Aging cognition: from neuromodulation to representation

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Basic cognitive functions, such as the abilities to activate, represent, maintain, focus and process information, decline with age. A paradigm shift towards cross-level conceptions is needed in order to obtain an integrative understanding of cognitive aging phenomena that cuts across neural, information-processing, and behavioral levels. We review empirical data at these different levels, and computational theories proposed to enable their integration. A theoretical link is highlighted, relating deficient neuromodulation with noisy information processing, which might result in less distinctive cortical representations. These less distinctive representations might be implicated in working memory and attentional functions that underlie the behavioral manifestations of cognitive aging deficits.

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Although average life expectancy in most societies has increased from about 45 years in 1900 to about 75 years in 1990 (Ref. 1), basic cognitive functions decline with advancing age. Thus, the rapid growth of aging populations worldwide is accompanied by an urgency to obtain integrated understanding of mechanisms and processes of cognitive aging at different levels.

Cognitive aging phenomena at different levels

Since the first studies on adult age differences in intellectual functioning were published in the 1920s (e.g. Ref. 2), cognitive aging phenomena have been studied at various levels (see Fig. 1). At the behavioral level, individual difference researchers have documented aging-related declines in many psychometric measures of fluid intelligence[3] (i.e. basic cognitive mechanics[4] for memorizing, reasoning, and learning). Furthermore, aging-related increases of intra-individual variability, inter-individual variability, and de-differentiation of ability structures (increased correlation between different cognitive abilities) are also common observations (see Ref. 5 for review). At the information-processing level, experimentally oriented cognitive aging researchers have proposed general processing resources, such as working memory capacity, attentional mechanisms, and processing speed, as explanatory mechanisms for the age differences in fluid intelligence observed at the behavioral level (see Refs 6,7 for review). At the neurobiological level, neuroscientists have been studying brain aging at the anatomical[8], metabolic, and neurochemical levels[9].

Integration across behavioral, information-processing, and neurobiological levels has been difficult to establish. Recent advances in neuroimaging and computational neuroscience open new avenues for exploring functional relationships between cognitive aging phenomena at different levels. The process of integrating data and theories from different levels provide opportunities for related fields to co-evolve by ways of cross-level hypothesis generation and testing[10,11]. In this article, we first review empirical data of cognitive aging at the behavioral, information-processing and neurobiological levels. We then consider recent cross-level computational theories[5,12–14] aiming at integrating findings of aging-related declines of neuromodulation and various benchmark cognitive aging deficits.

Aging, information processing, and neuromodulation

Aging affects three main facets of information processing. People's abilities to activate, to represent and maintain information in mind, to attend to relevant but ignore irrelevant information, and to process information promptly decline with advancing age. At the neurobiological level, the efficacy of neuromodulation also declines. Among various neurotransmitter systems, we focus on the monoamines (e.g. serotonin and the catecholamines, particularly dopamine and noradrenaline)[15–19] because they have been studied extensively with respect to declines in working memory[20] and processing speed[21] during normal aging. Other transmitters also affect cognitive aging. For instance, cholinergic transmission is important for long-term memory consolidation[22], which plays a role in Alzheimer pathology[23], and glutamate sometimes interacts with other transmitters (e.g. dopamine, GABA and acetylcholine)[24,25].

Deficits in various facets of information processing

'Working memory function' refers to an ensemble of processes allowing people to activate, simultaneously represent and hold information in immediate memory, while operating on the same or other information. Aging-related decline in working memory function[26] has been found in many memory span tasks (e.g. Ref. 27; summary data in Fig. 2a). Besides the more 'traditional' memory capacity view, working memory has recently been decomposed into processes of representing and maintaining context information subserving both mnemonic and attentional control functions[12].

Aging-related decrements in attentional mechanisms have been found in various selective and focused attention tasks (see Ref. 28 for review) and other interference tasks, such as the Stroop and proactive interference tasks. Lastly, speed is a ubiquitous aspect of information processing as all processes take time. There is ample evidence for aging-related slowing in many tasks (see Refs 29,30 for review; summary data adapted from Ref. 27 in Fig. 2b).

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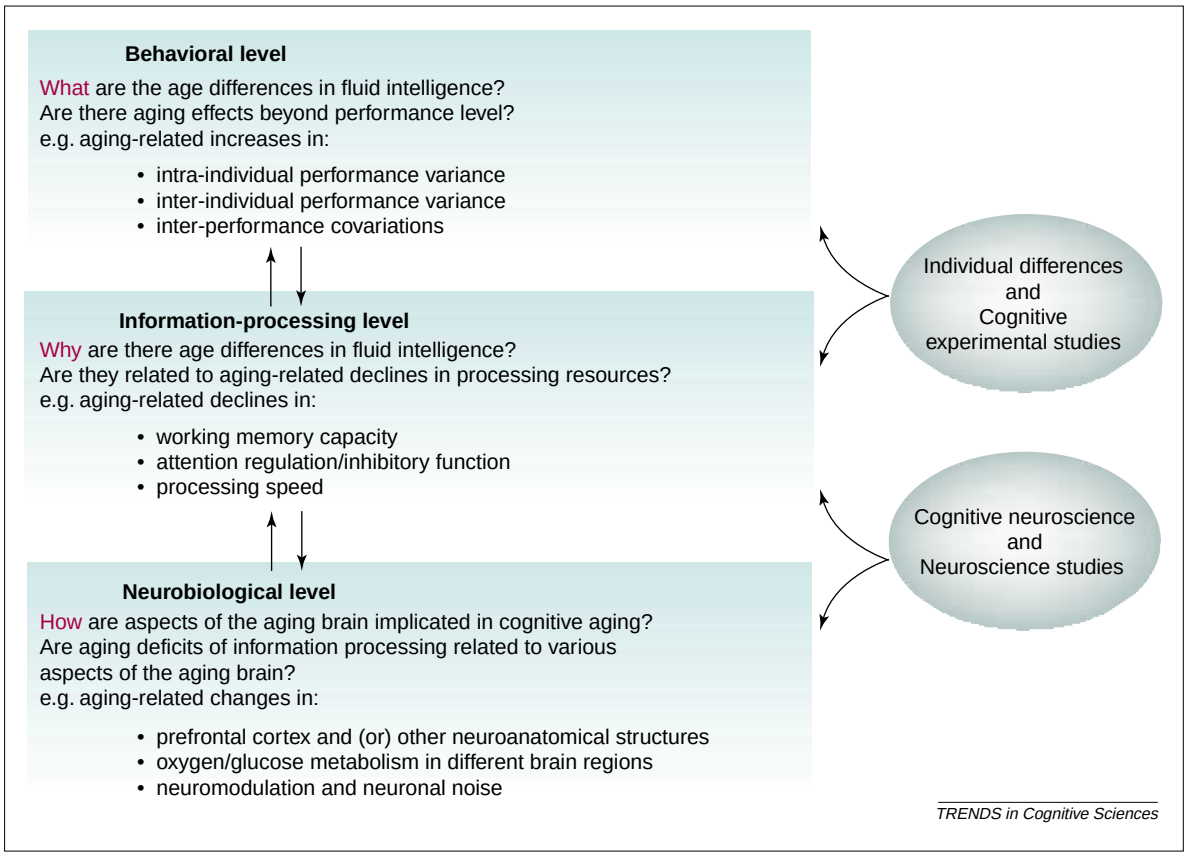

Fig. 1. A summary of cognitive aging issues addressed by researchers of different specializations working at various levels of analysis.

Limits of resource-reduction theories

Given the above evidence, theories of cognitive aging typically explain behavioral manifestations of cognitive impairments by positing that working memory, attention regulation, and processing speed act as cognitive resources that decline with aging (see Ref. 6 for review). However, two major difficulties confront the resource-reduction theories.

First, although the different processing resources are commonly considered as alternative explanations, they are conceptually and empirically interdependent. For instance, attentional control mechanisms involved in representing and maintaining context information could be important components of working memory[12]. Similarly, speed is an inevitable second-order phenomenon that might reflect the compound effect of all temporal demands incurred from attentional and storage mechanisms involved in processing a given task. Second, the resource-reduction accounts tend to be circular in nature. Reductions in processing resources are assumed to cause cognitive impairments, and, at the same time, old people's poor performances are taken as indications of resource reductions. It has been suggested that such circularity could be avoided by establishing explicit links between the processing resources and their potential neurobiological underpinnings[31].

Aging and deficient dopaminergic modulation

Severe neuroanatomical degeneration resulting from cell death and reduced synaptic density is typical for pathological aging (e.g. Alzheimer's disease). Recent evidence, however, suggests that milder cognitive deficits occurring during normal aging are likely to be due mainly to neurochemical shifts in still relatively intact neural circuits[32]. The dopaminergic system is a promising neurochemical correlate of cognitive aging for several reasons.

First, dopamine transmitter content and binding mechanisms in various brain regions decline during normal aging. Earlier studies focused mostly on dopamine mechanisms in the nigrostriatal region and found a reduction in the number of dopamine D2 receptors of about 10% per decade starting at the age of about 20 years[15,16]. Recent findings suggest that declines in striatal D2 receptors are related to attenuated extrastriatal glucose metabolism[18]. There is also new direct evidence of D2-receptor loss in various extrastriatal regions[19], such as the anterior cingulate cortex (13% per decade), frontal cortex (11% per decade, Fig. 2C), hippocampus (10%), and the amygdala (7%). Besides D2 receptors, dopamine D1-receptor loss has also been observed in the striatum[33] and frontal cortex[34], although currently the evidence is not as conclusive as that for D2-receptor loss. Recently, the roles of D1 receptors in aging and in schizophrenia have attracted increasing interest. With expanding knowledge of the structure and function of dopamine receptors, the

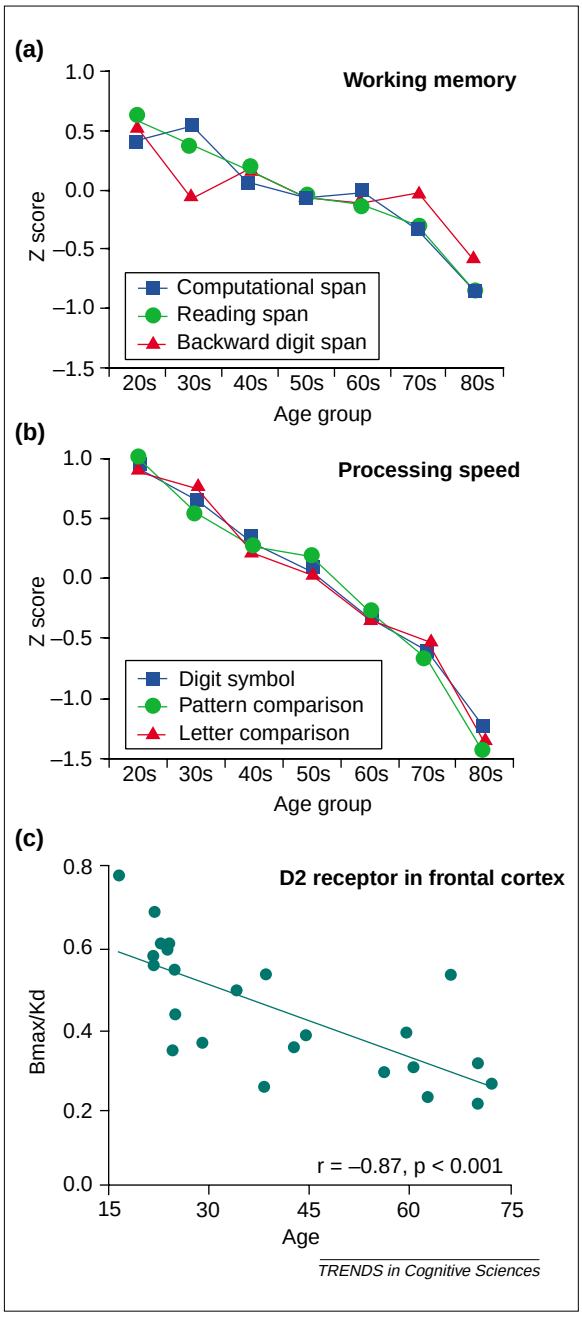

Fig. 2. Age-related changes in information processing and neurotransmitter density. (a) Negative adult age differences in working memory measured by three types of span test (computational, reading and backward digit span), scaled in Z score metric. (b) Negative adult age differences in processing speed measured by three perceptual speed tests (digit symbol substitution, pattern and letter comparison), scaled in a Z-score metric. (a and b adapted with permission from Ref. 27.) (c) Aging-related declines in dopamine D2-like receptor availability in the frontal cortex. (Adapted with permission from Ref. 19.)

relation between aging and the interactions between D1 and D2 (Refs 35,36), and other receptor subtypes can be investigated more systematically.

Second, cognitive aging deficits have been attributed, at least in part, to prefrontal cortex dysfunction (see Ref. 37 for review). More recent data suggest that the main locus of dysfunction associated with working memory deficits is a more specific region of the PFC – the dorsal lateral PFC (Ref. 38). Research over the last two decades suggests that dopamine modulates how well the PFC makes use of briefly activated cortical representations to circumvent constant reliance on environmental cues and to regulate attention towards relevant stimuli and appropriate responses[20]. Besides the direct influence of D2 receptor loss in the PFC, declines in nigrostriatal dopamine mechanisms could also contribute to aging-related PFC dysfunction, as the nigrostriatal area is well interconnected with the PFC via frontal–striatal circuits[39,40].

Third, besides the apparent parallelism between aging-related declines in working memory, processing speed, and D2 receptors across the adult lifespan (Fig. 2), there is also more direct experimental evidence for functional relationships between deficient dopaminergic modulation and cognitive declines. For instances, reduced dopamine receptor density in old rats' nigrostriatum is associated with decreased response speed and increased reaction time variability[21]. Drugs that facilitate dopaminergic modulation (e.g. D1 agonists) alleviate working memory deficits of aged monkeys with naturally occurring dopamine depletion in their PFC (Ref. 41). In humans, aging-related attenuation of the striatal D2-receptor binding mechanism is statistically associated both with decreased glucose metabolism in extrastriatal cortical regions innervated by dopaminergic pathways[18] and with age differences in processing speed and episodic memory[42].

Taken together, deficient dopaminergic modulation is implicated in cognitive aging deficits; however, the details of this link between neuromodulation and cognition await further explication. At the cellular level, empirical and theoretical investigations aimed at understanding how dopaminergic modulation affects the memory field and signal integration of PFC neurons have recently begun[43–46]. At a more molar level, studies are also underway that are exploring computational principles that might relate declines in neuromodulation to cognitive aging deficits observed at the information-processing and behavioral levels[12,13].

Recent computational theories linking neuromodulation with cognitive aging

In 1990, two mathematical theories of cognitive aging were proposed in part to resolve the interdependence and circularity problems facing the resource-reduction theories[47,48]. Although not operating at the level of neuromodulation, both theories foreshadowed cross-level conceptual orientation. The network-disconnection theory of aging and information-processing rate[47] makes broad reference to neuroanatomical changes that might involve the degeneration of axonal connections. The information-loss theory of aging-related cognitive slowing[48] assumes an increasing rate of neural information loss across processing steps.

Although both theories are oriented towards linking behavioral cognitive aging phenomena with conceivable properties of the aging brain, they do not suggest explicit neuronal mechanisms for attenuated axonal connections or increased information loss. Neuromodulation of synaptic transmission is a natural starting point for further theorizing about these missing links. In the light of accumulating evidence for aging-related deficiency of dopaminergic

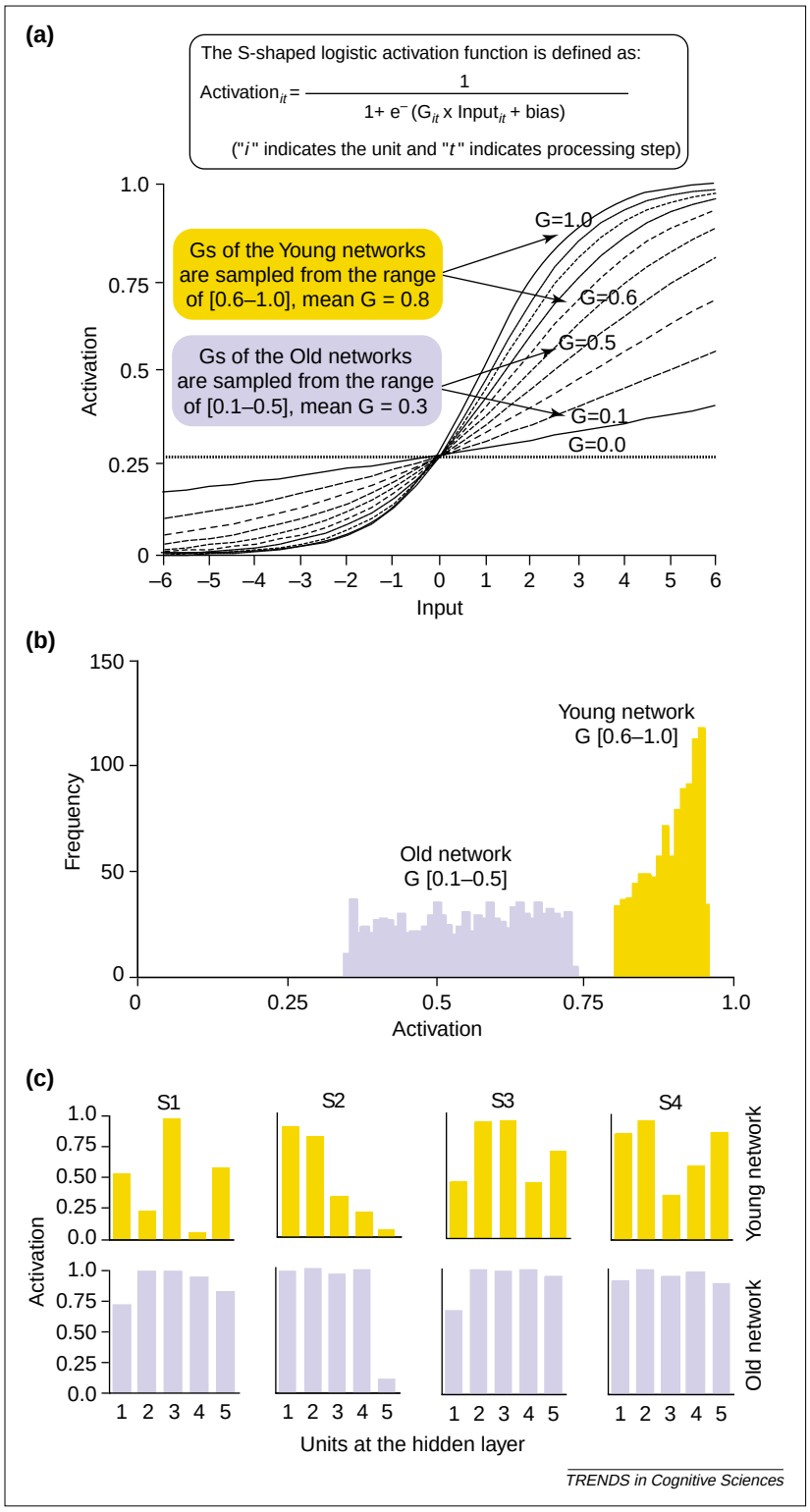

Fig. 3. Simulations from computational theories of cognitive aging: effects of deficient neuromodulation. (a) The *S*-shaped logistic activation function at different values of the gain parameter, G. Physiological evidence suggests that the logistic function with a negative bias captures the function relating the strength of an input signal to a neuron's firing rate, with its steepest slope around the baseline firing rate. Reducing mean G flattens the activation function such that a unit becomes less responsive. Aging-related decline of dopaminergic modulation can be simulated by sampling values of G from a distribution with a lower mean. (b) G and the variability of activation across processing steps. Reducing mean G (0.8 and 0.3 for the 'young' and 'old' networks, respectively) increases the temporal variability of a unit's response to an identical input signal (set to 4.0) across 1000 trials. (c) Internal activation patterns across five hidden units of one 'young' and one 'old' network in response to four different stimuli (S1 to S4). The internal representations of the four stimuli are much less differentiable in the 'old' than in the 'young' network. (Adapted from Ref. 13 with permission.)

modulation, more recent computational inquiries[12,13] explore mechanisms that could explicate aspects of the functional relationships between aging-related decline in dopaminergic modulation, neural information processing fidelity, and cognitive aging.

Although dopamine's modulatory effects vary widely, depending on cortical region and receptor type, a general feature of dopaminergic modulation can be conceptualized as altering the signal-to-noise ratio of neural information processing, thus regulating neurons' sensitivity to afferent signals. One way to model this effect is adjusting the gain (G) parameter of the sigmoidal activation function in feedforward backpropagation networks[49]. Other approaches, focusing specifically on modeling voltage-dependent dopaminergic modulation of PFC neurons' memory fields in recurrent networks, have also been proposed[44,45]. Although differing in implementation details, the overall neuromodulatory effect of tuning the signal-to-noise ratio is a common feature shared by these approaches.

Recently, two complementary computational theories extended the approach of manipulating the G parameter of the sigmoidal activation function[49] to model aging-related attenuation of dopaminergic modulation and cognitive aging deficits. One theory focuses on capturing functional interactions between dopaminergic modulation and the dorsal lateral PFC in regulating context representation and maintenance[12]. Operating at the level of neural signal processing in general, the other theory aims at elucidating a potential sequence of functional relations from deficient dopaminergic modulation to reduced neural information processing fidelity with ensuing consequences for cortical representational distinctiveness and cognitive aging deficits[13].

From deficient neuromodulation to neural noise

A classical hypothesis of cognitive aging at the neurobiological level is increased neural noise (haphazard activation during neuronal information processing)[50]. However, thus far, mechanisms leading to such an increase and its proximal and distal consequences have not been unveiled. Simulating aging-related decline of dopaminergic neuromodulation by attenuating the G parameter in neural networks hints at a possible chain of mechanisms relating deficient neuromodulation to increased neural noise and less distinctive cortical representations.

Reduced responsivity and increased noise in neural information processing

Conceptually, the G parameter captures dopaminergic modulation by altering the slope of the activation function. Reducing G simulates aging-related attenuation of dopaminergic modulation by reducing the slope and flattening the non-linearity of the *S*-shaped logistic activation function, such that a unit's average responsivity to excitatory and inhibitory input signals is reduced (Fig. 3a).

Furthermore, if the values of a unit's G across processing steps are randomly chosen (i.e. stochastic G; Ref. 13) from a set of values with a lower average, the unit's response to a given external signal becomes more variable, which implies a decrease in signal transmission fidelity (see Fig. 3b). Put differently, a given amount of random variations in G, simulating random fluctuations of transmitter release[51], generates more haphazard activation during signal processing if the average value of G of the processing units is reduced. This sequence of effects computationally depicts a potential neurochemical mechanism for aging-related increase in neural noise: as aging attenuates neuromodulation, the impact of transmitter fluctuations on the overall level of haphazard neuronal activity is amplified in the aging brain.

Less distinctive cortical representations

The computational simulations further show that as reduced responsivity leads to increased intra-network random activation variability, another subsequent effect is a decrease in the *distinctiveness* of the network's internal representations. Low representational distinctiveness means that the activation profiles formed across the network's hidden units for different stimuli are less readily differentiable from each other. To illustrate this, Fig. 3c shows the internal activation patterns captured by the activity levels across units of the hidden layer of a 'young' (higher average G) and an 'old' (lower average G) network in response to four input signals. As can be seen, the internal stimulus representations are *less* distinctive in the 'old' than in the 'young' network.

In terms of everyday examples, this effect implies that, as people age, mental representations of various events and the contexts within which the events occurred, such as conversations held with different individuals within a day in different social settings, become less distinct, and thus are more confusable with each other. This set of simulation results provides a computational analog for an earlier information-processing hypothesis, which suggests that old people's memory traces for encoded events are less distinctive because old people process information less elaborately than young people as a result of reduced attentional resources[52]. Couched within the cross-level theoretical framework, the simulation also suggests that deficient dopaminergic modulation of the PFC's attention regulation mechanisms might be the neural correlate of less elaborate processing.

Furthermore, we have recently shown that such computational effects (i.e. reduced representational distinctiveness as a result of lowering stochastic G) also generalize to networks with multiple processing modules (S-C. Li and S. Sikström, unpublished data). Reducing the mean G of units within two distinct processing modules leads to extensive activation overlap across modules.

Taken together, a potential biological implication of these theoretical effects could be that as declining dopaminergic modulation drives down cortical neurons' responsivity and increases neural noise in the aging brain, cortical representations elicited by different stimuli and contexts become less differentiated as people age. Cortical representations of concurrent external events (perception) and later reinstatements of these events (memory) are the primitives of subsequent cognitive processing carried out by various neural circuits. Therefore, deficient neuromodulation causing less distinctive cortical representations of different events and contexts may have far-reaching consequences for various facets of cognition. The theoretical link laid out here was tested and supported by a series of simulations capturing behavioral human cognitive aging phenomena (see Box 1). In this article, we have focused on dopaminergic modulation because of the converging evidence with respect to its functional effects on working memory, attention and processing speed, along with declines in its content and receptor mechanisms in various brain regions during normal aging. However, the computational formalisms demonstrated here could be generalized to other transmitter systems if they exhibit similar functional properties and aging gradients.

Implications: a paradigm shift towards co-evolving fields across levels

Details regarding the involvement of neuromodulation in cognitive aging deficits remain to be unraveled. Pieces of the puzzle are emerging in various sub-fields, and the field as a whole could benefit from a paradigm shift towards overarching frameworks seeking to integrate cognitive aging phenomena across different levels. The proposed theoretical link – from attenuated neuromodulation to increased neural noise and less distinctive cortical representations in the aging brain, and finally on to cognitive aging deficits – is only an initial proposal awaiting further vigorous empirical testing. Nevertheless, neural computational theories of the kind reviewed here[12,13] integrate evidence of aging-related decline of dopaminergic modulation with a broad range of human cognitive aging phenomena and suggest explicit mechanisms that could give rise to the functional relations – a task unlikely to be accomplished by either animal neurobiological or human neuroimaging studies alone.

A shift to cross-level paradigms generates more opportunities for hypothesis generation and testing across levels. For instance, neuromodulation might not only influence aging-related increases in intra-individual performance variability within individuals[53,54], but also inter-individual diversity at the group level. Future animal pharmacological studies could directly examine the effects of dopamine agonists and antagonists on intra-individual fluctuations and their effects on inter-individual diversity.

Questions for future research

- Is more distinctive stimulus representation computationally equivalent to sparse memory representation? How might spare memory representation be formally related to more efficient memory capacity and processing speed?
- Can differences in behavioral manifestations between cognitive aging and schizophrenic syndrome be linked to differences in the relative degree of impairment in various subtypes of dopamine receptors?
- What role does neuromodulation, in general, and the dopaminergic system, in particular, play in the course of normal cognitive development in childhood and in developmental disorders of attention? To what extent can child cognitive development be conceived of as an increase in the efficacy of neuromodulation and cortical representations?

Recent neuroimaging evidence suggests that cognitive processes that are carried out separately by either the left or right hemisphere in young adults co-activate both hemispheres in old people. For instance, people in their 60s and beyond showed bilateral activity when retrieving items from memory[55] or performing verbal and spatial working memory tasks[56]. Currently, these data are primarily interpreted in terms of a compensation view: suggesting that the increased bilateral activation in old adults might be one way to compensate for neurocognitive deficits[57]. There is some supporting evidence for this view.

For instance, memory performance of old adults who exhibit bilateral activity is better than that of those who do not[56] (Cabeza, Anderson, Kester, and Rajah, unpublished data). The recent finding of an association between striatal D2 receptor availability and glucose metabolism in the frontal cortex[18] raises the question of whether deficient neuromodulation and the increase in bilateral activation might be related. Aging-related declines in neuromodulation could be one aspect of neurocognitive deficits needing compensation. The effect of attenuating the G parameter, thus causing less distinctive internal representations and increased overlapping activation in different information-processing pathways (S-C. Li and S. Sikström, unpublished data), suggests that deficient bilateral activation might partly be related to deficient neuromodulation, in addition to reflecting possible compensatory reorganization of functional brain circuitry or compensatory behavioral strategies.

This review has focused on relating the different levels of cognitive aging phenomena, tracing a link from neuromodulation to cognition to behavior. In the foreseeable future, however, it will be necessary to examine more actively reciprocal influences from behavior to cognition to neural mechanisms, and to use the knowledge gained from basic research in real-life applications. This includes, for example, research on behavioral training that assists older adults in developing compensatory cognitive strategies (e.g. the use of mnemonics, external memory cues, and other environmental and contextual support)[58] that capitalize on using the cortical plasticity that the aging brain seems still to possess[59].

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Box 1. Simulations linking neuromodulation with behavioral data

Learning rate, asymptotic performance, and interference susceptibility

With advancing age people take longer to learn paired associates (arbitrary word pairs, such as '*computer–violin*'). In agreement with empirical findings that compared people in their 20s with those in their 50s (Ref. a), simulations show a comparable drop in performance: the 'old' networks (i.e. having a reduced mean gain, G) require more trials than the 'young' networks to reach increasingly strict recall criteria in paired-associate learning (Fig. Ia).

Besides slower learning rate, ample data about the effects of aging and practice on skill acquisition show that aging-related decrements persist even at old people's asymptotic performance levels[b], a phenomenon that can also be accounted for by reducing the average G of the network's processing units (Fig. Ib).

Another prominent cognitive aging deficit is older people's increasing susceptibility to interference. In the context of paired-associate learning, sixty-year-olds are more susceptible than forty-year-olds to interference of previously learned word pairs with the learning of new pairs, and they need more trials to learn new word pairs if interference is strong[c]. In line with the empirical evidence, the number of trials required for learning new word pairs under conditions of weak and strong interference differ more in the 'old' than in the 'young' networks (Fig. Ic).

Performance variability and covariation

Behavioral data also show aging-related increases of performance variations within a single individual across time (or different tasks), and differences across individuals, as well as covariation between tasks[d]. Aging effects on variance and covariation can also be accounted for by mean G reduction, suggesting that aging-related increase of intra-individual performance variability, inter-individual diversity, and ability de-differentiation might all be associated with decreasing efficacy of neuromodulation.

Simulations in which intra-network variability was tested by measuring a given network's performance variability across study lists in four conditions of paired-associate learning, show that the magnitude of average intra-network performance variability was larger in the 'old' than in the 'young' networks, across all conditions (Fig. Id). Across long and short lists, inter-network performance variability was also larger among the old networks (Fig. Ie). Furthermore, correlations between the performances across conditions were higher in the group of 'old' than in the group of 'young' networks (Fig. If).

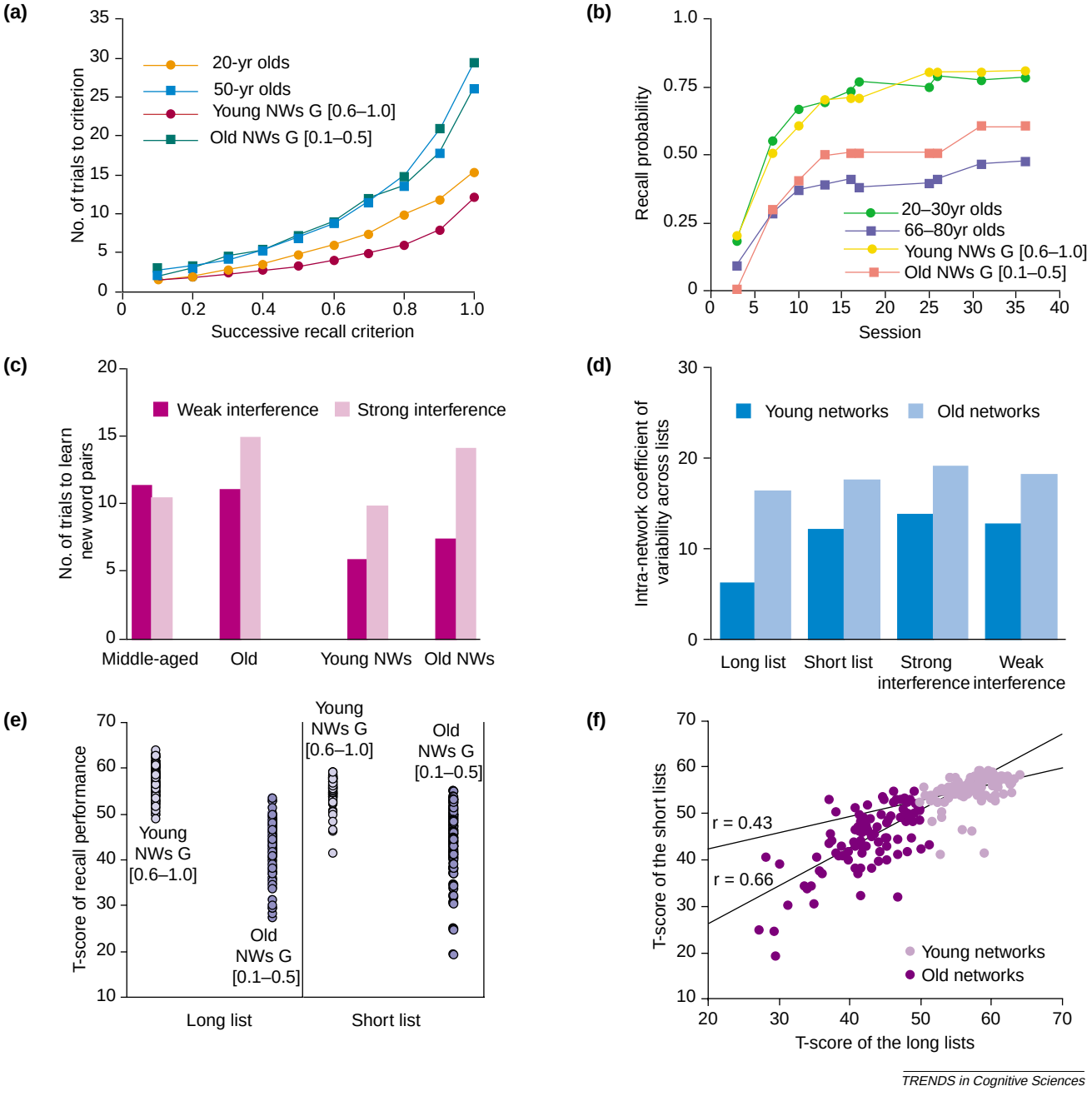

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Fig. I. Comparing simulations with human behavioral data. (a) Aging deficits in paired-associate learning in human subjects and simulations. There is good agreement between the simulations and human data: like the 50-yr olds the 'old' networks (NW) required more trials to reach harder recall criteria. (b) Aging impairments at asymptotic performance in human subjects and simulations. The human performance is reasonably well simulated by reducing the average gain (G) of the network's processing units. (c) Increases in susceptibility to interference in dual-list paired-associate learning are seen both in human subjects and in young and old network simulations. (d) The effect of mean G reduction on intra-network variability in performance level across different study lists in four conditions. The old networks (lower mean G) show a greater intra-network variability. (e) The G parameter and inter-network variability. Across different list lengths, reducing mean G not only reduces mean recall performance, but also increases *inter*-network variability. (f) G and covariation of performances. Reducing mean G increases the correlation between performances with short and long lists. The correlation is stronger for the 'old' ($r = 0.66$) than for the 'young' ($r = 0.43$) networks (difference between correlations is statistically significant, $z = 2.4$). (Adapted with permission from Ref. 13.)

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