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Review

Neuromodulation of associative and organizational plasticity across the life span: Empirical evidence and neurocomputational modeling

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Abstract

Developmental plasticity is the key mechanism that allows humans and other organisms to modify and adapt to contextual and experiential influences. Thus, reciprocal co-constructive interactions between behavioral and neuronal plasticity play important roles in regulating neurobehavioral development across the life span. This review focuses on behavioral and neuronal evidence of lifespan differences in associative memory plasticity and plasticity of the functional organization of cognitive and cortical processes, as well as the role of the dopaminergic system in modulating such plasticity. Special attention is given to neurocomputational models that help exploring lifespan differences in neuromodulation of neuronal and behavioral plasticity. Simulation results from these models suggest that lifespan changes in the efficacy of neuromodulatory mechanisms may shape associative memory plasticity and the functional organization of neurocognitive processes by affecting the fidelity of neuronal signal transmission, which has consequences for the distinctiveness of neurocognitive representations and the efficacy of distributed neural coding.

Keywords: Neural plasticity; Memory plasticity; Neuromodulation; Neural networks; Signal-to-noise; Neuroconstructivism

Contents

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1. Introduction

Lifespan development entails adaptations to the constraints and opportunities of the developmental context. Such adaptations require developmental plasticity—modifiability of the possible range of performance and function—on the part of the developing individual (Baltes et al., 2006a,b). Therefore, a central question in developmental cognitive neuroscience concerns the mechanisms through which processes and functional organizations of developing neurobehavioral systems are continuously modified by contextualized experiential tuning throughout the individual's life span. Traditionally, developmental plasticity, both with respect to experience-induced modifications at the behavioral (behavioral plasticity) and neuronal (neuronal plasticity) levels, has been considered primarily during early life periods. However, recent findings from animal and human research suggest that both behavioral and neuronal plasticity remain vital during adulthood and old age (see Li, 2003, for review). In addition, a range of co-constructive theories (e.g., neuroconstructivism and biocultural constructivism) suggest that reciprocal interactions between behavioral and neuronal plasticity allow brain and cognitive functions to be continually shaped by contextual and experiential influences both during early development (for reviews see Gottlieb, 1976; Nelson, 1999; Quartz and Sejnowski, 2000) and throughout the adult life span (Li, 2003; Baltes et al., 2006a,b).

Whereas empirical evidence and theoretical conceptions of co-constructive behavioral and neural plasticity have been accumulating, details about the interactions between these two levels are still not well understood. Extending the notion of "extended neurobehavioral systems"[1] (Clark, 2001), we maintain that a hallmark of plasticity is the individual's ability to use internal representations resulting from past behavior and context interactions to efficiently generate neurobehavioral changes in response to current contextual demands, and to continually update these internal representations based on newly acquired information from the external world. Thus, developmental plasticity depends on and results in the continual construction of neurobehavioral representations across the life span (cf. Li, 2003; Elman et al., 1996; Li and Lindenberger, 2002).

Although a certain amount of plasticity can be found throughout ontogeny, its relative extent may differ between individuals and across functional domains and life periods. Research on neurochemical modulation of the central nervous systems, both in invertebrates and vertebrates, has delineated the ways in which neuromodulatory mechanisms regulate the dynamics of neural activities to support communication among neural circuitries, and, eventually, organism–environment transactions (see Arnsten, 1998; Harris-Warrick and Marder, 1991; Miller and Cohen, 2001 for reviews). Within this broader context, the present review aims at delineating the relation between lifespan age differences in the efficacy of neuromodulatory mechanisms and developmental plasticity across the life span. Behavioral and neuronal developmental plasticity implicate various domains of psychological functions. Here, we focus on lifespan differences (a) in the plasticity of associative memory/learning, and (b) in the organizational plasticity of neurocognitive functions at behavioral and neuronal levels of analysis. After reviewing empirical findings, we present results from neurocomputational studies that are aimed at explicating the relations between lifespan differences in neuromodulation and developmental plasticity.

2. Lifespan differences in plasticity of associative learning and memory

From Aristotle over British associationists to modern researchers of associative learning and memory, it has been assumed that elements of perception and memory are associated (bound together) in the course of experience (see Anderson and Bower (1973) and Hinton and Anderson (1989) for historical review and early models). In fact, according to this view, associative learning and memory constitute the basic mechanisms of "experiencing" or, put differently, the elementary mode through which neurobehavioral systems construct, accumulate and modify their internal representations. A corollary assumption is that factors affecting associative learning and memory are essential to inter-individual and developmental differences in behavioral and neural plasticity. Mechanisms of associative learning and memory may be more uniform across individuals in their functional ranges during early phases of ontogeny when species-general evolutionary influences play a more prominent role than individualized ontogenetic experiences. However, with gradual construction, modification, and organization through person-specific experiences in the course of human ontogeny, higher-order functional organizations of basic representations emerge and feed back to further learning and development throughout most of adulthood, giving rise to possibilities for greater differences between individuals. In old age when species-general neurobiological constraints on person-specific expressions become strong again, the functional ranges of associative learning and memory as well as individual differences in these ranges may become more limited (cf. Li et al., 2004). Moreover, the extent of plasticity may differ across functional domains as well as life periods (see Pascual-Leone et al. (2005) for reviews). For instance, sensory cortical areas may be most sensitive to environmental influences during the earliest phases in life, whereas plasticity of cortical circuitries for higher cognitive functions (e.g., the prefrontal regions) may continue into adolescence and even maintain

[1] According to this notion, brain mechanisms are embodied in sensory and behavioral processes that are themselves, in turn, situated in experiential environmental contexts.

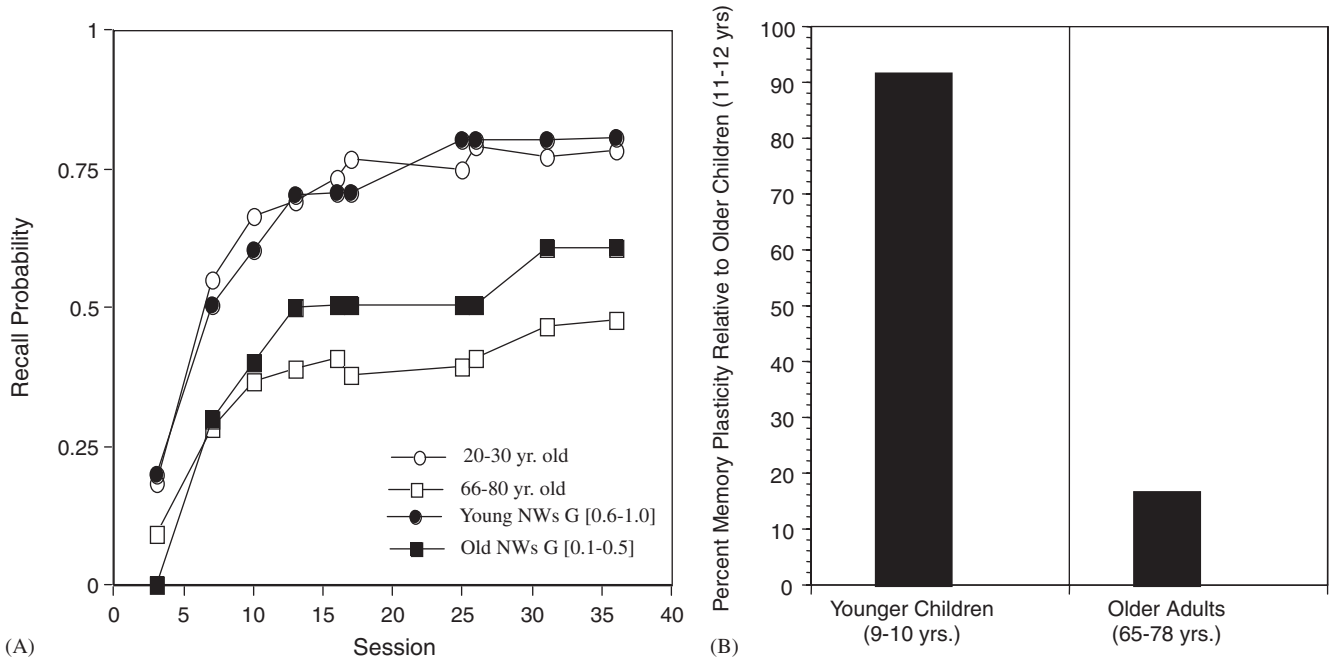


Fig. 1. Evidences from human studies of lifespan age differences in associative memory plasticity. (A) Empirical and simulation data of the effect of aging on associative memory plasticity (empirical and simulation data are adapted from Baltes and Kliegl (1992), and Li et al. (2000), respectively). (B) Direct comparison of associative memory between young children and old adults (data adapted from Brehmer et al., 2004).

certain level of preserved plasticity in old age (e.g., the hippocampal regions).

2.1. Behavioral evidence

For the most part, associative mechanisms in learning and memory in humans have been studied with paired associates. Although plasticity is commonly regarded as the hallmark of youth, memory plasticity (and cognitive plasticity in general) has been studied more extensively among adults than among children of different ages. In early behavioral studies of adult age differences in memory plasticity (Verhaeghen et al., 1992),[2] Paul Baltes and colleagues (Baltes and Kliegl, 1992; Baltes and Lindenberger, 1988; Kliegl et al., 1989) applied so-called "testing-the-limits" procedures, which involved instructing and providing adults of differing ages with opportunities of extensive, deliberate practice in a mnemonic strategy (Method of Loci; Bower, 1970), in order to assess adult age differences in the plasticity of associative memory. Evidence based on this paradigm yielded a dual picture: On the one hand, cognitively healthy older adults ranging from 60 to 80 years of age were found to possess a sizeable amount of baseline reserve plasticity, as indicated by significant improvements in memory for word pairs after initial mnemonic instruction. On the other hand, their developmental reserve plasticity as indicated by further memory gain as a function of extensive practice was severely reduced relative to 20–30 year olds (see in Fig. 1A for illustration). This aging-related constraint of developmental reserve plasticity was further accentuated among individuals beyond the eighth decade of life. For instance, individuals older than 85 years only showed small instruction-related gains but no further training-related gains (Singer et al., 2003).

Child cognitive developmental research over the past two decades has focused primarily on children's metacognitive strategies and more complex forms of knowledge representation than on basic mechanisms of learning and memory (see Siegler (2000) for review). Therefore, empirical evidence of early developmental differences in the range and limit of cognitive plasticity is scarce. However, one recent memory training study extended procedures similar to those previously applied in adult development to cover the age period from middle childhood to old age (Brehmer et al., 2004). Evidence from this study provides an initial empirical basis for comparing the amount of associative memory plasticity in young children and old adults. Specifically, a group of younger children aged 9–10 years was found to possess a greater extent of developmental reserve plasticity (indicated by performance gain after extensive practice and training) than a group of older adults around 70 years of age. At the same time, however, a measure of baseline reserve plasticity (indicated by performance gain right after mnemonic instruction) showed a tendency to be lower in children in comparison to old adults. Developmental reserve plasticity in associative memory in younger children and old adults amounted to about 92% and 17%, respectively, of the amount of

[2]Beyond memory plasticity, adult cognitive training research over the past two decades has provided a foundation for our understanding of the effects of aging on cognitive plasticity in general (Kramer and Willis, 2002 for review). For instance, there is evidence suggesting that older adults could still benefit from training to improve their reasoning ability (Saczynski et al., 2002) and dual-task performance (Kramer et al., 1999).

plasticity observed in a referencing group of older children aged 11–12 years (see Fig. 1B). The more limited baseline reserve plasticity in younger children in this case indicates that, unlike young and old adults, younger children may not have enough general knowledge to understand the memory strategy and apply it right after the instruction. However, the greater extent of developmental reserve plasticity in children than in old adults reveals that cognitive and neuronal mechanisms associated with implementing the memory strategy are more sensitive to training experiences during childhood than in old age.

In sum, behavioral evidence indicates that behavioral plasticity in associative memory changes in magnitude across the life span. Relative to young adulthood and middle childhood, old age is marked by a massive reduction in associative memory plasticity.

2.2. Neuronal evidence

Neuroscience evidence accumulated throughout the 20th century suggests that experience-dependent changes in the efficacy of synaptic plasticity across distributed neuronal cell assemblies are fundamental mechanisms of behavioral and memory changes. For instance, Hebb (1949) considered that even the perception of simple Gestalt figure requires construction from simpler elements, and that such construction initially requires associative learning. He further formulated that associative learning at the neuronal level takes the form of long-lasting increase in synaptic strengthening (i.e., later termed as long-term potentiation, LTP) between simultaneously firing pre- and postsynaptic neurons. There is general agreement that LTP corresponds to associative memory formation at the level of synaptic plasticity. A number of relevant neurochemical substances and mechanisms have been identified. For instance, neurotransmitters such as acetylcholine, norepinephrine, and dopamine are implicated in the modulation of LTP by regulating the ease of inducing LTP (see Rosenzweig, 1996; Squire and Kandel, 1999; Sweatt, 1999 for reviews; Wittmann et al., 2005).

Most in vivo animal studies on neural correlates of associative learning use simple associative conditioning tasks such as the avoidance-learning task. Regarding developmental plasticity early in postnatal life, Nishii et al. (1998) showed that performance in avoidance-learning tasks could be trained in 3-week-old mice (roughly the equivalence of middle to late childhood in humans). Furthermore, genetically manipulated mutant mice lacking tyrosine hydroxylase (TH) gene expression performed much worse in associative learning, due to severe dopamine depletion caused by the lack of TH regulation (Fig. 2A). As for the effect of aging on associative learning plasticity, and similar to findings from the human studies, Fetsko et al. (2005) showed that the effect of aging on the plasticity of associative learning is enormous; whereas 3-month-old adult mice reached 75% of successful avoidance responses after 5 days of training, 23-month-old aged mice only reached less than 20% of such responses after the same amount of training. Moreover, adult mice with dopamine D2 receptor deficiency showed similarly poor performance as aged mice (Fig. 2B). There is also evidence from in vitro animal studies on developmental and aging differences in LTP induction. The effectiveness of a single 100 Hz × 1 s tetanus to induce LTP in the CA1 region of the rat hippocampal slices show developmental changes with a peak for LTP induction at postnatal day 15–30, an age range that is roughly equivalent to childhood in humans (Izumi and Zorumski, 1995). The effect of aging on attenuating the relative ease of LTP induction is also established, particularly when low-intensity stimulation is applied (see Rosenzweig and Barnes, 2003, for review). Moreover, aging-related increase in the difficulty of LTP

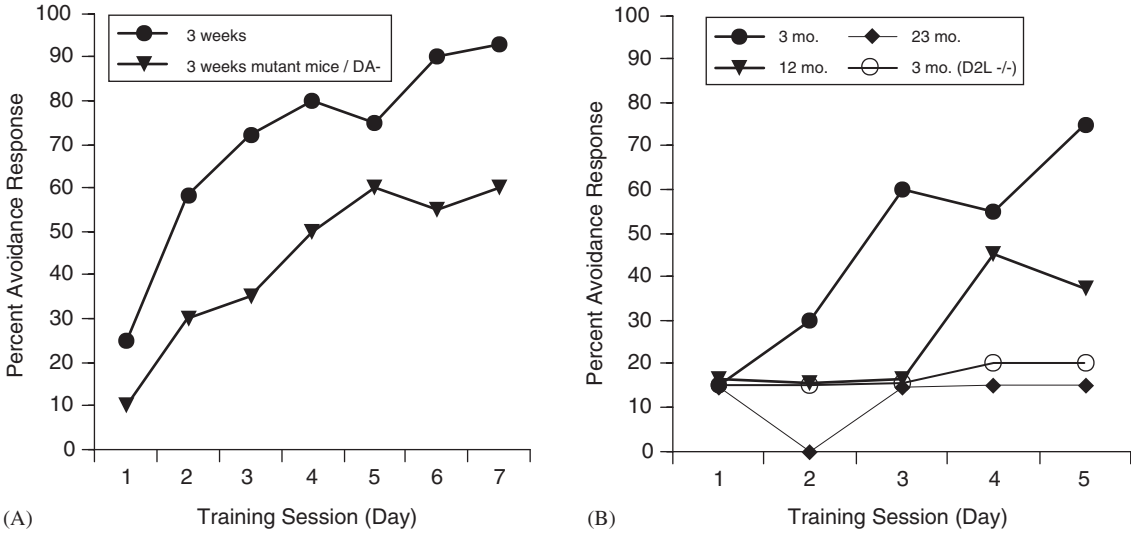


Fig. 2. Evidences from animal studies of lifespan age difference in associative learning plasticity. (A) Associative learning plasticity in early postnatal life and the effect of severe dopamine depletion (data adapted from Nishii et al., 1998 with permission. Copyright 1998 Wiley). (B) Adult age differences in associative learning and the effect of dopamine receptor deficiency (data adapted from Fetsko et al., 2005 with permission. Copyright 2005 Elsevier Science).

induction may be associated with declines in the catecholamines, e.g., norepinephrine and dopamine (Sweatt, 1999; Izumi and Zorumski, 1999).

Most animal studies are more apt for addressing factors affecting associative memory plasticity at the molecular level; however, findings from human brain imaging studies provide evidence for the effects of memory training on functional neuroanatomy. Parallel to the behavior memory training studies on memory plasticity reviewed above, Kondo et al. (2005) compared brain activity patterns before and after instructing their subjects (20–26 years) to use the method of loci mnemonic strategy to improve memory for serial associations. Other than showing improved memory recall at the behavioral level, Kondo et al. (2005) also showed that functional brain circuitry involved in episodic encoding and retrieval of associative information was modifiable by mnemonic training. Relative to activity before instruction, encoding after method-of-loci instruction was associated with activity increase in the right inferior frontal gyrus, bilateral middle frontal gyrus, and posterior cingulate gyrus, for instances. Retrieval after instruction was associated with activity increase in the parahippocampal gyrus, cingulate gyrus, and a few other regions. Whereas Kondo et al. (2005) studied neural correlates of strategy-related memory plasticity only in young adults, another study by Nyberg et al. (2003) investigated adult age differences in the functional plasticity of brain circuitry as a function of memory training. Similar to Kondo et al. (2005)'s findings, Nyberg et al. (2003) showed that encoding after strategy instruction was associated with activity increase in frontal as well as occipito-parietal regions in their young adult sample (mean 25.8 years). In contrast, accompanying their reduced memory plasticity as indicated by poor memory performance even after memory strategy training, older adults (mean 68.8 years) in the Nyberg et al. (2003) study did not show training-related increase in frontal activity, and only those older adults who benefited from memory training showed increased occipito-parietal activity.

Taken together, both animal and human studies have identified specific connections between lifespan changes in neuronal plasticity and lifespan changes in the plasticity of learning and memory. Animal models show that lifespan differences in neurochemical mechanisms at the level of synaptic signal transmission may play a fundamental role in LTP and the plasticity of associative learning. Evidence from human studies has provided initial evidence for adult age differences in the functional neural circuitries that may underlie memory plasticity.

3. Lifespan plasticity of cognitive and neuronal organization

Developmental plasticity also entails changes in the organization of cognitive and cortical processes. Neurobehavioral systems that are optimally adaptive in handling challenging environmental demands require a functional organization that is complex in the sense that both functional segregation (specificity) and dynamic integration are high (Tononi et al., 1998). The functional organization of cognitive and cortical processes varies across the life span. Unfortunately, systematic investigations of age differences in the dynamic integration of local and large-scale cortical activities (Singer, 1995) are, for the most part, lacking (see also Werkle-Bergner et al., this volume; cf. Klimesch, 1999; Thatcher, 1992). Therefore, the review below is restricted to evidence about functional specificity.

3.1. Behavioral evidence

Since Spearman (1904) discovered the ubiquitous positive manifold of intelligence (i.e., positive correlations among sub-facets of intelligence) in 1904, the functional organization of cognitive processes has been primarily considered as static by researchers of psychometric intelligence that focus on adult populations (see Sternberg, 1994, for reviews). However, in light of findings showing stronger correlations between subtests of intelligence in children than in adolescents, early developmentalists (e.g., Lewin, 1946; Garrett, 1946) put forward the notion of a general intellectual ability that gradually differentiates into fairly distinct aptitudes. This dynamic age-differentiation notion was later extended to cover the life span (Schaie, 1962) and motivated subsequent studies on age differences in the structure of intellectual abilities. For instance, taking a lifespan orientation and guided by early results showing that average correlations between subtests of intelligence were higher for people in childhood and late adulthood than in adolescents and adulthood (e.g., Garrett, 1946; Balinsky, 1941), the differentiation–dedifferentiation hypothesis of lifespan intelligence was formulated (Baltes et al., 1980). This hypothesis states that the functional organization of cognitive processes is rather undifferentiated in childhood, undergoes differentiation during child development leading to greater specificity that remains largely invariant during adulthood, and becomes relatively dedifferentiated again during aging.

Until recently, support for the differentiation–dedifferentiation hypothesis has mostly been derived from piecing together results from separate studies covering different portions of the life span (e.g., Baltes and Lindenberger, 1997; Burt, 1954; Garrett et al., 1935; Schaie et al., 1998). A recent lifespan study with 291 individuals aged 6–89 years provided direct empirical support for lifespan transformations in the structure of mental abilities and cognitive processes (Li et al., 2004). Greater amounts of shared variance among 15 psychometric tests that reflected five categories of mental abilities (memory, reasoning, perceptual speed, verbal knowledge and fluency) were found at both ends of the life span. Further results showed that the correlations among measures of processing speed across a wide range of basic cognitive tasks (e.g., visual and memory search, response competition, choice reaction) were also higher at both ends of the life span than during adulthood (Fig. 3). Together, these cross-sectional,

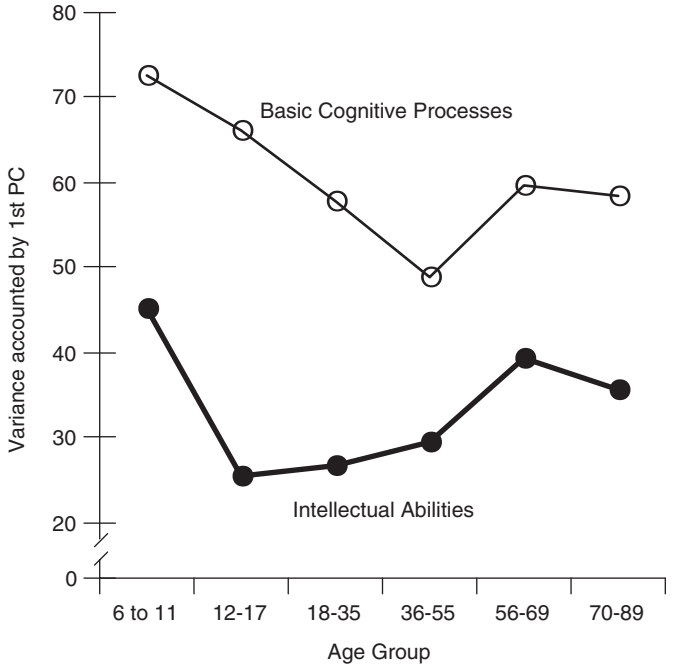


Fig. 3. Differentiation and dedifferentiation of basic cognitive processes and intellectual abilities across the life span (data adapted from Li et al., 2004).

interindividual differences based findings suggest that the functional organization of cognitive processes is less specific (less differentiated) at both ends of the life span, and more differentiated during adulthood.

To the extent that the cross-sectional behavioral evidence in lifespan differences in the structure of cognitive abilities generalize to the intra-person level, it may indicate a greater overlap between neurocognitive processes invoked by different environmental demands in children and old adults. During childhood, the transactions between environmental affordances and neural maturation would engender an increase in specificity, coupled with the development of dedicated mechanisms for large-scale integration (Thatcher, 1992). In old age, the highly differentiated and integrated adult system would be compromised by senescent changes operating at various levels of specificity (e.g., mechanisms of neuroanatomical and neurochemical declines).

3.2. Neuronal evidence

The behavioral evidence review above is remarkably consistent with recent findings from cognitive neuroscience demonstrating increments in processing specificity during maturation, and decrements in specificity during senescence. At the functional level, neural circuitry is constantly reorganizing itself in adaptation to influences such as environmental stimulation, experience, brain development, or brain damage. For instance, the functional circuitry and cortical dynamics involved in face and object processing differ between young infants and adults. In infants, face processing involves both left and right ventral visual pathways but in adults face processing primarily involves the right ventral visual pathway (de Haan et al., 2002). Similarly, in infants, the behavioral indicators of the emergence of visual object formation based on Gestalt principles seem to coincide with the emergence of specification of cortical dynamics that support such perceptual processes in adults, with the transition occurring around 6–8 months of age (Csibra et al., 2000). Development under conditions of deprived sensory inputs also reveals the importance of neural plasticity at the functional level. For instance, the visual cortex is reorganized for processing tactile and auditory information in blind individuals (Hamilton and Pascual-Leone, 1998), and the auditory cortex is dominated by visual processing in congenitally deaf individuals (e.g., Neville et al., 1998). It has been suggested that mechanisms underlying compensatory, cross-modal plasticity during early development may resemble mechanisms of synaptic plasticity underlying associative memory formation (Rauschecker, 1995).

In sharp contrast to the phenomena of developmental specification and differentiation during early phases of the life span, there is growing evidence that cortical processes dedifferentiate during aging. In terms of brain imaging findings, the dedifferentiation of cortical processes is usually reflected as more diffused brain activity patterns, though at different levels of analyses. At one level, dedifferentiation is expressed as less distinctive cortical representations of sensory/cognitive stimuli. For instance, in an animal study of aging and the topographic organization of somatosensory cortex (Spengler et al., 1995) it was found that the receptive fields of the hind-paw representations in sensorimotor cortex and the cortical areas elicited by tactile point-stimulation to be highly nonspecific and overlapping in older rats, but relatively specific and focused in young rats. In another study on aging and spatial learning, the hippocampal place cells of older rats exhibited less experience-dependent plasticity than those of young rats, showing less expansion in their place fields, which in turn, may lead to less precise population codes for spatial location (Shen et al., 1997). As for findings from human studies Park et al. (2004) recently showed that functional brain activities in the ventral visual cortex become less differentiated, indicating less neuronal specificity, when viewing different object categories in older than in younger adults. At another level, dedifferentiation also has been observed across brain regions and hemispheres, especially in prefrontal areas. Relative to young adults, people in their 60s and beyond show more bilateralized (bihemispheric) activity during memory retrieval (e.g., Bäckman et al., 1997; Cabeza et al., 1997), and during both verbal and spatial working memory processing (e.g., Reuter-Lorenz et al., 2000). These data may indicate that the aging brain "recruits" cortical areas from the other hemisphere to compensate for neurocognitive declines

during aging, thereby helping to maintain cognitive performance (see Cabeza, 2002; Reuter-Lorenz, 2002). Whereas some evidence on old adults' increased bilateral activations supports the compensation view, showing that activating additional brain regions improves performance (see reviews in Cabeza, 2002; Reuter-Lorenz, 2002), recent findings of an association between striatal dopamine D2 receptor availability and glucose metabolism in the frontal cortex (Volkow et al., 2000), however, suggest that deficient neuromodulation may increase the likelihood of accidental co-activation of task-irrelevant functional circuitry (see also Bäckman et al. this issue for further discussions). Taken together, current findings on aging and dedifferentiated, more diffused functional distribution of cortical activations at different levels of analyses could not be simply interpreted from the adaptive, compensatory view. In some cases, more diffused distribution of cortical activations could reflect less distinctive cortical processing with respect to sensory/perceptual stimuli (Spengler et al., 1995; Shen et al., 1997; Park et al., 2004), non-selective recruitment (Logan et al., 2000), and may be related to aging-related declines in neuromodulation (e.g., Volkow et al., 2000).

4. Neuromodulation and lifespan changes in plasticity

Theories on the morphofunctional architecture of the brain emphasize the importance of connectivity and communication between cellular elements (Shepherd, 1991). Cortical functioning is implemented by the brain's structural and functional organization (Shepherd, 1991; Kinsbourne and Hicks, 1978). Furthermore, neurochemical processes influence the dynamic properties of cortical information processing by affecting ongoing neural activity representation and information transfer within and between cortical regions. Thus, neuromodulatory activity can alter the functional components of a network by dynamically generating a large number of active circuits from a single anatomically defined network (Harris-Warrick and Marder, 1991).

Various neurotransmitter systems, such as acetycholine and the monoamines, regulate the signal-to-noise ratio of cortical responses and modulate the threshold of experience-dependent modifications of synaptic connectivity that underlie neural plasticity (see Gu (2002) for review). Neuromodulatory fine-tuning of the brain's ongoing representations hence allows the cortical networks to be versatile in adapting its functional processes to changing behavioral and environmental demands.

4.1. Lifespan changes in dopaminergic neuromodulation

In good agreement with animal studies reviewed above, empirical evidence from humans shows that neuromodulation plays an important role in brain and cognitive development across the entire life span (for early ontogeny, see Pascual-Leone et al., 2005; Philpot and Kirstein, 2004; Quartz and Sejnowski, 2000; for late ontogeny, see Bäckman et al., this issue; Park et al., 2004). A variety of studies have demonstrated that the monoaminergic neurons, particularly those involving dopamine, continue to proliferate and increasingly innervate various brain regions, such as the prefrontal cortex (PFC), until early adulthood (see Bens, 2002, for review), at which point gradual but steady decline starts and continues throughout adulthood and old age (e.g., Bäckman et al., this issue, Bäckman and Farde, 2005; Kaasinen et al., 2000). Furthermore, recent evidence suggests that synaptogenesis (e.g., developmental changes in synaptic structure, such as the growth of dendritic length and branching) are, in part, modulated by neurochemical mechanisms. In addition to modulating the excitability of cortical neurons in the mature brain, the monoamines (norepinephrine, dopamine, and serotonin) affect early brain development by controlling cell proliferation and dendritic outgrowth, thereby generating structural and functional changes in brain regions in which monoaminergic innervation is rich, such as the anterior cingulate cortex (ACC) and the PFC (e.g., Levitt et al., 1997).

In most species including humans, dopamine D1 and D2 receptor proteins are already measurable prenatally, and increase throughout prenatal and postnatal development to reach mature levels of expression (e.g., Schambra et al., 1994). There is also evidence to suggest that the increasing efficacy of dopaminergic modulation in PFC is associated with infant monkeys' improvements on prefrontal working memory and control functions (e.g., Brown and Goldman, 1977; Lewis and Harris, 1991). By contrast, in conditions where D1 receptor protein coupling is reduced during early brain development, such as through prenatal in utero exposure to cocaine, neurons in the affected region show uncontrolled neurite outgrowth (Jones et al., 2000; Stanwood et al., 2001). Early abnormalities in dopaminergic regulation of brain development have implications for later cognitive developmental outcomes. For instance, although children with reduced D1 receptor coupling due to prenatal cocaine exposure did not differ physically at birth from children in the control group, they had lower IQ scores and were more likely to show attentional deficits by 3 years of age (e.g., Richardson, 1998). Evidence from studying children who have been treated early and continuously for phenylketonuria (PKU) points to a similar relation between abnormal dopaminergic regulation and impaired cognitive development. Even with special dietary treatment, children with PKU have an imbalance between two types of amino acid: A high level of phenylalanine (Phe), but a low level of tyrosine (Tyr). Given that Tyr is the precursor of dopamine and that dopaminergic neurons in PFC fire rapidly and turn over dopamine very quickly, even moderate reductions in the CNS levels of Tyr reduce dopamine synthesis in PFC significantly. Children with PKU thus have a selective reduction in dopamine synthesis in the PFC, which may, in part, contribute to their below average IQs (usually in the 80s or 90s) and, particularly,

their deficits in working memory and inhibitory control functions (see Diamond, 1996, for review). More recently, both child developmental (Diamond et al., 2004) and aging (de Frias et al., 2004) studies showed that individuals with advantageous dopaminergic gene polymorphism performed better cognitively on tasks that are sensitive to dopaminergic modulation.

In summary, cognitive and neuronal processes undergo profound changes across the life span. Relative to adulthood, experience-related processing specificity is more limited in children and older adults. It is conceivable that neurochemical mechanisms of synaptic plasticity that allow for the formation of new association during learning and memory are, at the same time, a major driving force for lifespan changes in cortical organization. In line with this conjecture, empirical evidence points to marked and behaviorally consequential changes in the efficacy of dopaminergic modulation (see also Bäckman et al., this volume). However, the mechanisms that link neuromodulation to lifespan changes in both associative and organizational plasticity are not yet fully understood. In this context, theoretical models of neuromodulation that investigate the relation between neuromodulatory tuning of neural signal transmission and the functional complexity of neurocomputation are a versatile computational tool for exploring possible links between neuromodulation and lifespan differences in both associative and organizational plasticity.

5. The role of neuromodulation for lifespan changes in associative and organizational plasticity: computational approaches

At the computational level, various approaches have been taken to model the plasticity of cortical development (see Munakata (2004) for review). For instance, Garlick (2002) modeled individual differences in neural plasticity by manipulating the learning rate of neural networks to simulate different degrees of synaptic connectivity. Regarding the brain's functional organization, Shrager and Johnson (1996) proposed a dynamic plasticity theory to account for the time course of the gradual, experience-dependent functional organization of cortex during brain development. The specification of higher cortical functions (e.g., association and frontal areas) through earlier developing areas (e.g., primary sensory and motor areas) is modeled by propagating pools of parameter values that dynamically simulate the concentration of neural trophic factors across training cycles to modulate the plasticity of the network's connection weights. In this manner, Shrager and Johnson (1996) demonstrated how a corticotrophic wave of optimal brain plasticity is able to organize the brain into functionally distinct areas. As for attempts to model individual and developmental differences in synaptic connectivity at the neuroanatomical level (e.g., dendritic growth), various approaches focus on manipulating either the number of connections or the number of processing units (e.g., Mareschal and Shultz, 1996; Thomas and Karmiloff-Smith, 2002).

5.1. Model dopaminergic neuromodulation and developmental plasticity

Regarding individual and developmental differences in neurochemical mechanisms of neural plasticity, others have demonstrated that parameters affecting the response properties of the activation function are suitable candidates for theoretical investigations of general principles of neuromodulation of cortical functioning, even in the absence of structural alterations (see Hasselmo (1995) for review). For instance, Cohen and Servan-Schreiber (1992) manipulated the gain parameter of the network's sigmoid activation function to simulate dysfunctional dopaminergic modulation in individuals suffering from schizophrenia.

More recently, the approach introduced by Cohen and Servan-Schreiber (1992) has been adapted and extended to an unifying framework that relates aging-related declines in cognitive and intellectual functioning at the behavioral and information-processing levels with aging-related declines in dopaminergic modulation at the neurochemical level (Li et al., 2000). Specially, Eq. (1) shows the sigmoidal activation function of a neural network, with i and t indexing the network's units and processing steps, respectively. The gain parameter (G) of each unit is randomly sampled at each processing step from uniform distributions with identical range but different means. The random sampling of gain parameters simulates probabilistic fluctuations in transmitter release (Hessler et al., 1993). As shown in Fig. 4, reducing the G parameter flattens the activation function, such that the processing unit becomes less responsive (Fig. 4A), which subsequently leads to a greater amount of random activation fluctuation (Fig. 4B) and less distinctive internal stimulus representation (Fig. 4C) in the G reduced, simulated "old" network. Simulating aging-related decline in neuromodulation by stochastically reducing the G parameter of network units' activation function at each processing step attenuated neural information-processing fidelity, with ensuring consequences for less distinctive internal stimulus representations and various cognitive deficits observed at the behavioral level, raging from age differences in learning rate, asymptotic performance, interference susceptibility, performance fluctuation, and stochastic resonance (Li et al., 2000, 2006). Below, we review results obtained from this approach that are aimed at relating age differences in neuromodulation with age differences in the plasticity of associative memory, functional organization, and developmental transitions.

$$Activation\,(G_{i_t}, input) = \frac{1}{1 + e^{-(G_{i_t} input_{i_t} + bias)}}. \quad (1)$$

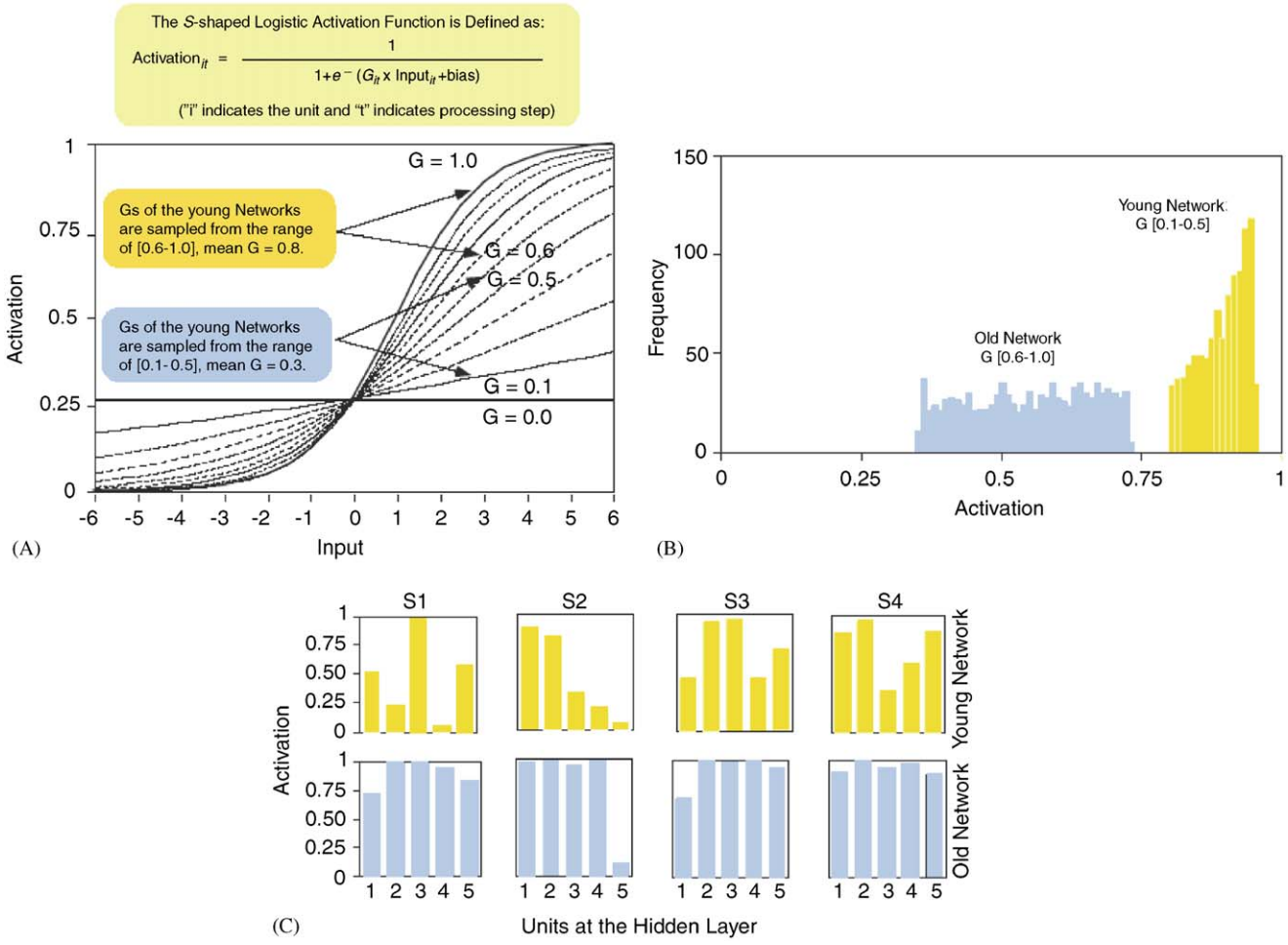
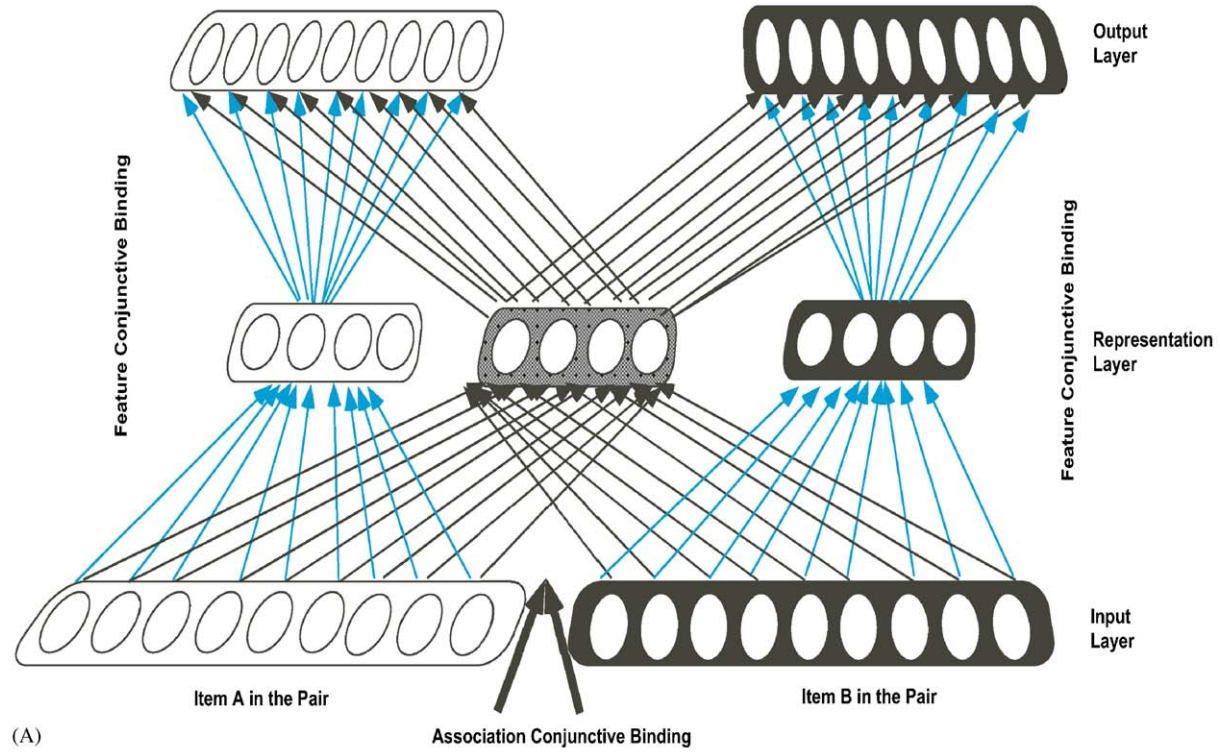


Fig. 4. Simulations of stochastic gain modulation, neuromodulation, and aging. (A) The S-shaped logistic activation function at different values of *G*. Aging-related decline of dopaminergic modulation can be simulated by sampling values of *G* from a distribution with a lower man. (B) *G* and fluctuations in activation across processing time steps. Reducing mean *G* (0.8 and 0.3 for the young and old networks, respectively) increases the temporal fluctuation 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–S4). The internal representations of the four stimuli are much less differentiable in the old than in the young network (adapted from Li et al. (2000), with permission. Copyright 2000 Elsevier Science.)

5.2. *Deficient neuromodulation and adult age differences in associative plasticity*

To simulate the effects of aging-related decline in dopaminergic neuromodulation on associative memory, Li et al. (2000) generated "young" and "old" neuronal networks that differed only in the means of the distributions from which their gain parameters were sampled at each processing step. A higher level of mean gain simulates optimal dopamingeric modulation in younger adults, whereas a lower level of mean gain simulates attenuated neuromodulation in older adults. The networks were trained to learn paired associates. The stochastic gain manipulation as implemented in Li et al. (2000) accounts for adult age differences in associative memory plasticity. Similar to older adults, although the old networks do improve their memory performance as a function of training, the rate and asymptote of their training gain was much more limited relative to those of the young networks (see simulation results presented in Fig. 1A).

In a more recent simulation (Li et al., 2005), the stochastic gain manipulation was applied in a dual-path feature-association conjunctive binding network to further investigate aging-related associative binding deficit. The network had parallel processing paths for intra-item feature and inter-item associative binding (see Fig. 5A). Features of each item in a given pair were distributedly processed within the corresponding feature-binding path, whereas the associative-binding path processed inter-item associations. The simulation results captured Naveh-Benjamin (2000)'s empirical evidence of aging-related deficit in associative binding, particularly when associations needed to be encoded intentionally. Of specific interest here is that the simulation result suggests that old networks' disproportionately poor associative binding was related to less efficient conjunctive coding of associative



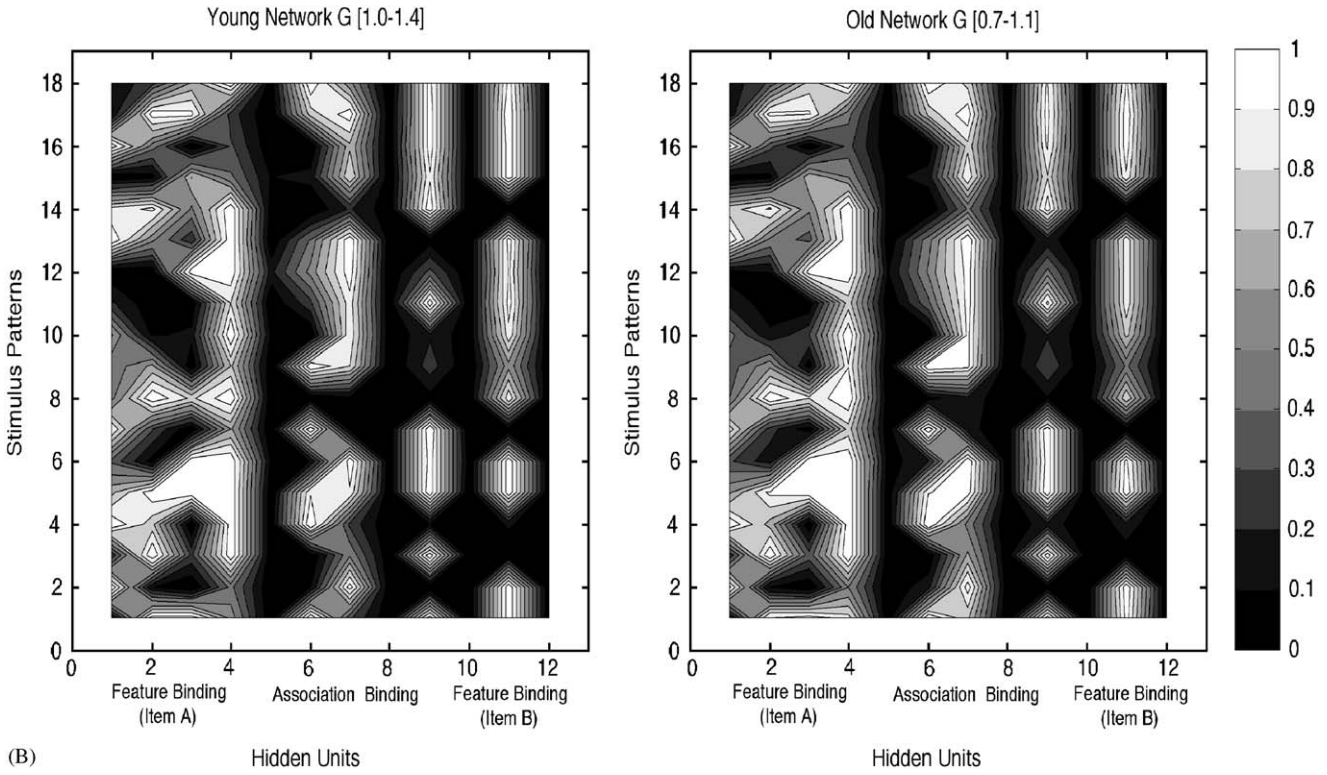


Fig. 5. Modeling adult age differences in associative memory binding deficits. (A) Schematic diagram of the dual-path feature-association conjunctive-binding model. (B) Summary hidden-unit activation maps illustrating the effects of reducing mean G on the distinctiveness of distributed coding of associative information (data adapted from Li et al., 2005).

information. As shown in Fig. 5B, reducing mean G had relatively little effect on internal representations of the item feature-binding pathways (activations across the left-most and the right-most four units), but a clearer effect on the associative binding pathway (activations across the middle four units). The distributed conjunctive coding of associa-

tive binding was less distinctive in the old than in the young network, with a large number of highly activated units responding to different stimulus pairs (i.e., larger patches of red, coding high activation across the middle four units).

Overall, these simulations suggest that neuromodulatory processes play a basic role in binding by affecting the efficiency of distributed conjunctive coding. When neuromodulatory processes function suboptimally, patterns of neural activities become less distinct. Consequently, the neurocognitive system's task of appropriately binding together representations of experienced memory events becomes harder. This chain of effects provides a viable explanation for deficit in associative memory plasticity in old age.

Table 1
Correlations between simulated categorization tasks analyzed for networks with different mean gain parameter values that simulate aging-related declines in neuromodulation (data based on Li and Lindenberger, 1999, p. 132)

	Young network		Old network	
	Gain parameter [0.6–1.0]		Gain parameter [0.2–0.6]	
Task	1	2	1	2
2	0.62	—	0.94	—
3	0.31	0.8	0.81	0.9
Variance accounted for by 1st principal component (%)		72.2		92.8

5.3. Deficient neuromodulation and adult age differences in organizational plasticity

The stochastic gain manipulation had also been applied to examine adult age differences in the organizational plasticity at the cognitive and neuronal levels. Regarding aging-related ability dedifferentiation at the behavioral level, as shown in Table 1, the correlations among three simulated categorization tests were higher among networks with gain parameter values sampled from a lower range ("old networks") than among networks with a higher mean gain ("young networks"). Thus, the stochastic gain manipulation was able to account for aging-related dedifferentiation of abilities (Li and Lindenberger, 1999, p. 132). Analogous variations would also be able to account for the increasing differentiation of abilities during child development, although differences in the mechanisms and the neuronal context of maturation and senescence are likely to be involved.

To further explore the effect of aging-related declines of neuromodulation and changes in functional processing specificity, Li and Sikström (2002) specified a dual-module network with separate processing pathways for verbal and spatial memory. Reducing the mean G of units within the two processing modules was associated with extensive activation overlap across the two modules (see Fig. 6). In "young" networks (i.e., networks with an optimal mean G), stimulus patterns representing the verbal items activated only hidden units in the verbal processing module. In "old" networks (i.e., networks with a lower than optimal mean G), most units in both the verbal and spatial modules

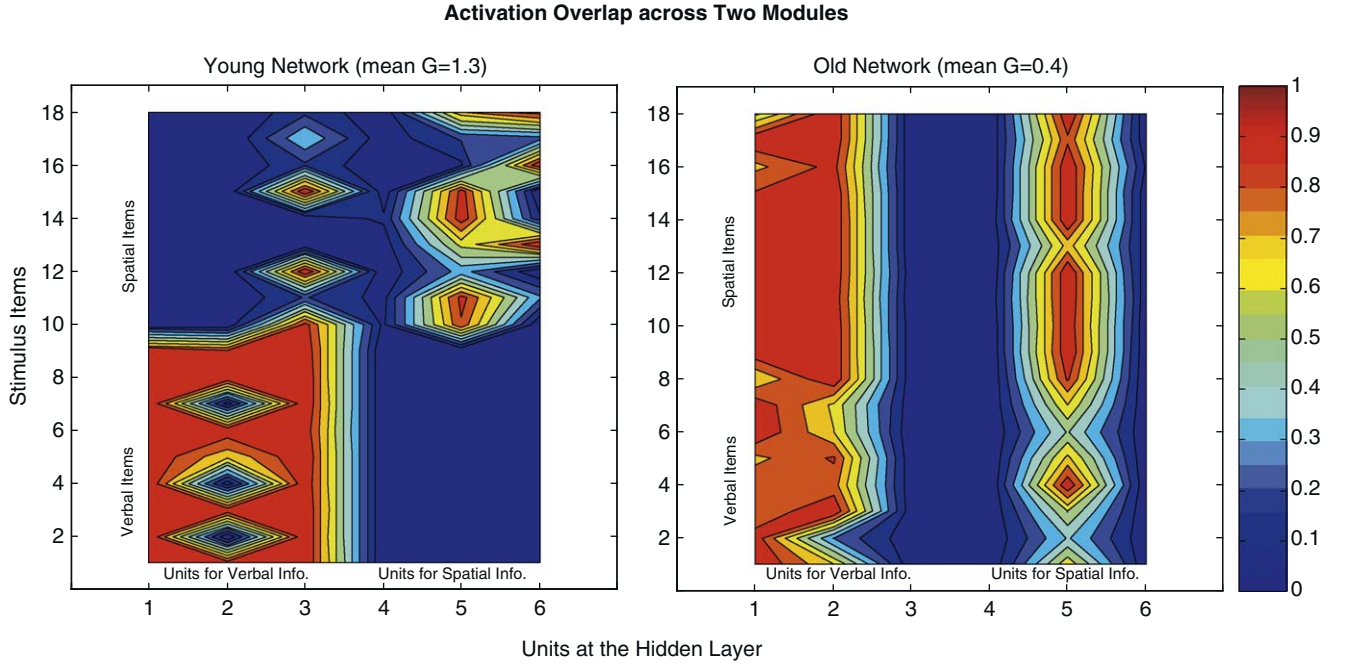


Fig. 6. Modeling adult age differences in the co-activation of different processing pathways. (Data adapted from Li and Sikström, 2002). Given that the training patterns of the verbal stimuli were presented in one fixed spatial location, there is a small amount of activation across the spatial units even in the young network.

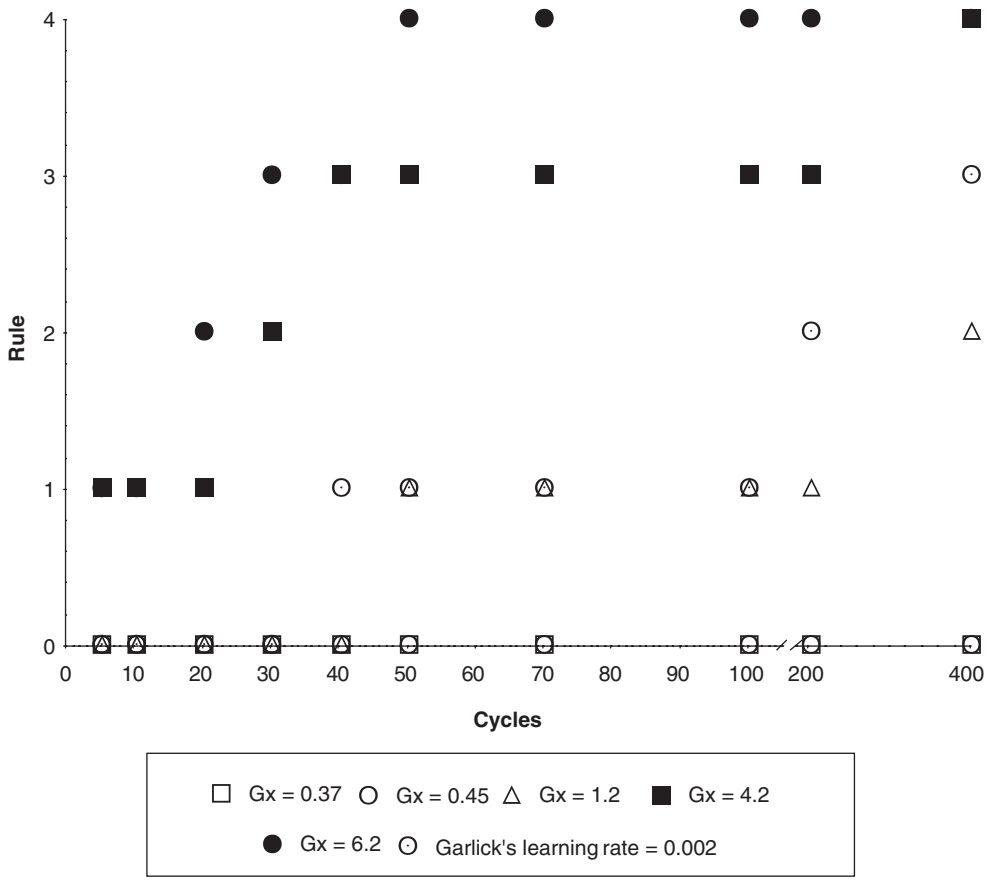


Fig. 7. Modeling child developmental differences in the balance beam task.

were activated when processing both verbal and spatial items. In other words, with attenuated *G*, the mapping of the two task types onto processing modules was blurred by concomitant activation of the other module, amounting to a loss in functional specificity of neuronal processing.

5.4. The role of neuromodulation in child development: initial neurocomputational explorations

Recently, Garlick (2002) suggested that the learning rate of neural networks could be used to simulate the neuronal correlates of cognitive changes during childhood, such as performance on the balance beam task (Inhelder and Piaget, 1958; Siegler, 1976). In line with our earlier work on neuronal and cognitive changes in adulthood and old age, we examined whether manipulations of the gain (*G*) parameters may offer a viable alternative to manipulations of learning rate. In our view, variations in gain would match up closely with empirical evidence on neurotransmitter influences on brain and cognitive development (e.g., Diamond, 1996; Diamond et al., 2004; Levitt et al., 1997).

In simulating child developmental differences in the balance beam task, we set up networks (cf. McClelland and Jenkins, 1991) with input units that code weight and distance on both sides of the beam and output units that represent two alternative behavioral responses (i.e., left or right side down). The input and output units are connected through a layer of hidden units. For each mean level of the gain parameter values the performance was based on the average of simulations carried out across ten networks. For purposes of direct comparison, we also simulated a case in which the *G* parameter was fixed to 1 for all units, but the learning rate was fixed at 0.002 as in one of the conditions simulated by Garlick (2002, p. 133). Results presented in Fig. 7 show that the gain parameter manipulation accounts for the four typical patterns representing the developmental progression observed with the balance beam task. Networks with smaller mean gain simulating lower efficacy of neuromodulation required more learning trials to reach levels of performance that index more complex reasoning rules (i.e., Rules 3 and 4). In cases with extremely small mean gain (e.g., $G_{\bar{x}} = 0.37$), simulating severe developmental deficits in neuromodulation, the network did not learn Rule 1 even after 400 cycles of learning.[3]

[3]In contrast, networks with the learning rate set at 0.002 and a constant unity gain performed about as well as networks with a learning rate of 0.001 and mean stochastic gain of 1.2. Note particularly that the networks with a unity gain and a learning set at 0.002 actually acquired Rule 3 after 400 cycles of training, quite contrary to Garlick's claim that a network with such a small learning rate will not be able to learn rules more complex than Rule 1 even with extensive training. On a methodological level, this simulation demonstrates that the stochastic gain manipulation as

6. Conclusion and future directions

In this article, we reviewed empirical evidence on lifespan differences in associative memory plasticity, organizational plasticity of cognitive and cortical processes, and dopaminergic neuromodulation. We noted that all three phenomena undergo profound changes at both ends of the life span and reviewed empirical evidence pointing to mechanisms that link these changes. We then reported a series of neurocomputational studies that seeks to formalize these links. Taken together, the available empirical evidence and our neurocomputational results suggest that age changes in neuromodulation may affect the distinctiveness of representations, which in turn may account for age differences in associative and organizational plasticity. According to this account, suboptimal neuromodulation underlies less distinctive representations, which in turn, result in less efficient conjunctive binding of associative information and more cross-process co-activation, undermining associative plasticity and functional specificity. So far, the particular neurocomputational approach reviewed here has been applied more in terms of a heuristic tool to integrate diverse aspects of empirical data at the neuronal to behavioral levels. However, in the future it would be important to utilize the models to make predictions about conditions under which age differences in the different aspects of plasticity reviewed here could be minimized or accentuated. Model-based predictions can guide experimental designs to generate new data for understanding the inconsistency between compensatory versus disruptive effects of dedifferentiated cortical processing, for instance. Although still being limited in scope, the predicative utility of the reviewed computational approach has recently been demonstrated in the case of modeling aging-related differences in stochastic resonance (i.e., beneficial effect of external noise for perceptual discrimination). With more limited plasticity, simulated "old" networks actually adapt to external noise less, thus lose the beneficial effect of stochastic resonance slower than "young" network, when been repeatedly exposed to external input noise (Li et al., 2006). This prediction is counterintuitive at first glance. Empirical validations of it, however, will generate new data for further investigations of age differences in plasticity.

The evidence and concepts discussed in this paper warrant the conclusion that neuromodulation acts as a general mechanism of lifespan changes in various aspects of developmental plasticity. However, this conclusion needs some qualification. Neuromodulation is not more than one of many mechanisms that shape lifespan cognitive development; other mechanisms, such as changes in cortical connections, cortical volume, neurogenesis, angiogenesis, and the influence of behavior on each of these neuronal mechanisms including neuromodulation are likely to play a role as well. Because neuromodulation is embedded within these other changes, its systemic effects are likely to change with age. For instance, during early development dopamine regulates cognitive change beyond modulating pre- and post-synaptic signal transmission by controlling cell proliferation and dendritic outgrowth. In old age, dopaminergic neuromodulation is complicated by additional neurodegenerative changes such as loss of connectivity (see Sullivan and Pfefferbaum; Raz and Rodrigue this volume). Furthermore, dopaminergic neuromodulation affects brain regions that differ widely in rates of maturation and senescence (e.g., Sowell et al., 2003; also see Lenroot and Giedd, this issue). Subcortical regions such as the basal ganglia and medial temporal brain structures develop earlier in life than the prefrontal regions. However, all of these regions show parallel signs of aging-related decline during adulthood and old age. Thus, whereas older adults' plasticity limits may be related to deficit neuromodulation in both cortical and subcortical regions, the potential for plasticity increments in middle childhood may relate more specifically to neuromodulatory in areas of the PFC.

Although extant evidence does not allow fine-grained differentiations between the functional effects of lifespan age differences in tonic and phasic dopaminergic mechanisms involving D1 and D2 dopamine receptors in this review, very recent findings suggest that future studies should consider the dynamics between the two. Specifically, Goto and Grace (2005) recently showed in adult rats that the balance between D1-associated tonic limbic system (e.g., hippocampal) activation and D2-associated phasic prefrontal inactivation (i.e., the so-called reward or incentive motivational dopaminergic system) jointly regulate the animal's behavioral flexibility in goal-directed performance. Given accumulating evidence on (i) behavior- and reward-dependent transient, phasic activation in midbrain dopamine neurons (e.g., Schultz, 2000; Stark et al., 2004), (ii) the effects of aging on dopamine-modulated reward-based learning and decision-making (see Marschner et al., 2005, for review) as well as (iii) developmental differences in the vulnerability of mesolimbic dopamine pathways to substance abuse (see Philpot and Kirstein, 2004, for review), future empirical and theoretical studies need to consider lifespan differences in the dynamics between the prefrontal and limbic dopaminergic subsystems operating at different timescales and their interactions with motivational aspects of neurobehavioral plasticity. Of particular interest here is that Goto and Grace (2005) showed that applying a D1 agonist to hippocampal neurons and a D2 antagonist to PFC neurons, respectively, had the effect of enhancing the slope of the neurons' sigmoid-activation function in ways analogous to the simulated effects of the gain parameter. Future research combining age comparative pharmacological neuroimaging studies with neurocomputational theories may serve

(*footnote continued*)
implemented here can more easily capture individual differences in performance asymptotes (i.e., maximum developmental plasticity), in addition to differences in the rate of acquisition (see also Li et al., 2000). Note that this finding is fully consistent with the claim that learning rate and G parameter are formally interchangeable when G is fixed.

as a starting point for exploring these interactions. Furthermore, it will be of interest to examine lifespan differences in the time course of the phasic response, its interactions with tonic level dopaminergic activity, and the relation of both to attentional and motivational aspects of behavior.

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