Connecting the Many Levels and Facets of Cognitive Aging

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Abstract

Basic cognitive mechanisms, such as the abilities to briefly maintain, focus and process information, decline with age. Related fields of cognitive aging research have been advancing rapidly, but mostly independently, at the biological, information-processing and behavioral levels. To facilitate integration, this article reviews various aspects of cognitive aging occurring at the different levels, and describes a recent integrative theory relating cognitive aging deficits with deficient neurotransmission causing noisier information processing and less distinctive cortical representation. Modeling age-related attenuation of catecholaminergic modulation by lowering a neural network parameter to reduce the signal-to-noise ratio of information processing accounts for benchmark phenomena observed in humans, ranging from age differences in learning rate, asymptotic performance and interference susceptibility to intra- and interindividual variability and ability dedifferentiation. Although the details of the conjectured sequence of effects linking neuromodulation to cognitive aging deficits await further empirical validation, cross-level theorizing of the kind illustrated here could foster the coevolution of related fields through cross-level data synthesizing and hypothesis testing.

Keywords

Cognitive Aging; Catecholaminergic Modulation; Cortical Representation; Neural Networks; Performance Variability

Gradual declines in fundamental aspects of cognition pervade the aging process. Biologically, brain aging involves structural losses in neurons and synaptic connections along with deterioration in neurotransmitter systems. Behaviorally, people's abilities to keep information in mind briefly (termed working memory), attend to relevant information and process information promptly are compromised with age. Explanations for these cognitive aging deficits have been postulated at various levels. At the cognitive level, some assume age-related reduction in processing resources, such as working memory, attention regulation and processing speed. At the biological level, others hypothesize age-related increase of neuronal noise or dysfunction of the prefrontal cortex (PFC), a frontal area of the cerebral cortex thought to be critical for working memory functions. Designs and results from animal neurobiological studies are not always readily testable in human cognitive studies, and vice versa. Therefore, until the recent advances with neuroimaging techniques, data and theories of cognitive aging have been mostly confined within their respective levels. The present article focuses on synthesizing the different facets and perspectives of cognitive aging using a cross-level theory aimed at elucidating a probable sequence of effects from deficient neuromodulation to increased neuronal noise, to dedifferentiated cortical representation, and finally on to different aspects of behaviorally manifested cognitive aging phenomena in humans.

AGING, CATECHOLAMINES AND COGNITIVE PROCESSING RESOURCES

Although progressive neuroanatomical degeneration resulting from cell death and reduced synaptic density is characteristic of pathological aging such as Alzheimer's disease, there is now evidence suggesting that milder cognitive problems occurring during normal aging are mostly due to neurochemical shifts in still-intact neural circuitry (Morrison & Hof, 1997). Among different neurotransmitter systems, the catecholamines, including dopamine (DA) and norepinephrine (NE), are important neurochemical underpinnings of age-related cognitive impairments for several reasons. First, there is consensus for age-related decline in

catecholaminergic function in the PFC and basal ganglia (a system of subcortical structures lying beneath the neocortex, mainly including the striatum and substantia nigra). Across the adult lifespan, dopaminergic function in the basal ganglia decreases by 5-10% each decade (Gabrieli, 1998). Furthermore, many DA pathways in the basal ganglia are interconnected with the frontal cortex through the frontal-striatal circuits (Graybiel, 1990), hence are in close functional association with the PFC mechanisms. Second, research over the last two decades suggests that catecholamines modulate the PFC's utilization of briefly activated cortical representations of external stimuli to circumvent constant reliance on environmental cues and to regulate attention to focus on relevant stimuli and appropriate responses (Arnsten, 1998). Third, there are many findings indicating, specifically, functional relationships between age-related deficits in the dopaminergic system and reduced cognitive processing resources. For instances, reduced dopamine receptor density in old rats' nigrostriatum decreases response speed and increases reaction time variability (MacRae, Spirduso, & Wilcox, 1988). Drugs that facilitate dopaminergic modulation alleviate working memory deficits of aged monkeys who suffer from 50% dopamine depletion in their PFC (Arnsten & Goldman-Rakic, 1985). In humans, age-related attenuation of dopamine D2 receptor's binding mechanism is associated with declines in processing speed and episodic memory (Bäckman et al., 2000).

MODELING AGE-RELATED DECLINE OF CATECHOLAMINERGIC MODULATION

Although there is growing evidence for the catecholamines' involvement in various age-related cognitive impairments, the details of these functional relationships await further explication. Empirical investigations aimed at understanding detailed cellular mechanisms of how dopaminergic modulation affects the memory field and signal integration of PFC neurons have recently begun (reviewed in Arnsten, 1998). Theoretical inquiries into general signal processing effects that might underlie some aspects of the association between deficient catecholaminergic modulation and cognitive aging have also been undertaken.

The specifics of catecholamines' modulatory roles notwithstanding, a general feature of catecholaminergic modulation has been conceptualized as altering the signal-to-noise ratio of neural information processing, thus regulating the neurons' sensitivity to afferent signals. One way to model this effect is adjusting the gain (G) parameter of artificial neural networks (Servan-Schreiber, Cohen, & Prinz, 1990). Neural networks are computational models which consist of multiple interconnected layers of simple processing units whose responsivity can be regulated. Neural signal transmission in such systems is simulated by propagating (forwarding the effect of) an external stimulus signal, represented by the activity profile across units at the input layer, to output units via the intermediate layer. The activity level ("activation") of each of the intermediate and output units is usually mathematically defined by an S-shaped logistic function, which simply transforms the input signal into patterns of activation at these two subsequent layers. The thus transformed activation profile across units at the intermediate layer constitutes the network's internal representation for a given external stimulus. Conceptually, the G parameter captures catecholaminergic modulation by altering the slope of the S-shaped logistic function, thus regulating a processing unit's sensitivity to input signals (Fig. 1A). Recently, this approach was specifically extended to model age-related attenuation of catecholaminergic modulation. The randomness inherent in mechanisms of neurotransmitter release can be implemented by randomly choosing the values for the G parameters of the network's processing units at each processing step. Reducing the mean (average) of these values can then simulate age-related decline in catecholaminergic function (Li, Lindenberger, & Frensch, 2000).

From Deficient Neuromodulation to Neuronal Noise and Representation Dedifferentiation

A classical hypothesis regarding cognitive aging is age-related increase in neuronal noise; however, thus far mechanisms leading to such an increase and its proximal consequences have not been unveiled. Simulating age-related decline of neuromodulation by attenuating the average of the G parameter values hints at a possible chain of mechanisms relating deficits in

catecholaminergic modulation to increased neuronal noise and dedifferentiated cortical representations of external stimuli.

Reducing mean G reduces the slope and flattens the non-linearity (curvature) of the *S*-shaped logistic activation function, such that a unit's average responsivity to excitatory and inhibitory input signals is reduced (Fig. 1A). Furthermore, when the values of a unit's G are randomly chosen from a set of values with a lower average, the unit's response to a given external signal varies more across processing steps. This implicates an increase in random activation variability within the network; which, in turn, decreases signal transmission fidelity. Put differently, a given amount of random variations in G, simulating random fluctuations of transmitter release, generates more haphazard activation variability during signal processing if the average of the processing units' Gs is reduced. This sequence of effects computationally depicts a potential neurochemical mechanism for age-related increase of neuronal noise: as aging attenuates neuromodulation, the impact of transmitter fluctuations on the overall level of neuronal noise is amplified in the aging brain.

Moreover, reduced responsivity and increased intra-network random activation variability subsequently decrease the distinctiveness of the network's internal representations. Low representational distinctiveness means that the activation profiles formed at the network's intermediate layer for different external stimuli are less readily differentiable from each other. To illustrate, Fig. 1B shows the internal activation patterns captured by the activity levels across units at the intermediate layer of one "young" (higher average G) and one "old" (lower average G) network in response to four input signals. Clearly, the internal stimulus representations are much less distinctive in the "old" than in the "young" network. In daily terms, this effect implies that, as people age, the mental representations of different events, such as various scenes viewed at an art exhibition, become less distinct, thus more confusable with each other. A potential biological implication of this theoretical property could be that as the declining catecholaminergic modulation drives down cortical neurons' responsivity and increases neuronal

noise in the aging brain, cortical representations (presumed biological substrates of mental representations) elicited by different stimuli de-differentiate as people age. Cortical representations of concurrent external events (perception) and later reinstatements of these events (memory) are the primitives of subsequent cognitive processing. Therefore, deficient neuromodulation causing dedifferentiated cortical representations of different events could thus have influential impact on various aspects of cognitive functioning.

SIMULATIONS LINKING NEUROMODULATION WITH BEHAVIORAL DATA

The theoretical path from age-related impairment of neuromodulation to increased neuronal noise in the aging brain to dedifferentiated cortical representation and on to cognitive aging deficits was tested and supported by a series of simulations with multiple constraints from behavioral human cognitive aging phenomena.

Aging, Learning Rate, Asymptotic Performance and Interference Susceptibility

Behavioral memory research shows that with advancing age it takes people longer to learn paired-associates (arbitrary word pairs, such as “computer-violin”). In agreement with empirical findings comparing people in their 20s with those in their 50s, the “old” networks require more trials than the “young” networks to reach increasingly strict recall criteria in paired-associate learning (Fig. 2A). If old and young people differ only in how fast they can learn, one would expect, that given enough training, old people would eventually reach young people’s performance level. Alas, ample data about the effects of aging and practice on skill acquisition show that negative age differences often persist even at old people’s maximum (asymptotic) performance levels. The lower asymptotic performance observed in people in their 60s and onwards can also be accounted for by reducing average G, with the “old” networks displaying poorer asymptotic performance (Fig. 2B). Another prominent cognitive aging deficit is older people’s increasing susceptibility to interference (increasing distractibility by irrelevant or no-

longer relevant information). In the context of paired-associate learning, sixty-year-olds are more susceptible to proactive interference (interference of previously learned word pairs with subsequent learning of new pairs) than forty-year-olds and they need more trials to learn new word pairs if proactive interference is strong. In line with empirical evidence, the simulations show that 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. 2C).

Aging, Performance Variability and Covariation

In addition to decreases in performance levels, behavioral data also point to age-related increases of performance variations within a person across time (or different tasks) and differences between individuals. Furthermore, aging also seems to affect the relations between different cognitive abilities. Psychometric studies conducted since the 1920s show that, as people age, performances of different tasks become more correlated with each other. These less explored cognitive aging phenomena can also be accounted for by mean G reduction, suggesting that age-related increase of intraindividual performance variability, interindividual diversity and ability dedifferentiation might in part be associated with declining neuromodulation (Li et al., 2000). As an example, Fig. 2D shows simulation results where intra-network variability was tested by examining a given network's performance variability across different study lists in four conditions of paired-associate learning. Across all conditions, the magnitude of average intra-network performance variability was larger in the "old" than in the "young" networks.

CO-EVOLVING FIELDS:
CROSS-LEVEL DATA SYNTHESIS AND HYPOTHESIS GENERATION

Accumulating evidence indicates that catecholaminergic neuromodulation is an influential biological underpinning of many cognitive aging deficits. However, details of the effects leading up to this neurobiological-behavior link remain to be unraveled. Pieces of the puzzle are

emerging from the various sub-fields, but the field as whole needs overarching frameworks to integrate existing data and guide concerted research efforts. The cross-level computational theory described in this article is only an initial attempt to arrive at such integrative frameworks. Indeed, the theory's main tenet from attenuated neuromodulation to increased neuronal noise and dedifferentiated cortical representations in the aging brain, and lastly on to cognitive aging deficits awaits more direct and vigorous empirical scrutiny in the future. However, currently the computational simulations integrate evidence of age-related decline of catcholaminergic modulation with a broad range of human cognitive aging effects observed with respect to performance level, variability and covariation—something that still cannot be easily implemented in animal neurobiological or human neuroimaging studies alone.

En route integration, the theory also generates some cross-level hypotheses for future research. For instance, it suggests that neuromodulation might influence age-related increases in intraindividual performance variability and interindividual diversity at the group level. Contrary to the traditional focus on average performance, this hypothesis motivates investigations of aging and intraindividual variability, an issue that is just now starting to be more broadly examined. Recent studies showed that intraindividual fluctuations in old people's (60 to 80 years old) trial-by-trial RT predicted dementia group membership (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000) and fluctuations in sensorimotor performance predicted verbal and spatial memory (Li, Aggen, Nesselroade, & Baltes, in press). These results affirm that understandings of aging, performance variability and its sources may offer insight into age-related changes in the brain-behavior link. At a different level, animal pharmacological studies could directly examine the effects of catecholamine agonists on intraindividual fluctuations and its impact on performance diversity at the group level. While questions of drug effects on performance level and fluctuations are commonly examined, group diversity issues are more rarely addressed because individual differences traditionally play little role in animal research.

Recent neuroimaging evidence suggests that cortical information processing becomes less differentiated as people age. For instance, people in their 60s and beyond showed bilateralized (bi-hemispheric) activity during retrieval (e.g., Cabeza et al., 1997) and during both verbal and spatial work memory tasks (Reuter-Lorenz et al., 2000). The effect of attenuating the average values of the G parameter causing dedifferentiated internal representations suggests that age-related reduction in hemispheric functional lateralization (the notion of the left and right hemispheres dealing separately with different processes) might be related to neurochemical changes in the aging PFC. This raises questions of how cellular mechanisms of neuromodulation might affect the vividness of cortical representations of external stimuli and how qualities of cortical representations might affect working memory, attention regulation, processing speed, and the distribution of information processing across different neural circuitry. Finally, given catecholamines' involvement in developmental attentional disorders (reviewed in Arnsten, 1998), investigations of whether the relations between the ontogeny of neuromodulation and basic cognitive functions can also be captured with reversals of the proposed mechanisms might aid the search for unifying accounts of cognitive development and aging.

Note

1. Address correspondence to Shu-Chen Li, Max Planck Institute for Human Development, Lentzeallee 94, D-14195 Berlin, Germany. E-mail: shuchen@mpib-berlin.mpg.de. With this review, the author would like to commemorate Prof. Alan T. Welford (1914-1995), who over four decades ago ventured to speculate about the neuronal-noise hypothesis and persisted. The author thanks the MPI and Prof. Paul Baltes for sponsoring this research.

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Figure Captions

Fig. 1 (A) The S-shaped logistic activation function at different values of 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. Small increments in excitatory signals produce greater changes in firing frequency than those produced by the same amount of increment in inhibitory signals. Reducing mean G flattens the activation function such that a unit becomes less responsive. For instance, an excitatory input and an inhibitory input, +1 and –1, produce a much greater difference in activation when G=1.0 (0.5 vs. 0.12) than when G=0.1 (0.29 vs. 0.25); and when G=0 (the limiting case) the unit's response always remains at its baseline activation. Age-related decline of catecholaminergic modulation can be simulated by sampling the values of Gs from a distribution with a lower mean. (B) Internal activation patterns across five intermediate 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 Neurocomputing, 32-33, S.-C. Li, U. Lindenberger and P. A. Frensch, "Unifying cognitive aging: From neuromodulation to representation to cognition", pp. 879-890.

Fig. 2 (A) Negative age effect on learning paired-associates in simulations and humans [the empirical results can be found in Monge, H. R. (1971). Studies of verbal learning from the college years through middle age. Journal of Gerontology, 26, 324-329]. (B) Negative age difference in asymptotic performance in simulations and human [the empirical results can be found in Baltes, P. B., & Kliegl, R. (1992). Further testing the limits of cognitive plasticity: Negative age differences in a mnemonic skill are robust. Developmental Psychology, 28, 121-125]. (C) Age-related increase in susceptibility to proactive interference in dual-list paired-associate learning in simulations and humans [the empirical results can be found in Lair, C. V., Moon, W. H., & Kausler, D. H. (1969). Associative interference in the paired-associative learning of middle-aged and old subjects. Developmental Psychology, 5, 548-552]. (D) The effect of mean G reduction on intra-network performance variability across different study lists in four conditions (reviews of age-related increase in intraindividual variability can be found in Li & Lindenberger, 1999). Intra-network variability is reported in units of coefficient of variance, i.e., standard deviation divided by mean. Adapted from Li, Lindenberger and Frensch (2000) with permission from Elsevier Science.

Fig. 1

Figure 1

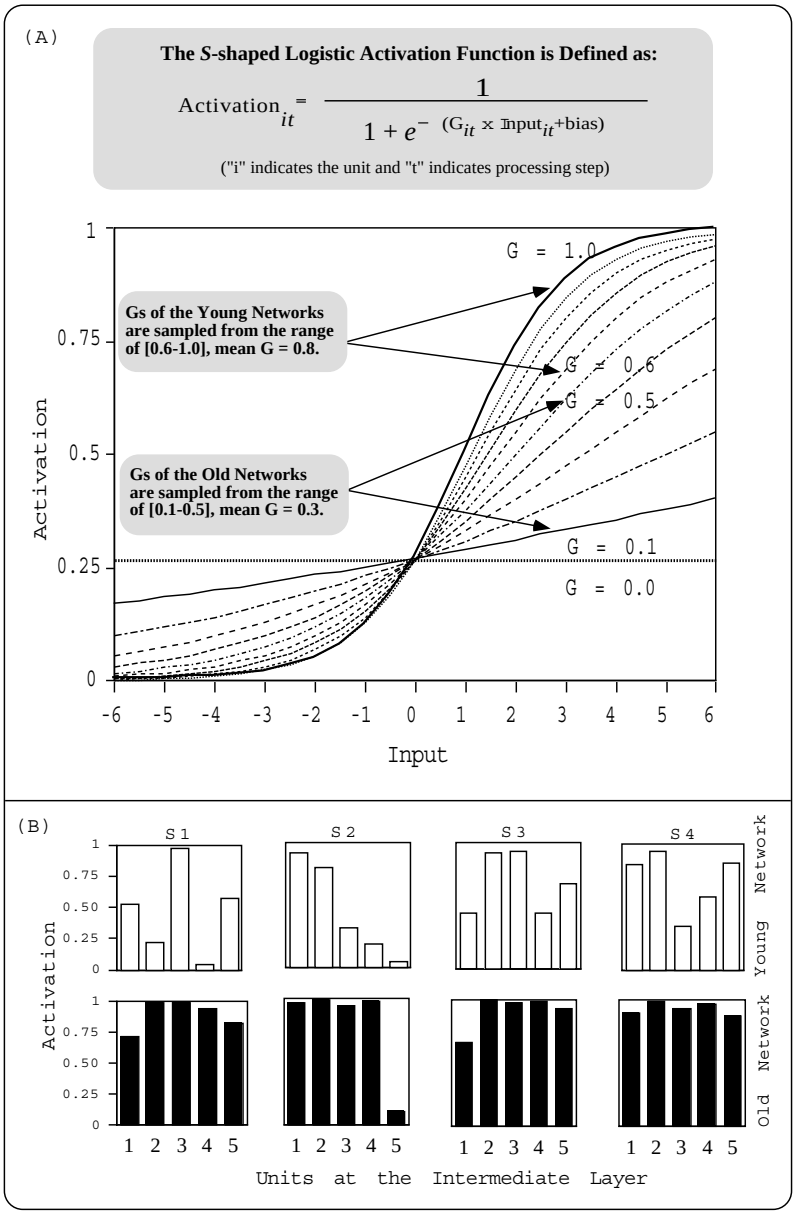
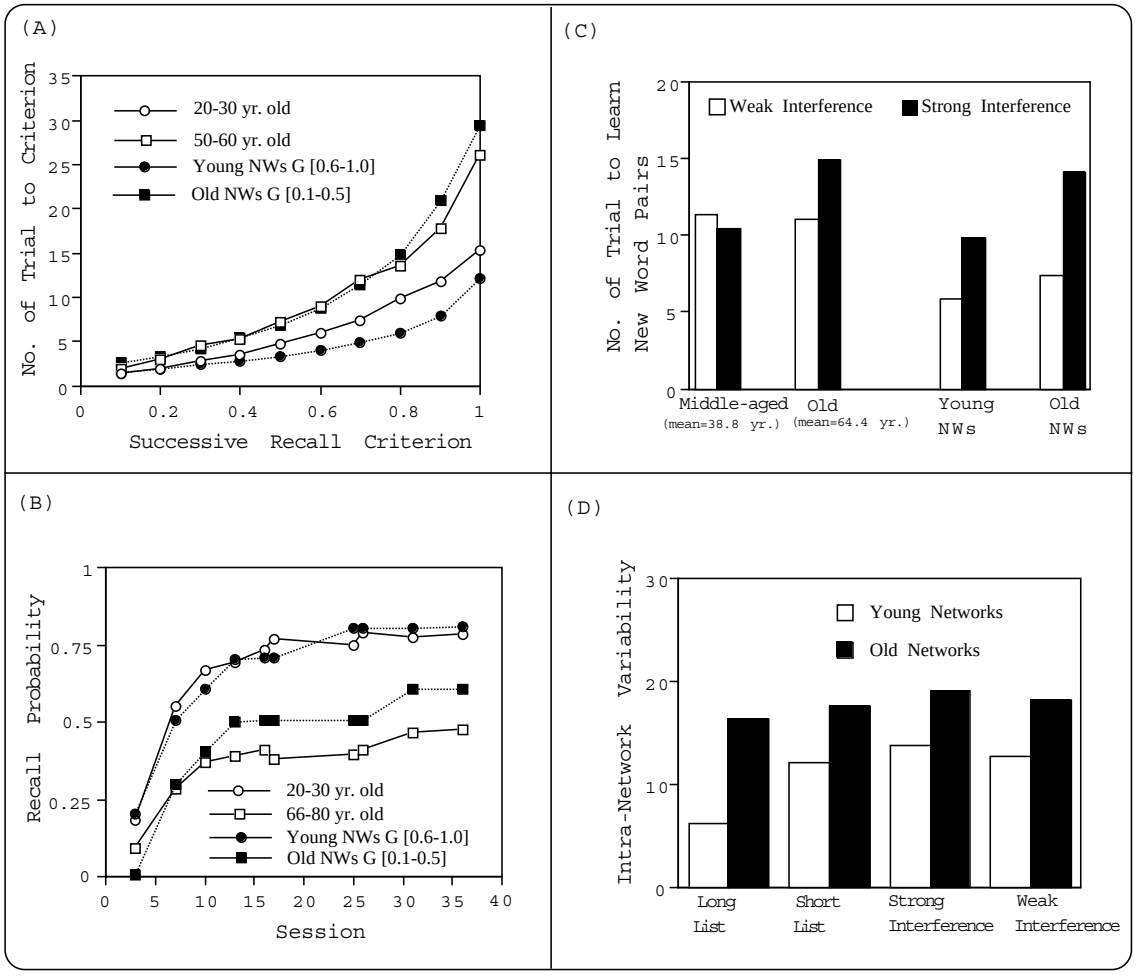


Figure 2


(A)
No. of Trial to Criterion
Successive Recall Criterion
20-30 yr. old
50-60 yr. old
Young NWs G [0.6-1.0]
Old NWs G [0.1-0.5]
(C)
No. of Trial to Learn New Word Pairs
Weak Interference
Strong Interference
Middle-aged (mean=38.8 yr.)
Old (mean=64.4 yr.)
Young NWs
Old NWs
(B)
Recall Probability
Session
20-30 yr. old
66-80 yr. old
Young NWs G [0.6-1.0]
Old NWs G [0.1-0.5]
(D)
Intra-Network Variability
Young Networks
Old Networks
Long List
Short List
Strong Interference
Weak Interference