Fluid intelligence and the locus coeruleus–norepinephrine system

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The last decade has seen significant progress identifying genetic and brain differences related to intelligence. However, there remain considerable gaps in our understanding of how cognitive mechanisms that underpin intelligence map onto various brain functions. In this article, we argue that the locus coeruleus–norepinephrine system is essential for understanding the biological basis of intelligence. We review evidence suggesting that the locus coeruleus–norepinephrine system plays a central role at all levels of brain function, from metabolic processes to the organization of large-scale brain networks. We connect this evidence with our executive attention view of working-memory capacity and fluid intelligence and present analyses on baseline pupil size, an indicator of locus coeruleus activity. Using a latent variable approach, our analyses showed that a common executive attention factor predicted baseline pupil size. Additionally, the executive attention function of disengagement—not maintenance—uniquely predicted baseline pupil size. These findings suggest that the ability to control attention may be important for understanding how cognitive mechanisms of fluid intelligence map onto the locus coeruleus–norepinephrine system. We discuss how further research is needed to better understand the relationships between fluid intelligence, the locus coeruleus–norepinephrine system, and functionally organized brain networks.

brain basis of intelligence | locus coeruleus | pupil size | cognitive ability | individual differences

In this article, we outline what we see as a potentially important relationship for understanding the biological basis of intelligence: that is, the relationship between fluid intelligence and the locus coeruleus–norepinephrine system. This is largely motivated by our findings that baseline pupil size is related to fluid intelligence (1, 2); the larger the pupils, the higher the fluid intelligence. The connection to the locus coeruleus is based on research showing that the size of the pupil can be used as an indicator of locus coeruleus activity (3–8). A large body of research on the locus coeruleus–norepinephrine system in animal and human studies has shown how this system is critical for an impressively wide range of behaviors and cognitive processes, from regulating sleep/wake cycles, to sensation and perception, attention, learning and memory, decision making, and more (9–12). The locus coeruleus–norepinephrine system achieves this primarily through its widespread projection system throughout the cortex, strong connections with the prefrontal cortex, and the effect of norepinephrine at many levels of brain function (10). Given the broad role of this system in behavior, cognition, and brain function, we propose that the locus coeruleus–norepinephrine system is essential for understanding the biological basis of intelligence.

Individual Differences in Intelligence

The ability to regulate perception, cognition, and behavior is a fundamental characteristic of any complex organism that allows them to successfully navigate and adapt to changing and uncertain environments. The field of differential psychology emphasizes the fact that there is a large diversity in these abilities between individuals, species, and across the lifespan. One of the most robust findings from differential psychology is that performance across a large variety of cognitive tasks tend to positively correlate with one another. This finding, known as the positive manifold, has been used as evidence for the existence of a general factor of intelligence (*g*) that underlies performance and behavior across a large domain of tasks (13, 14). However, many have argued against the explanatory value of *g* as a psychological or biological mechanism (15–17). For example, process overlap theory proposes that *g* is a statistical phenomenon that arises based on an overlapping of processes involved in the performance of different cognitive tasks (15). That is, there is no single process that explains the positive manifold, or *g*.

An important distinction in the intelligence literature is that between crystallized and fluid intelligence (18–20). Crystallized intelligence reflects already-acquired knowledge and learned perceptual and behavioral patterns, and is often measured using general knowledge tests. Fluid intelligence, on the other hand, is the ability to reason, solve novel problems, and learn quickly from experience and is measured using novel problem-solving tasks that require generating and testing hypotheses. Hierarchical models of intelligence include several other broad abilities under the umbrella of general intelligence, such as visual and auditory processing (21). In this article, when using the term "intelligence," we are referring more so to fluid intelligence than crystallized intelligence or other broad abilities.

Significance

To understand mind and behavior we must understand the biological basis of intelligence. Despite significant progress, we lack a complete picture that integrates different levels of brain function and explains individual differences in cognitive ability. We propose that the locus coeruleus, the source of norepinephrine for the brain, plays a key role in this puzzle. It does so at all levels of brain function, regulating processes of learning, memory, and attention. We use baseline pupil size, which covaries with locus coeruleus activity, to anchor the present analyses of the role of the locus coeruleus in cognitive ability. This work provides a foundation for future research integrating different levels of brain function with individual differences in cognitive ability.

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However, it is important to point out that statistically (15) and conceptually fluid intelligence and general intelligence (*g*) are highly related constructs.

Modern thinking on intelligence is heavily influenced by the discovery that individual differences in working-memory capacity are highly correlated with fluid intelligence (22–24). This relationship has provided a compelling cognitive mechanism for explaining differences in intelligence. As a construct, working memory emerged as a result of experimental research in cognitive psychology (25–27). In its original conceptualization, working memory consisted of multiple domain-specific stores of information and a central executive, which supervised and coordinated attention so that only relevant information occupied working memory. More broadly, working memory can be thought of as a workspace in which representations are actively maintained in consciousness and manipulated to influence information processing. As an individual differences construct, working-memory capacity reflects an individual's ability to actively maintain representations in an accessible state in the face of distraction and interference (28). Working-memory capacity is typically measured using tasks that challenge participants to remember items while performing a secondary task, which prevents the active rehearsal of memory items.

While it has been argued that working-memory capacity causes differences in fluid intelligence (29–31)—that is, the more information one can maintain and manipulate within working memory, the more effectively one can generate and test hypotheses to solve novel reasoning problems—we have a different interpretation of this relationship. We argue that working-memory capacity and fluid intelligence are related because the tasks used to measure these constructs both require the executive control of attention to organize processing around task demands (32, 33). The executive control of attention directs thoughts and behaviors in a goal-relevant manner. Some people are better at controlling their attention than others, which in turn determines how effectively they handle complex and changing environments. This is true, particularly in situations characterized by distraction and interference, in which attending to useful information and disengaging from no-longer-relevant information is critical. What we refer to as "attention control" (or the executive control of attention) overlaps with terms such as executive functions, inhibition, cognitive control, binding, and the central executive.

The executive attention view of the working-memory capacity/fluid intelligence relationship was further specified in the maintenance–disengagement theory (33). According to the theory, executive attention organizes processing around task goals via two broadly defined functions, maintenance and disengagement. Maintenance keeps representations in an active, accessible state in the face of distraction or interference. Conversely, disengagement removes no-longer relevant representations from consciousness, preventing them from adversely affecting ongoing cognition. As such, disengagement can help to reduce proactive interference and perseveration on thoughts and behaviors. This definition of disengagement is related to and likely overlaps with "updating" in the executive functions literature (34). Generally, tasks that measure working-memory capacity require more maintenance, whereas tasks that measure fluid intelligence require more disengagement; however, both sets of tasks require both maintenance and disengagement to some extent. From this perspective, fluid intelligence and working-memory capacity are correlated because maintenance and disengagement both rely on the executive control of attention, and they are distinct constructs to the extent that one relies more on functions of disengagement and the other functions of maintenance.

It is important to point out that there may also be other cognitive mechanisms that are uniquely related to fluid intelligence and uniquely related to working-memory capacity, the maintenance–disengagement theory is meant to only explain their commonality. Additionally, while a stronger version of the maintenance–disengagement theory would state that the executive control of attention is the only variable needed to explain the relationship between fluid intelligence and working-memory capacity, a softer version can allow for other cognitive processes, other than executive attention, to explain their relationship, but executive attention would explain the bulk of the relationship. Although there are other theories as to the nature of individual differences in intelligence, most of them agree that the executive control of attention (and other domain-general executive processes) is central to understanding differences in intelligence and other cognitive abilities. See Burgoyne et al. (35) for a comparison of our perspective with process overlap theory.

Scientists have long been tempted by the idea of discovering a single explanatory variable for intelligence, whether it be a cognitive, genetic, cellular, or brain mechanism (13, 36–40). Others have argued that intelligence emerges as a result of a complex dynamic system of processes operating at different levels of cognitive and biological function and at different developmental stages (15, 16, 41, 42); therefore, no one variable or mechanism can fully explain differences in intelligence. Nevertheless, there may be specific cognitive and biological functions, as well as stages of development, that are more important than others. We propose that the functions of the locus coeruleus–norepinephrine system represent one of these variables, which are particularly important to understanding the biological basis of intelligence.

The Locus Coeruleus–Norepinephrine System

The locus coeruleus is a relatively small cluster of norepinephrine-producing neurons, ∼28,000 to 50,000 in the human brain (10, 43), located near the fourth ventricle in the pontine brainstem (Fig. 1). It is the sole source of norepinephrine in the neocortex. Norepinephrine is one of several neurotransmitters that have a modulatory effect at target synaptic and nonsynaptic sites. One property that distinguishes the locus coeruleus–norepinephrine system from other neuromodulatory systems (e.g., dopamine) is its widespread efferent projections throughout the brain (11, 12).

The properties of the locus coeruleus–norepinephrine system (discussed in more detail below) uniquely positions it as a central mechanism for regulating many brain and cognitive functions.* As such, it is not surprising that the locus coeruleus–norepinephrine system has been implicated in many cognitive and brain disorders, including attention deficit hyperactivity disorder (ADHD), depression, posttraumatic stress disorder, Parkinson's disease, and Alzheimer's disease (10, 44–46). Overall, the extensive literature suggests that the locus coeruleus–norepinephrine system is critical for healthy and optimal brain function. We will review a subset of the literature on the locus coeruleus–norepinephrine system and its role at different levels of brain function and how they relate to cognition: cellular energy production and functioning, neuron and glial functions, intramodular functions, and intermodular functions.

Cellular Energy Production and Functioning. Cellular energy production and functioning refers to any cellular-level process involved in the production and transfer of energy. Geary (38, 39) has argued that mitochondrial functioning, including the production of adenosine triphosphate, is fundamental to all higher levels of brain function and is therefore related to a range of health (47, 48) and cognitive outcomes (38, 39; for a critique see ref. 41). For example, it is hypothesized that

*There are many extensive reviews and theoretical articles on the locus coeruleus–norepinephrine system, including; Aston-Jones and Cohen (9), Berridge and Waterhouse (10), Moore and Bloom (11), and Sara (12).

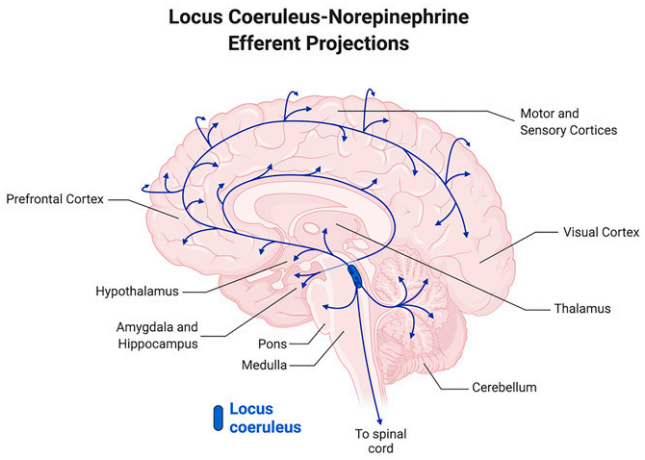

Fig. 1. A depiction of the locus coeruleus–norepinephrine projection system throughout the brain. Created with BioRender.com.

mitochondrial efficiency is a common mechanism underlying performance differences across all cognitive tests (38). In general, Geary suggests that mitochondrial functioning can explain why cognition, health, and aging are correlated with one another.

Consistent with the mitochondrial hypothesis, a neuroenergetics theory has been proposed in which behavioral and cognitive impairments are explained by a failure to meet cellular energy demands (49). According to neuroenergetics, a breakdown during energy production—which is required for sustained neuronal firing—is related to behavioral and cognitive deficits, such as ADHD and attentional lapses (46, 49, 50). In tasks that require sustained attention, the rapid depletion of energy within neurons is hypothesized to impair sustained attention and cognitive performance unless the energy supply is quickly restored. Maintaining precise timing of neuronal firing above baseline levels requires rapid energy restoration, either from mitochondria in neurons (51, 52) or from lactate produced in glial astrocyte cells by glycogenolysis (i.e., glucose metabolism) (46). The release of norepinephrine stimulates increased glucose uptake by astrocytes, which produces more lactate, which in turn is transported to nearby neurons and axon terminals, where it is converted to adenosine triphosphate. This process, referred to as the astrocyte-neuron lactate shuttle, is the primary source of energy fuel for sustained neuronal firing (50, 53). As such, norepinephrine is a key rate-limiting factor for the rapid restoration of energy supply within neurons. Given that the locus coeruleus is responsible for the production of norepinephrine, dysregulation of the locus coeruleus may lead to deficits in sustained attention, a symptom of conditions such as ADHD (46, 49).

The energy supply from aerobic glycolysis and the astrocyte-neuron lactate shuttle (46) also supports the functional organization of resting-state brain networks (54). The energy demands to sustain baseline neuronal firing is actually greater than the energy demands of task-evoked neuronal firing (54, 55). Spontaneous fluctuations in baseline neuronal firing are highly organized into distinct brain networks (56, 57), with the default-mode network playing a central role (54), a point we return to in *Intermodular Functions*. The distribution of aerobic glycolysis is nonuniformly distributed, with elevated levels in the default-mode network and dorsolateral prefrontal cortex (54). Therefore, norepinephrine is implicated as a critical rate-limiting step in cellular energy production not only for task performance, but also the functional organization of the resting-state brain. In general, these models of cellular energy production and functioning are converging on a greater understanding of how lower-level metabolic and molecular functions support higher-level brain systems that give rise to differences in biologically based fluid intelligence.

Neuron and Glial Functions. Neuron and glial functions refer to the functioning of individual cells and include processes that modulate short-term and long-term responsiveness to patterns of input. The effect of norepinephrine on neurons and glial cells may depend on the receptor subtypes (α_1, α_2, and β) and their location (10). Norepinephrine receptors can be found at postsynaptic and presynaptic sites and on glial cells. Norepinephrine belongs to a class of neurotransmitters, along with dopamine and serotonin, known as neuromodulators. Neuromodulators enhance the sensitivity (i.e., neural gain) of postsynaptic neurons to incoming excitatory and inhibitory signals. The release of norepinephrine at postsynaptic sites increases the signal-to-noise ratio by reducing baseline firing rates and increasing firing to salient or relevant stimuli. As such, phasic activation of locus coeruleus neurons and the corresponding release of norepinephrine is thought to act as an attentional filter (9), or to facilitate dynamic reorganization of targeted brain networks for behavioral adaptation to changing demands (58).

The effect of norepinephrine also has more long-term functions related to learning and memory. At the neuronal level, learning and memory are supported by long-term potentiation—the long-lasting strengthening of synapses—and particularly in the hippocampus (59–61). Norepinephrine has been shown to have effects on long-term potentiation in all subfields of the hippocampus (10, 12, 62) and has a more direct effect on long-term potentiation and synaptic plasticity through the intracellular cascading mechanisms activated by the β-receptor subtype on postsynaptic neurons (12). Biosynthesis of neuropeptides, lipids, and proteins, which is essential for maintenance of long-term potentiation in neurons, is also enhanced by norepinephrine through the astrocyte-neuron lactate shuttle. The transfer of lactate from astrocytes to presynaptic neurons for energy production switches glucose metabolism in neurons away from energy production and toward biosynthesis and neuroprotection, a process referred to as the reverse Warburg effect (54). The locus coeruleus–norepinephrine system has also been shown to regulate transcription rates of plasticity-related genes, such as brain-derived neurotropic factor (10). Taken together, these data show that there is substantial evidence that norepinephrine plays a role in the cellular mechanisms and brain regions that support learning, memory, and attention.

Intramodular Functions. The next level of brain functioning is intramodular functions, and this refers to clusters of neurons separated into different brain regions that specialize in processing specific information. The locus coeruleus–norepinephrine system is essential to many intramodular brain functions, such as selective processing in sensory cortices, memory retrieval in the hippocampus, and executive control and working memory in prefrontal cortex regions. It achieves this diverse functional role via its widespread projections throughout the cortex (Fig. 1).

Sensory cortices. Norepinephrine has been shown to modulate activity in sensory cortices to enhance processing of sensory-specific information (10, 12). For example, the neural gain effects of norepinephrine enhance the frequency tuning of auditory cortex neurons so that they fire at more specific frequency ranges (63). Neural gain effects of norepinephrine also alter feature extraction properties of individual sensory neurons, such as visual receptive fields (64), and increase the precision of object representations in the ventral temporal cortex (65). This effect of norepinephrine on sensory cortices provides a mechanism for the effect of top-down attention on perception in models, such as the biased competition model of attention (66, 67). In fact, we have shown that fluid intelligence and the ability to make fine sensory discriminations (e.g., identify which of two tones has a higher pitch) are positively correlated; and furthermore, that differences in attention control fully mediates that relationship (68). It would be interesting to further investigate whether the locus coeruleus–norepinephrine system is

involved in the association between cognitive ability and sensory discrimination.

Prefrontal cortex. The prefrontal cortex is well-known for its role in executive control processes, such as cognitive control, working memory, and decision making. Early studies demonstrated the importance of dopamine levels in the prefrontal cortex for healthy cognition and working-memory functions (69, 70). More recent studies have shown that norepinephrine is also essential for prefrontal cortex function (71, 72). Norepinephrine projections from the locus coeruleus and dopamine projections from the ventral tegmental area converge in the prefrontal cortex, suggesting that the functioning of the prefrontal cortex in regulating behavior is dependent on the joint interaction of dopamine and norepinephrine systems.

Understanding how dopamine neurons from the ventral tegmental area and the locus coeruleus–norepinephrine system interact to influence prefrontal cortex functioning is an ongoing and active area of research. However, cortical projections of these two systems outside the prefrontal cortex are quite different; the ventral tegmental area–dopaminergic system primarily innervates regions associated with motivation and reward, such as the nucleus accumbens, whereas the locus coeruleus is more widespread throughout the entire cortex.[†] One possibility is that the locus coeruleus acts as an attentional filter by enhancing the signal-to-noise ratio in sensory and motor cortices, the ventral tegmental area reinforces behavior and task-engagement by signaling the nucleus accumbens to elicit reward, and these two areas work together to support working-memory functions in the prefrontal cortex (71).

Hippocampus. There is ample evidence for a role of norepinephrine in hippocampal functions related to memory consolidation and retrieval, primarily through β-receptors in hippocampal neurons. In general, locus coeruleus activation leads to enhancement of hippocampus-based learning and facilitates both long-term potentiation and long-term depression for spatial learning (62). Additionally, norepinephrine release in the prefrontal cortex can enhance synaptic plasticity of the hippocampus-prefrontal cortex pathway (73). The locus coeruleus also modulates the interaction between the amygdala and hippocampus, which is related to emotional memory and stress response (44). In fact, the use of the β-receptor blocker propranolol can alleviate anxiety symptoms and the development of posttraumatic stress disorders (44).

Anterior cingulate cortex. The anterior cingulate cortex is another area that highlights the functional significance of the locus coeruleus (9). The anterior cingulate cortex plays a critical role in cognitive control, primarily signaling conflict, task difficulty, errors in performance, and even pain (74). The anterior cingulate cortex, along with the orbitofrontal cortex, are primary areas that project to the locus coeruleus. While the orbitofrontal cortex sends signals of reward (positive valence), the anterior cingulate cortex sends signals of performance-related cost (negative valence) (9).

The regulation of locus coeruleus phasic and tonic activity by these brain regions provides a potential mechanism of top-down control in the brain. Specifically, the adaptive gain theory of locus coeruleus function (9) suggests that the orbitofrontal cortex and anterior cingulate cortex regulate phasic and tonic locus coeruleus activity and the balance between exploitative (i.e., optimize task performance) and explorative (i.e., disengagement from a current task to search for alternative sources of reward) modes of behavior. High tonic locus coeruleus activity drives explorative modes of behavior and is associated with distractibility during task performance. By contrast, moderate tonic and high phasic activation of the locus coeruleus drives exploitative modes of behavior and is associated with optimal performance and task focus. More broadly, the regulation of the locus coeruleus by the anterior cingulate and orbitofrontal cortices suggests that the locus coeruleus is an important intermediary for instantiating top-down control throughout the cortex.

Intermodular Functions. At the highest level of brain function are intermodular functions of large-scale brain networks to integrate different types of information across distant brain regions. Critical to understanding how the brain supports complex and intelligent behavior is how the brain reorganizes the interaction between brain networks as goals, intentions, and context changes. There is a large body of evidence suggesting a robust relationship between cognitive ability and functional connectivity of brain networks. In general, studies have shown that stronger functional connectivity is related to higher fluid intelligence and working-memory capacity (75–87).

Particularly relevant is the interaction between the default-mode network and task-positive networks (88). The default-mode network consists of regions along the medial midline of the brain, such as the posterior cingulate cortex, precuneus, medial prefrontal cortex, and hippocampus. Task-positive networks include several networks related to attention (dorsal and ventral attention networks) and cognitive control (central executive, salience, fronto-parietal networks) as well as sensorimotor functions (57, 89–91).

The default-mode network is involved in a complex array of internally generated self-referential thoughts, such as daydreaming, rumination, autobiographical memory retrieval, and future planning (92). The processes in the default-mode network interfere with more externally oriented cognition during demanding tasks that are supported by the task-positive networks. While brain regions in task-positive networks tend to show activation in the context of preforming cognitively demanding tasks, the default-mode network shows deactivation compared to rest (93). This antagonistic relationship can also be observed in resting-state functional connectivity, with a negative correlation between the default-mode network and the task-positive networks (88); interpreted as reflecting interfering processes between the networks. However, the default-mode and task-positive networks can also show a cooperative relationship during certain mental tasks that require actively producing internal trains of thought or self-relevant representations (94). It has been suggested that the default-mode network in combination with executive and attention networks are involved in self-relevant problem solving to generate representations of oneself in past and future scenarios (39, 95, 96).

The locus coeruleus–norepinephrine system has been implicated in modulating the interaction between various brain networks (58, 65, 97, 98). It does so by way of the effect of norepinephrine on neural gain to enhance signal transmission between brain regions, increasing the connectivity between brain regions within a network and altering the connectivity between brain regions in different networks (10, 65, 98). Additionally, as discussed earlier, norepinephrine is a critical rate-limiting factor in the metabolic processes that support intrinsic functional organization of the brain (54).

The network reset theory of locus coeruleus–norepinephrine function proposes that phasic locus coeruleus activity initiates functional reorganization of small- and large-scale brain networks for optimal behavioral performance (58, 99). For example, it has been proposed that there are two functionally distinct attention networks: a dorsal frontoparietal network and a ventral frontoparietal network (97). The dorsal network supports the top-down effects of goal-driven attention on biasing the processing of relevant stimulus features and locations. The

[†]For an excellent depiction comparing dopamine and norepinephrine pathways, see figure 2 in Sara (12).

ventral network signals a reorientation of attention to salient and relevant stimuli or for switching between functional networks, depending on task demands. A functional relationship between the locus coeruleus–norepinephrine system and the ventral attention network has been proposed (97); the phasic activation of the locus coeruleus initiates a shift or "reset" in cognitive state, which is mediated by the ventral attention network reorienting from one task set to another (99). Therefore, the flexible adaptation of attention networks to meet task demands may be partially driven by activity in the locus coeruleus.

One of the most popular models for the biological basis of intelligence is the parieto-frontal integration theory (100), which proposes that integration of large-scale brain networks across frontal, parietal, temporal, cingulate, and occipital cortices to efficiently process information underlies individual differences in intelligence. However, the specific mechanisms that link the integration of large-scale brain networks with key biological and cellular processes—such as long-term potentiation, which is crucial for learning and memory—are not yet clear. We would argue that because learning and memory are central to intelligence, any biological theory of intelligence must clarify this connection. As discussed earlier, the locus coeruleus–norepinephrine system is one potential mechanism that could provide this explanation.

Cognition and Theories of Locus Coeruleus Function. The preceding sections provided indirect evidence for the relation between the locus coeruleus–norepinephrine system and cognitive abilities by discussing the effects of this system on various brain functions. However, many human and animal studies have examined the effects of norepinephrine on attention and working memory directly (10). Animal studies have found that the depletion of norepinephrine leads to performance deficits only when distractors are included in the task (101), thus demanding greater attention control. Attention-related EEG waveforms, such as the P300 response to infrequent target stimuli, are modulated by phasic activation of locus coeruleus neurons (102, 103). Norepinephrine may also explain age-related cognitive deficits; aged monkeys with decreased norepinephrine innervation of the prefrontal cortex show deficits in working-memory performance (10). Yet, when administered a norepinephrine α2-agonist, which binds to and activates norepinephrine receptors, aged monkeys showed large improvements on working-memory tasks, particularly when distractors were present.

Researchers have proposed various theories to explain the relationship between tonic and phasic locus coeruleus activity and behavior and cognition. As one example, the adaptive gain and optimal performance theory (9) proposes that high phasic activation serves as an attentional filter to facilitate behavioral responses to task-relevant stimuli. By contrast, high tonic activity serves to disengage from task performance as rewards wane, to facilitate exploratory behaviors that seek other sources of reward. As another example, the network reset theory (58, 99), proposes that phasic activity serves to initiate shifts in network reorganization to facilitate adaptive (i.e., task-relevant) sensory processing. Finally, the locus coeruleus–norepinephrine account of working-memory capacity and attention control (104) proposes that high working-memory capacity individuals have better regulation of arousal, and therefore exhibit moderate levels of tonic locus coeruleus activity and high phasic activity. Low working-memory capacity individuals, by comparison, are worse at regulating arousal and therefore have more variability in tonic and phasic locus coeruleus activity, indicative of dysregulation.

Summary. Thus far, we have reviewed evidence suggesting that the locus coeruleus–norepinephrine system is critical across levels of brain function. At the most fundamental level, the release of norepinephrine is a rate-limiting factor in aerobic glucose metabolism, which helps meet the energy demands of the brain for biosynthesis, sustained activation, and functionally organized intrinsic neuronal activity. Norepinephrine also supports long-term potentiation and synaptic plasticity through intracellular cascading mechanisms activated by the β-receptor subtype on postsynaptic neurons. The locus coeruleus performs many of its functions via the effect of norepinephrine on neural gain, which strengthens functional connectivity, enhances precision and sensitivity of processing in sensory and association cortices, and modulates working memory and cognitive control in the prefrontal cortex. The locus coeruleus is well-situated for regulating activity due to its widespread efferent projections throughout the cortex, including the prefrontal cortex and hippocampus. Regulation of activity in the locus coeruleus by the anterior cingulate and orbitofrontal cortices provides a mechanism by which top-down control is instantiated. Finally, several theories have argued that tonic and phasic locus coeruleus activation plays a central role for optimal behavioral and cognitive performance.

Despite its seeming ubiquity, the locus coeruleus does not act alone. Other neuromodulatory systems, such as dopamine and serotonin, and neuropeptides such as orexin (105), also influence a host of similar brain processes. Additionally, recent evidence suggests that the locus coeruleus itself is not a homogenous cluster of neurons that all fire in synchrony; it displays considerable heterogeneity (106). Nevertheless, it is truly impressive how a small cluster of neurons in the brainstem have such far-reaching effects across levels of brain function, and it is for this reason we believe the locus coeruleus–norepinephrine system is critical to understanding the biological basis of fluid intelligence.

Baseline Pupil Size: A Window into Brain Function

Historically, scientific research on the role neurotransmitter systems play in cognition and behavior has been dominated by nonhuman animal studies, primarily due to the invasive methods required to study the brain at this level. With regard to the locus coeruleus–norepinephrine system, this has started to change with the use of pupillometry as a convenient way to study this system in a noninvasive manner (107). The advancement of more affordable eye-tracking systems has allowed psychologists not traditionally trained in the behavioral neurosciences to have relatively easy access to studying the relationship of the locus coeruleus–norepinephrine system to behavior and cognition.

Researchers have typically investigated task-related changes in pupil size and their associations with mental effort, attentional state, arousal, and so on (5, 108). However, differences in baseline pupil size, measured in a passive task-free condition (e.g., stare at a computer monitor with only a central fixation cross), may also provide insight into cognition and brain function. We have found that differences in baseline pupil size persist over weeks and months (Fig. 2, *Right*), suggesting that such differences reflect reliable trait-level characteristics and not just state-level differences in arousal and mental effort (1).

Our laboratory first reported differences in baseline pupil size and their relation to cognitive ability in a relatively small sample of high and low working-memory capacity individuals (109). As this finding was only incidental, we attempted to replicate it. Across a series of studies, we showed that baseline pupil size is related to fluid intelligence and working-memory capacity (1). First, we showed that baseline pupil size was related to working-memory capacity even after controlling for mental effort (Fig. 2, *Left*). Next, we showed that this relationship was highly reliable over multiple weeks of repeated testing (Fig. 2, *Right*). Finally, in a much larger sample ($n = 337$) with considerable variability in fluid intelligence and working-

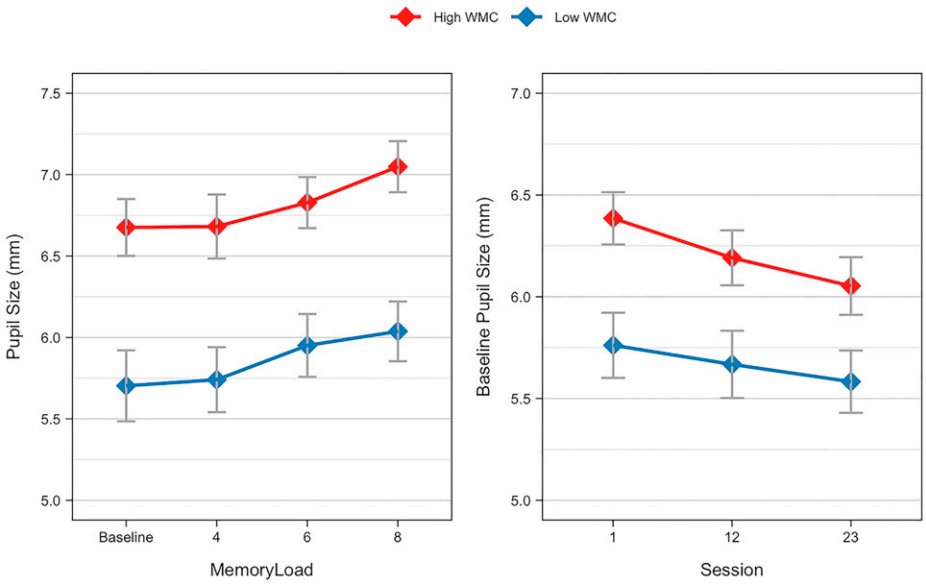

Fig. 2. Baseline pupil size as a function of mental effort and repeated measurement. (*Left*) Baseline pupil size was about 1 mm larger for high working-memory capacity subjects (n = 20) than for low working-memory capacity subjects (n = 20). Pupil size was measured in a simple memory span task during a 30-s interval after the last presented memory item and before recall. Memory load set sizes of four, six, and eight were administered. Pupil size increased with larger set sizes, suggesting an increase in mental effort. However, pupil size for low working-memory capacity subjects at the largest set size was still smaller than pupil size at baseline for high working-memory capacity subjects. This suggests that differences in mental effort at baseline cannot explain why high working-memory capacity subjects have a larger baseline pupil size. (*Right*) Baseline pupil size was larger for high working-memory capacity subject (n = 57) than for low working-memory capacity subjects (n = 53), replicating our previous findings. Baseline pupil size was repeatedly measured across multiple testing sessions during a working-memory training study. Subjects came in for 23 sessions over the course of 3.5 to 16.5 wk. Although baseline pupil size decreased over the testing sessions, high working-memory capacity subjects still had a larger baseline pupil size at sessions 12 and 23 compared to low working-memory capacity subjects. Therefore, working-memory capacity differences in baseline pupil size are highly reliable over time and repeated testing. Additionally, baseline pupil size correlated strongly across the three testing sessions (average r = 0.79). This suggests that baseline pupil size captures reliable trait-level characteristics and not simply state-level variables, like arousal and mental effort. These figures were adapted from experiment 1 (*Left*) and experiment 2 (*Right*) of Tsukahara et al. (1).

memory capacity (Fig. 3, *Upper*), we found that baseline pupil size correlated more strongly with fluid intelligence than with working-memory capacity. Furthermore, after controlling for their shared variance, only fluid intelligence—not working-memory capacity—uniquely predicted baseline pupil size (Fig. 3, *Lower*), and this result held after controlling for potential confounds, such as age. We took this as evidence baseline pupil size is more closely related to fluid intelligence than working-memory capacity.

Nevertheless, we need to point out that some studies that looked at the relationship between baseline pupil size and working-memory capacity (i.e., not fluid intelligence) did not replicate our findings (110, 111). However, these studies suffer from methodological problems, including restriction of range on baseline pupil size, likely due to lighting conditions too bright for optimal measurement. To test this, we conducted two studies manipulating lighting conditions (2). The results were clear: 1) the correlation between baseline pupil size and cognitive ability was reduced or eliminated in excessively bright lighting conditions (Fig. 4 and Table 1); and 2) the relationship between baseline pupil size and working-memory capacity is not nearly as robust as pupil size is with fluid intelligence (Table 1).

The question then is why does baseline pupil size correlate with fluid intelligence? We suspected that it has to do with the locus coeruleus and activity in resting-state brain (the brain in a passive task-free baseline). Therefore, we hypothesized that fluid intelligence is related to the functional organization of the resting-state brain, which arises from the neuromodulatory role of the locus coeruleus–norepinephrine system (1). We based this hypothesis on our baseline pupil size finding and broader evidence suggesting a connection between the locus coeruleus–norepinephrine system, functional connectivity of brain networks, and intelligence.

To summarize the broader evidence: 1) pupil size can be considered a valid indicator of locus coeruleus activity (4–8). 2) The locus coeruleus–norepinephrine system is involved in learning and memory, attention, and working memory. 3) The resting-state brain exhibits intrinsic organization characterized by multiple functional brain networks (112). 4) The integrity of the functional organization of brain networks has important implications for cognition and behavior (54, 88, 91) and correlates with higher intelligence, working-memory capacity, and positive life outcomes (75–86). 5) The brain uses most of its energy on maintaining resting-state brain function, and norepinephrine supports the metabolic processes required to meet this energy demand (46, 54). 6) Norepinephrine influences global levels of functional connectivity, and pupil size corresponds to this effect on functional connectivity (10, 11, 65, 98, 113, 114). 7) Fluctuations in baseline pupil size correlate with blood–oxygen level-dependent (BOLD) fMRI activity in key default-mode network regions (6, 115). Therefore, this body of evidence suggests a connection between the locus coeruleus–norepinephrine system, pupil size, and functional connectivity in the resting-state brain.

Maintenance–Disengagement and Baseline Pupil Size

The maintenance–disengagement theory provides a useful framework to understand how the cognitive mechanisms underlying intelligence map onto various brain functions. We would argue that the executive control of attention is largely responsible for, and maps most closely onto, top-down mechanisms instantiated through the locus coeruleus. The functions of maintenance and disengagement may be supported by the locus coeruleus–norepinephrine system depending on how these functions relate to different brain regions and functional networks. However, more research is needed to better understand how individual differences in the executive control of attention, maintenance, and disengagement are related to the locus coeruleus–norepinephrine system.

Our research has shown that baseline pupil size correlates more strongly with fluid intelligence than working-memory capacity. One hypothesis for this is that baseline pupil size, and thereby the locus coeruleus, is more closely related to individual differences in disengagement than maintenance. This would be consistent with our position that fluid intelligence tests draw more heavily on disengagement, whereas working-memory capacity tests emphasize maintenance. To test this hypothesis, we

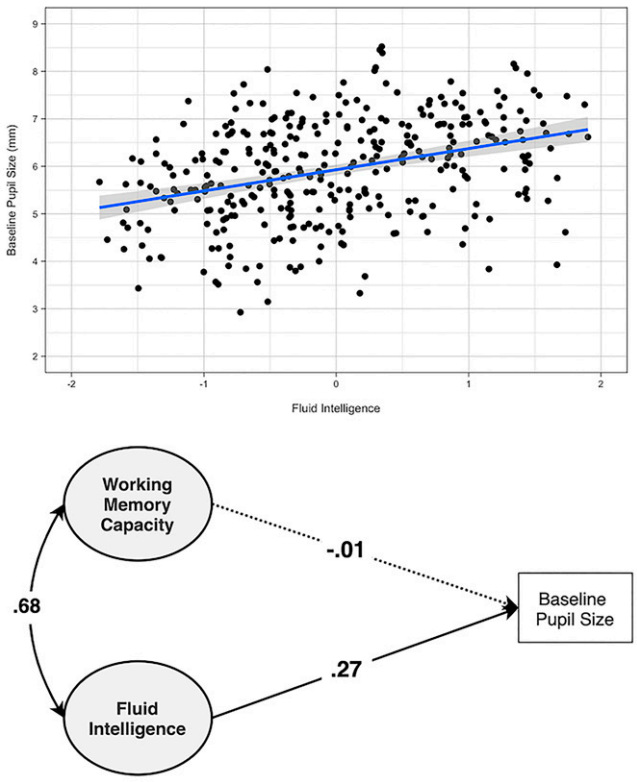

Fig. 3. Relationship of baseline pupil size to working-memory capacity and fluid intelligence. (*Upper*) Baseline pupil size correlated with fluid intelligence, $r = 0.35$, $P < 0.05$, $n = 337$. Error bar represents the SE of measurement. (*Lower*) Fluid intelligence and working-memory capacity were highly correlated, $r = 0.68$. After accounting for this shared variance, only fluid intelligence uniquely predicted baseline pupil size ($n = 337$). The *Lower* figure was adapted from experiment 3 of Tsukahara et al. (1).

analyzed baseline pupil data from two recent studies (2, 116) using the maintenance–disengagement framework. These two studies included measures of fluid intelligence, working-memory capacity, and reliable and valid measures of attention control. This collection of measures allowed us to test models that are theoretically consistent with the maintenance–disengagement framework.

We first conducted a model with a common executive attention factor and unique fluid intelligence and working-memory capacity factors. If there is a relationship between the executive control of attention and the locus coeruleus, then we would expect the common executive attention factor, and not the unique factors, to predict baseline pupil size. On the other hand, if fluid intelligence or working-memory capacity are related to the locus coeruleus independently of executive attention, then we would expect the unique factors to predict baseline pupil size. We tested this model by loading all cognitive tasks onto a common executive attention factor with fluid intelligence and working-memory capacity tasks cross-loaded onto their respective factors (Fig. 5). For both datasets, only the common executive attention factor uniquely predicted baseline pupil size, consistent with our hypothesis that it is the executive control of attention that is related to the locus coeruleus.

Next, we tested whether maintenance or disengagement uniquely predicted baseline pupil size. If the locus coeruleus is related more to individual differences in disengagement than maintenance, then we would expect a disengagement factor—and not a maintenance factor—to predict baseline pupil size. We tested this model by loading the attention control and working-memory capacity tasks onto a maintenance factor and attention control and fluid intelligence tasks onto a disengagement factor (Fig. 6). For both datasets, only disengagement uniquely predicted baseline pupil size, consistent with our hypothesis. Data and analysis scripts are available at: https://osf.io/2pu3q/.

Disengagement and the Locus Coeruleus–Norepinephrine System

The maintenance–disengagement models of baseline pupil size suggest that the reason baseline pupil size correlates with fluid intelligence, more than working-memory capacity, is because fluid intelligence tasks draw more heavily on the ability to control attention to disengage from no-longer relevant information (33). A key aspect of disengagement is reducing interference from processes and representations that are no longer relevant to task goals. The default-mode network is thought to support self-relevant processes, such as daydreaming, mind wandering, future-oriented thinking, and autobiographical memory, at the expense of (or creating interference with) externally oriented cognition (88, 93, 117). Internally driven and self-relevant processes, which are supported by the default-mode network, may be relevant and useful when not performing a particular task. However, during externally driven task performance, these processes may be irrelevant and even interfere with task performance. A greater negative correlation between the default-mode network and task-positive networks may indicate greater ability to disengage from default-mode processes to support optimal task performance. In this context, disengagement, instantiated through the locus coeruleus, may serve to switch cognition from a default-mode to a task-focused and goal-oriented mode.

Although there are a number of task-positive networks, the dual-network model of control posits the frontal-parietal (central executive) network and cingulo-opercular (salience) networks as particularly important for initiating attention control in order to maintain task goals and adjusting behavior for optimal performance (89–91). Therefore, executive attention, and specifically the function of disengagement, might be related to the interactions between the default-mode, central executive, and salience networks by way of the locus coeruleus. This would be consistent with the proposal that the locus coeruleus drives the interaction between dorsal attention (central executive) and ventral attention networks (58, 97).

Similarly, it has been proposed that some individuals are better at regulating activity in the locus coeruleus (104), and this allows them greater flexibility to switch from one mental state to another; specifically, switching between a high tonic exploration mode (9, 118, 119) to a phasic exploitation mode of locus coeruleus activity. This function of the locus coeruleus for switching from one mental state to another would also be consistent with the network-reset theory of locus coeruleus function (58) and various interpretations of the pupil size–cognitive ability relationship (104, 119). If this is the case, it might be expected that individuals high on disengagement are more efficient when switching from an alert resting condition to a task-oriented mode of engagement. This is supported by a number of studies showing that high intelligent individuals display less (more efficient) glucose use in the brain during performance on an intelligence test (120), show smaller pupil dilations (suggestive of less mental effort), while solving difficult math problems (121), and more efficient network reconfiguration from resting-state to task-engagement (81).

Conceptually, there are parallels between maintenance and disengagement as tapped by fluid intelligence tests and the tradeoff between exploitative and explorative modes of locus coeruleus function (9). According to our hypothesis that fluid intelligence primarily taps disengagement, the ability to disengage from hypotheses that have been ruled out and to generate new hypotheses is critical to quickly and accurately solve novel problems. Maintenance, on the other hand, plays a role during hypothesis

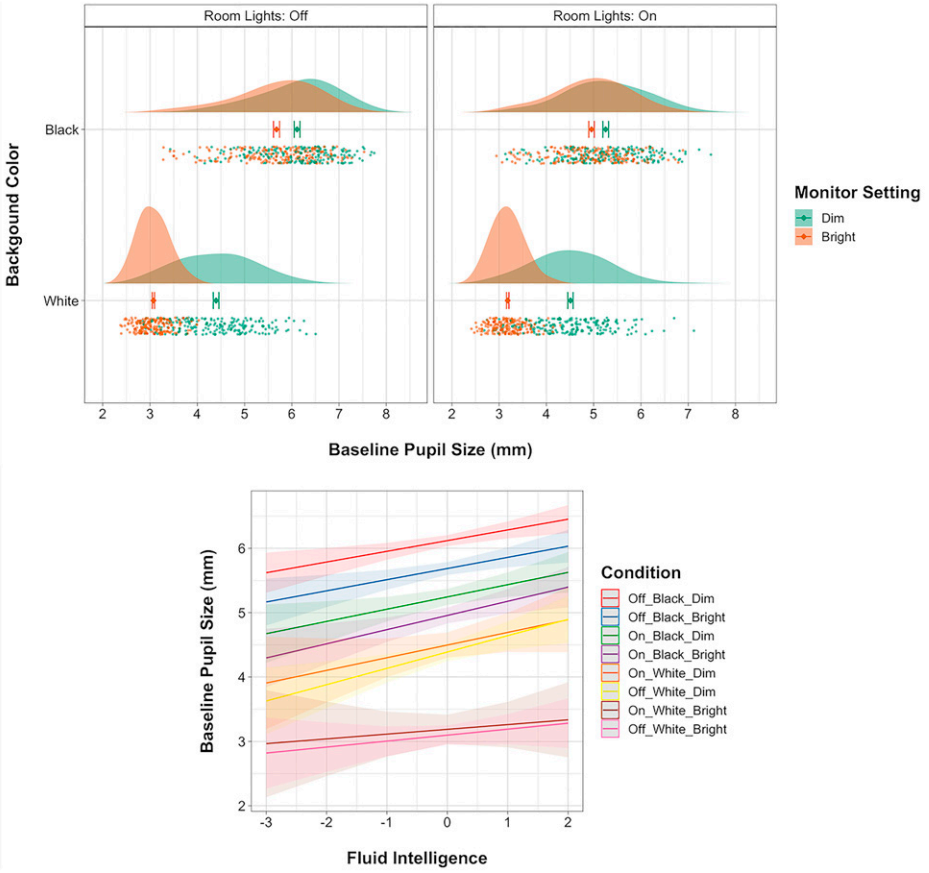

Fig. 4. Baseline pupil size as a function of lighting conditions. (*Upper*) Baseline pupil size as a function of room lighting, background color on the monitor, and monitor brightness settings; each factor was independently manipulated for a total of eight conditions (n = 201). In the two brightest lighting conditions (room lights on/off, white background, and bright monitor settings), the mean and variability of baseline pupil size values were severely restricted, such that the mean approached the physiological minimum pupil size. Error bars represent the within-subject SE of measurement. (*Lower*) Hierarchical linear modeling results showing that fluid intelligence predicted baseline pupil size in all the lighting conditions except for the two brightest conditions (n = 201).

testing because one must keep track of the relations between problem elements. This tradeoff of maintaining focus on a current hypothesis and searching for other hypotheses requires a balance of exploitation (e.g., test current hypothesis) and exploration (e.g., generate new hypotheses) modes of locus coeruleus function. The function of the locus coeruleus to initiate shifts in network reconfiguration might facilitate these different stages of problem solving by activating the default-mode network during exploration of possible solutions and the executive or attention networks during evaluation and testing of a hypothesis. Tests of working-memory capacity, on the other hand, may not require as much of a tradeoff between these two modes and instead place a much heavier emphasis on maintenance/exploitation. This may explain why baseline pupil size correlates with fluid intelligence more strongly than working-memory capacity.

Finally, the dual-network model of control argues that the central executive network is more related to trial-by-trial adjustments in performance, whereas the salience network supports goal maintenance over a longer period of time (91). This suggests a possibility that the function of disengagement is more related to the central executive network, given that both are important for flexible adaptations in behavior, and the function of maintenance is more related to the salience network.

Of course, there are other possibilities, and future research will be needed to determine how maintenance and disengagement are differentially related to certain brain functions and the locus coeruleus–norepinephrine system. Recent advances have been made assessing fMRI of locus coeruleus BOLD response (122, 123). Although there is general consensus across studies on the functional activation and connectivity of the locus coeruleus, there are some differences, possibly due to different localization methods and scanning parameters (122). Nevertheless, this advancement provides an opportunity to test the relationships between the locus coeruleus, functional brain networks, pupil size, and cognitive ability.

Table 1. Correlations between baseline pupil measures and cognitive abilities

	Pupil size	
Cognitive ability	Gray	White
Fluid intelligence	**0.29**	**0.16**
Working-memory capacity	**0.21**	0.09
Attention control	**0.25**	0.09

Gray represents baseline pupil size measured with a gray background color on the monitor (n = 315). White represents baseline pupil size measured with a white background color on the monitor (n = 292). Values in bold font are statistically significant at $P < 0.05$.

The Search for Intelligence in the Brain

The search for intelligence in the brain has been a long sought-after holy grail for intelligence, brain, and genetic researchers; and the last decade has seen significant progress identifying genetic and brain differences related to intelligence (124–129). Although neuroimaging and genetic techniques have improved considerably, more work is needed to integrate these approaches with cognitive psychology and psychometrics to understand the cognitive and brain mechanisms that give rise to differences in intelligence (124). Part of the problem has been how researchers define and measure intelligence. Most scientists searching for the biological basis of intelligence adopt the *g*-factor approach, in which researchers either use a diverse set of cognitive tests and extract a single "general intelligence" score from them or use a single task as an indicator of general intelligence. These

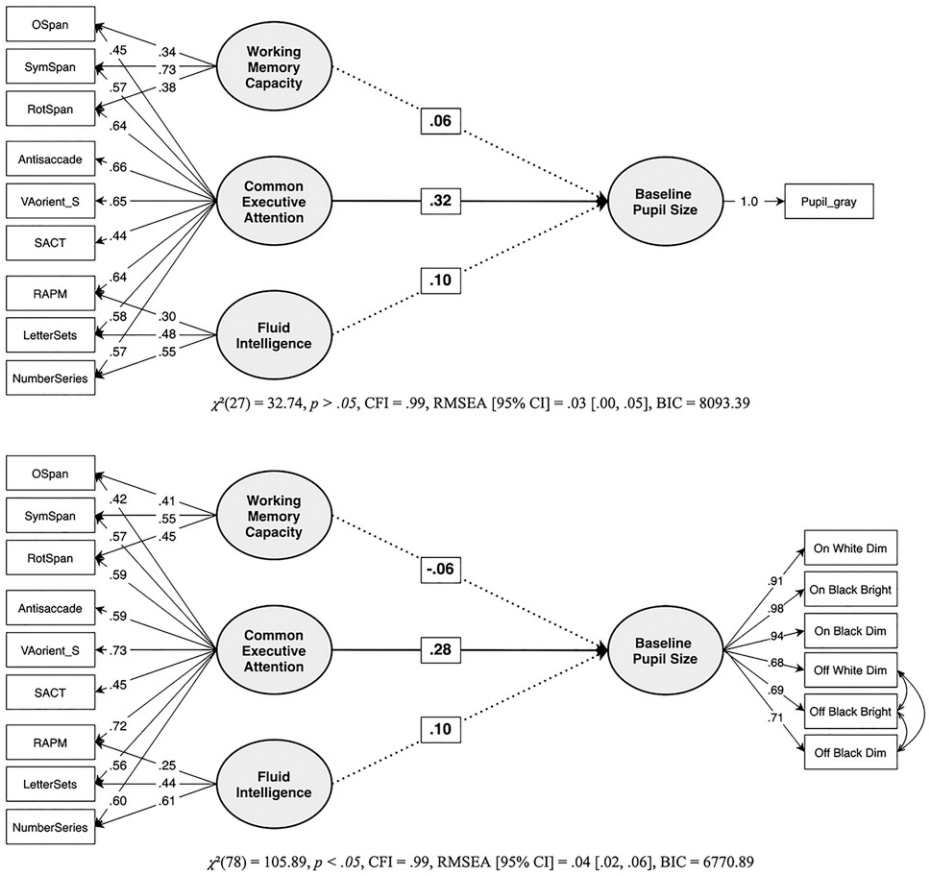

Fig. 5. Structural equation model with a common executive attention factor and unique working-memory capacity and fluid intelligence factors predicting baseline pupil size from study 1 (*Upper*) and study 2 (*Lower*) of Tsukahara and Engle (2). Dotted lines represent nonsignificant regression paths and factor loadings, $P < 0.05$.

approaches are ubiquitous in genetic and brain studies on intelligence (36–39, 124, 130).

Our position is that intelligence is itself a multifaceted construct comprising numerous cognitive abilities, and that the *g*-factor approach is inherently reductionist. That is not to say the *g*-factor approach is without use; it can provide an exploratory means of identifying genetic and brain sources that could explain differences in intelligence. However, as Kovacs and Conway note: "Positing a general factor gives the false impression that there is a psychological explanation, whereas the actual explanation is purely statistical" (131).

As an alternative to the *g*-factor approach, a correlated latent-factors approach can allow one to tease apart correlated yet distinct broad cognitive abilities, such as fluid intelligence, working-memory capacity, attention control, and others, and investigate how they relate to genetic and brain differences. We have demonstrated the strength of this approach with our maintenance–disengagement models on baseline pupil size to better understand how the locus coeruleus–norepinephrine system is related to intelligence (see ref. 132 for an approach that is consistent with process overlap theory). Regardless of the approach used, the field not only needs further refinement of genetic and brain techniques, but critically, greater integration with the strengths of cognitive psychology, psychometrics, and latent variable analysis.

The scientific study of behavior and cognition incorporates a wide range of methods and disciplines. On one hand, the experimental tradition of carefully manipulating variables to understand the mechanics governing psychological and biological phenomena has yielded tremendous insights into the inner workings and dysfunctions of the mind. However, a relative blind spot of the experimental tradition is the lack of consideration for how individuals differ on the processes that govern behavior and cognition (133, 134). The differential tradition of psychology, on the other hand, analyzes this variance to characterize and understand the ways individuals differ in terms of cognitive ability, personality, motivation, and so on. Considerable experimental research has been conducted on the locus coeruleus–norepinephrine system, but little work has addressed how individuals differ in its functioning. One benefit of combining experimental and differential approaches to study the locus coeruleus is that it may shed light on intervention mechanisms at different levels of brain function, resulting in more effective treatments for cognitive dysfunctions (10, 46, 135) and possibly the development of methods to train attention and improve fluid intelligence by targeting the locus coeruleus–norepinephrine system. In general, we view the search for intelligence in the brain as less about coming up with a single answer, and more about generating new research questions and refining our methodology in a way that contributes to an ever-growing body of knowledge.

Conclusion

The locus coeruleus–norepinephrine system is essential to understanding the biological basis of intelligence. It is important for a wide range of behavior and cognition and plays a central role at different levels of brain function: cellular energy production and functioning, neuron and glial functions, intramodular functions, and intermodular functions. We presented analyses that show that a common executive attention factor predicts baseline pupil size, and that this is related to the executive attention function of disengagement, not maintenance. Based on these analyses, we conclude that the ability to control attention to disengage from no-longer relevant information is related to the functional organization of the resting-state brain, which arises from the neuromodulatory role of the locus coeruleus–norepinephrine system.

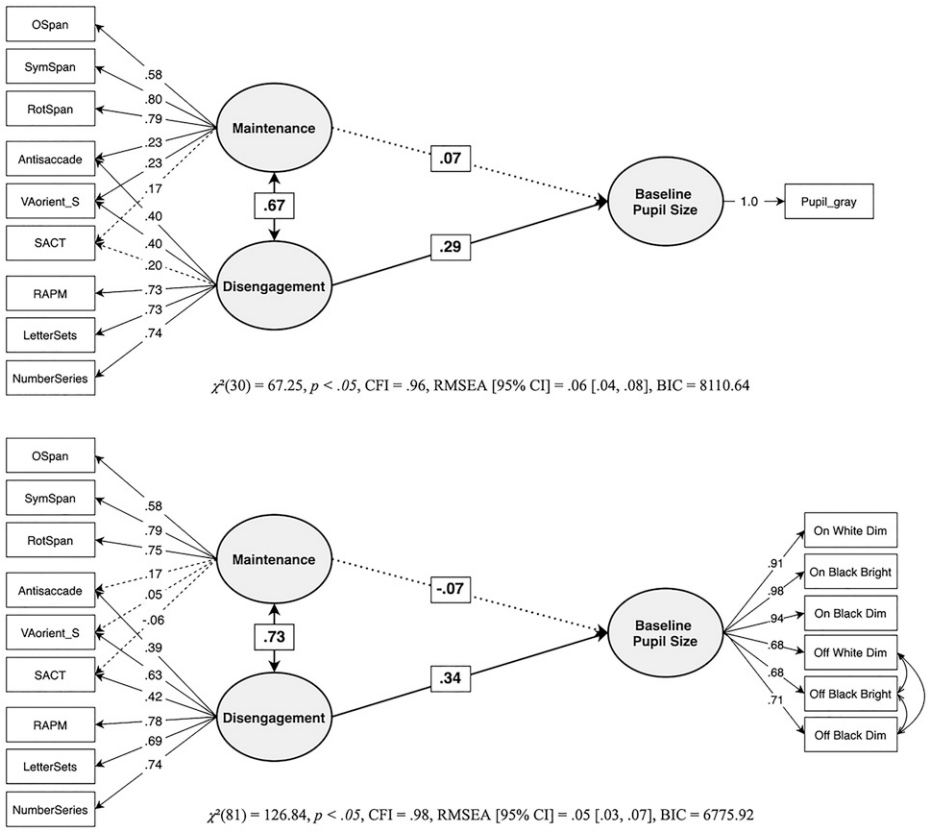

Fig. 6. Structural equation model with maintenance and disengagement factors predicting baseline pupil size from Study 1 (*Upper*) and Study 2 (*Lower*) of Tsukahara and Engle (2). Dotted lines represent non-significant regression paths and factor loadings, $P < 0.05$.

Various brain theories of intelligence have been proposed that range from lower-order metabolic functions (38, 39) to higher-order functions, such as the functional organization of large-scale brain networks (100). The properties and functions of the locus coeruleus–norepinephrine system connect the lower-order and higher-order brain functions, and therefore it has explanatory power to bridge various brain theories of intelligence. In general, subcortical and brainstem structures are at the intersection of sensory, cortical, and motor brain functions, and they need to be considered for a more complete picture of the biological basis of intelligence and cognitive abilities to emerge (136). We hope that the work presented here will inspire new research questions and lead to methodological improvements in the search for intelligence in the brain. Regardless of the direction future research will take, for a relatively small cluster of neurons in the brainstem, it is clear that the locus coeruleus is at an axis of cognition, brain function, health, and disease.

Data Availability. Raw data and R analysis files have been deposited in the Open Science Framework (https://doi.org/10.17605/OSF.IO/2PU3Q). Previously published data were used for this work (2).

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