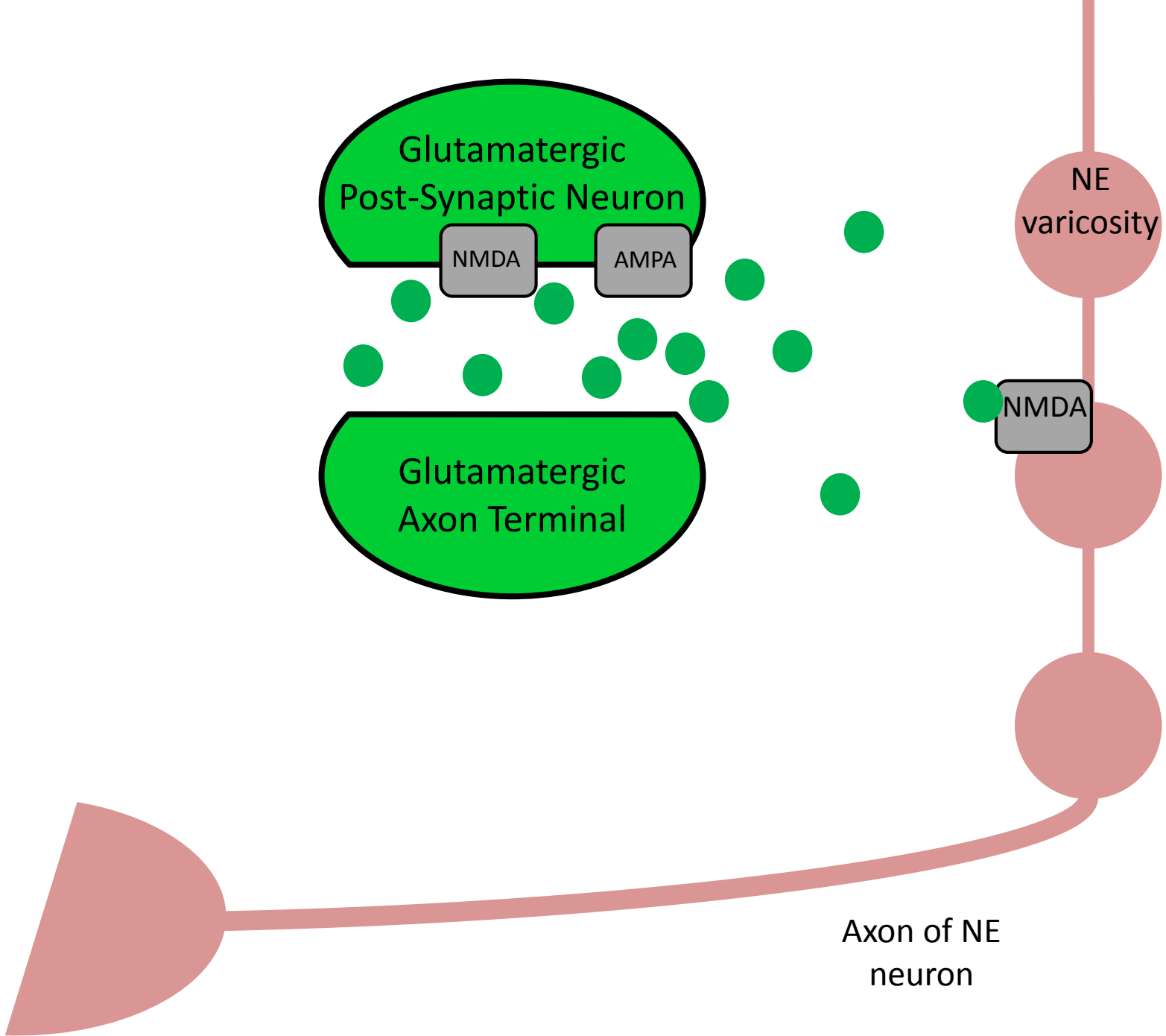
Figure II. Glutamate and norepinephrine interact to further amplify excitation where there are high levels of glutamatergic activity in sensory and limbic regions. This type of hotspot occurs when (A) glutamate released at a synapse spills over and activates NMDA receptors on NE neuron varicosities while (B) concomitant depolarization of the LC neuron stimulates local NE release.

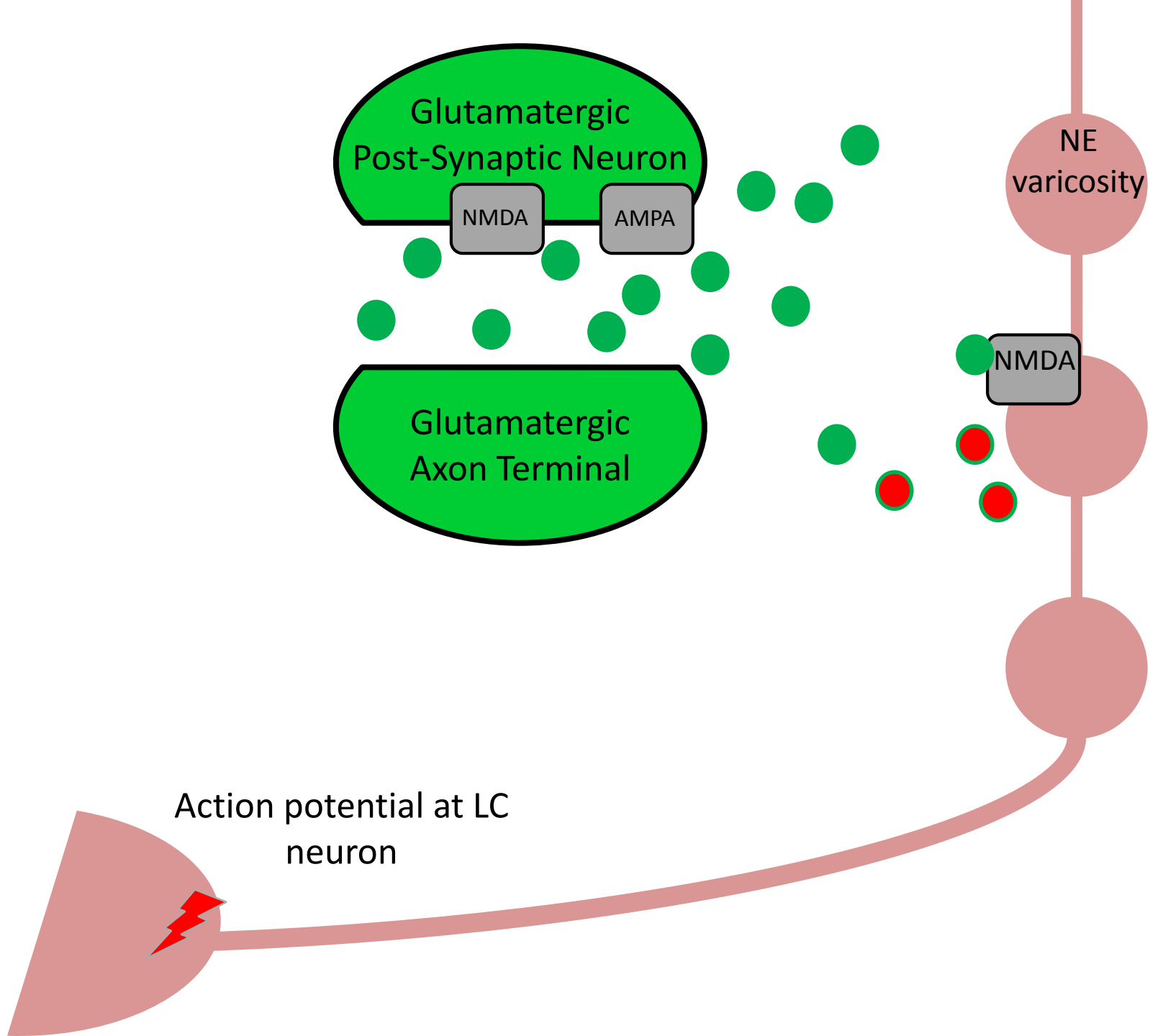
Outstanding Questions

- How much does LC-NE system decline in aging account for cognitive decline? For instance, memory consolidation, selective attention, task switching, distractability, flexibility all depend on LC function and show significant decline in aging.
- Does tau pathology seen in the LC and its targets in early adulthood correlate with cognitive performance?
- How can one protect the LC from tau pathology?
- How can one prevent the 'prion' like spread of abnormal tau from LC neurons to other brain regions?
- Are genetic risk factors for Alzheimer's disease such as the APOE e4 allele associated with an earlier appearance of hyperphosphorylated tau in LC neurons?
- Do different noradrenergic receptor types fare differently in aging?
- Do tonic levels of LC firing decrease in aging (as suggested by decreased baseline pupil dilation in aging; see Box 3)? If so, what accounts for the higher plasma and lumbar cerebrospinal fluid levels of NE seen in aging and Alzheimer's disease?
- Does aging influence the pattern of LC firing? For instance, are phasic, selective LC responses to salient stimuli (reflective attentiveness and alertness) any less likely? Are "baseline" levels of firing when awake any higher or lower?
- Given that sporadic (late onset) Alzheimer's disease is a uniquely human disease and that all aging adults are affected by the LC-tau aspects of the disease process to some degree, how effectively can animal models inform us about the effects of aging on the function of the LC?
- How do LC changes in aging interact with changes in other neuromodulator systems, such as dopamine?
- Relative to age-related change in other brain regions and other neuromodulatory systems, how influential is the LC-NE system for predicting the course of cognitive aging?









Glossary

Adrenergic antagonists: Chemicals that block the action of catecholamines at adrenergic receptors.

β -amyloid: A protein with 38-43 amino acids derived from amyloid precursor protein. In Alzheimer's disease it forms small aggregates called oligomers and eventually larger aggregates known as plaques. The oligomer form is believed to be the most damaging form.

Caspases: Enzymes that are critical in apoptosis or programmed cell death.

Catecholamines: Monoamine neurotransmitters derived from the amino acid tyrosine. Epinephrine, norepinephrine and dopamine are catecholamines.

Excitotoxicity: The process of damaging or destroying neurons by overactivating receptors (usually with glutamate).

Glutamate: The brain's primary excitatory neurotransmitter.

Mitochondrial depolarization: Mitochondria normally have an electrochemical gradient across their inner membrane that supports their function (i.e., they are polarized). Depolarization is often a precursor of mitochondrial death.

Monoaminergic neurons: Neurons that use neurotransmitters with one amino group. Monoamines include catecholamines as well as serotonin and histamine.

Neurofibrillary tangles: When tau protein becomes hyperphosphorylated (i.e., a portion of its phosphorylation sites resist dephosphorylation), it no longer binds to microtubules and can become insoluble and form tangles.

NMDA receptor: A glutamate receptor that is important for strengthening or weakening synaptic responses to glutamate as a function of two events: activation of the glutamate input and strong cell depolarization. These synaptic changes control a circuit's future likelihood of being activated by input and are thought to be central to memory creation.

Noradrenergic agonists: Chemicals that bind to noradrenergic receptors.

Tau pathology: Hyperphosphorylated and aggregated tau. Neurofibrillary tangles are a type of aggregated tau.

Tau protein: In healthy brains, tau proteins help stabilize microtubules that transport nutrients and other substances within nerve cells. These proteins have positively charged binding domains that allow them to bind to negatively charged microtubules.