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Editorial

Dopaminergic modulation of cognition across the life span

Half a century ago, dopamine (DA) was discovered as a neurotransmitter in its own right (see Björklund and Dunnett, 2007 for review). Since then, dopaminergic systems have been studied in the context of neuropsychiatric and other disorders (e.g., attention deficit hyperactivity disorder, schizophrenia, Parkinsonism and drug addiction), as well as from the perspectives of cognitive child development and aging. This broad interest in DA primarily reflects its important neuromodulatory functions in (a) subcortical and cortical neural networks, (b) a wide range of cognitive functions, and (c) age-graded changes in behavior across the lifespan.

Compared to research on dopaminergic modulation of cognition in healthy young adults and various patient populations, investigations of the link between lifespan changes in DA systems and cognitive functions have been sparse. Hence, drawing evidence from studies of adolescents, younger and older adults, the present collection of review articles was assembled to promote research on the relations between changes in dopaminergic modulation and cognition across the lifespan (Bäckman et al., 2000, 2006; Li and Lindenberger, 1999; Li et al., 2001). The articles discuss recent empirical and theoretical progress in understanding the maturation and senescence of DA systems and their influences on cognition. They cover a wide methodological spectrum, ranging from behavioral studies and behavioral genetics over genomic imaging to pharmacological and neurocomputational approaches.

1. DA systems: components, pathways, and functions

The physiological effects of DA are mediated by pre- and post-synaptic mechanisms (see Fig. 1 for a schematic illustration of the striatal DA synapse). DA is synthesized at the pre-synaptic terminal, a process regulated by the enzyme tyrosine hydroxylase (TH) that converts tyrosine to the DA precursor, Dopa. The DA transporter (DAT) is a membrane-bound protein that serves as a regulator of the synaptic concentration of DA at nerve terminals (Giros et al., 1992). The DAT provides a rapid and efficient mechanism for re-uptake of synaptic DA and is essential for the regulation of DA neurotransmission (e.g., Giros et al., 1996). The concentration of DAT serves as a marker of the homeostatic tone of the DA system (Jaber et al., 1997; Jones et al., 1998). The highest concentrations of the DAT are found in the striatum, with much lower concentration in the brain stem and thalamus (e.g., Ito et al., 2008).

Most DA receptors, however, are located on post-synaptic neurons. Five receptor subtypes (D1–D5) are currently identified. The DA receptor subtypes have distinct anatomical distributions in the brain (Meador-Woodruff, 1994) and can be viewed as markers for different clusters of DA-related functions. The five subtypes are grouped into two families on the basis of structural homology and biochemical characteristics. The family of D1-like receptors includes the D1 and D5 subtypes, and the family of D2-like receptors includes the D2–D4 subtypes. DA receptors exhibit tissue- and cell-specific expressions that are altered during maturation, senescence and in conditions such as Parkinson's disease (e.g., Laurier et al., 1994; Stoessl and de la Fuente-Fernandez, 2003). D1 receptors are more abundant than D2 receptors, reflecting high concentrations not only in the striatum but also throughout the neocortex (Hall et al., 1994). D2 receptors are highly concentrated in the striatum; lower concentrations are expressed in the brainstem and thalamus, and concentrations are minute in the neocortex (Kessler et al., 1993). Knowledge accumulation is rapid concerning different genes coding for these components of the DA systems (for review, see Haile et al., 2007). Thanks to recent progress in genomic research, individual differences in these DA-relevant genotypes have been found to be associated with a range of cognitive functions such as working memory, attention, episodic memory and reward processing, as well as with psychiatric disorders (for review, see Gizer et al., 2009; Meyer-Lindenberg and Weinberger, 2006) and addiction (for review,see Le Foll et al., 2009).

Originating in the midbrain, DA neurons widely innervate various subcortical and cortical regions that make up the nigrostriatal, mesocortical, mesolimbic (see Lewis and Sesack, 1997 for review) as well as the thalamic (Sánchez-González et al., 2005) dopaminergic systems (see Fig. 2). The nigrostriatal and mesolimbic pathways form the two major subcortical DA systems. The cell bodies of the nigrostriatal DA system are located in the substantia nigra. The neurons project to the striatum, a region with dense dopaminergic innervation. The mesolimbic DA system originates from a more diffuse collection of neurons in the ventral tegmental area. One portion of the neurons here projects to limbic regions such as the nucleus accumbens, the amygdala, the hippocampus and the anterior cingulate cortex. A third pathway, referred to as the mesocortical DA system, also originates from the ventral tegmentum and projects throughout the neocortex. A fourth pathway that projects to the thalamus and may be independent from the nigrostriatal and mesolimbic systems has only recently been identified in the primate brain (Sánchez-González et al., 2005). Through these four pathways, the DA systems are involved in a wide spectrum of cognitive functions, including reinforcement

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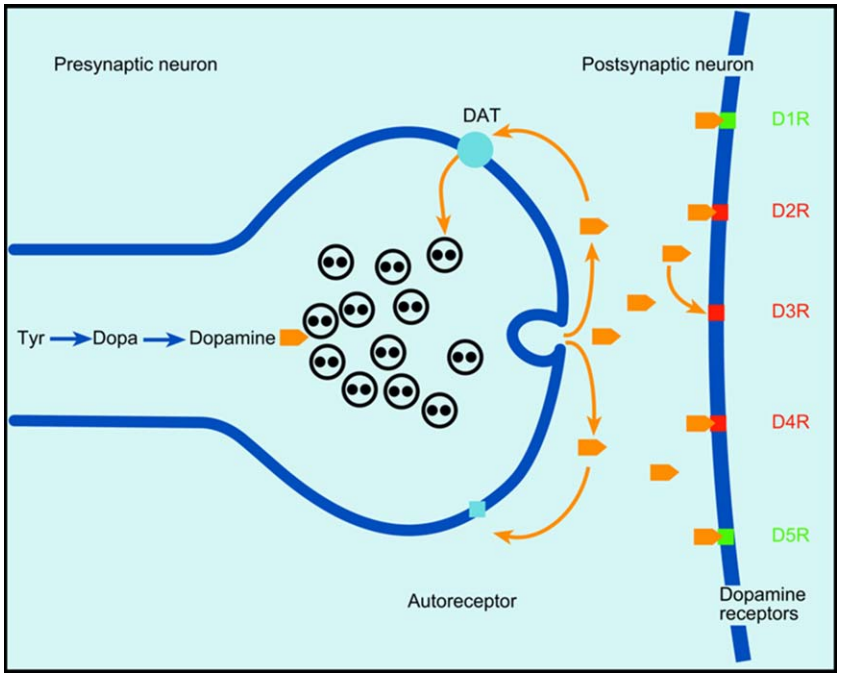

Fig. 1. A schematic diagram of a striatal DA synapse with pre- and post-synaptic components (adapted from Li et al., 2009 with permission; copyright Oxford University Press).

learning, reward- and novelty-related motivational processing as well as episodic memory, working memory and cognitive control processes.

2. DA modulation of neural noise and representation distinctiveness

At a general level, one of the functional effects of DA is its role in regulating neuronal noise (for review, see Winterer and Weinberger, 2004). Various computational approaches have been advanced to understand the mechanisms by which dopaminergic modulation affects cognition. These attempts range from realistic biophysical firing rate models of how D1 and D2 receptors affect the stability of working memory representations (Durstewitz et al., 2000; see also Seamans and Yang, 2004, for review) to more abstract models of dopaminergic effects on the dynamic connectivity between basal ganglia and prefrontal cortex (e.g., O'Reilly and Frank,

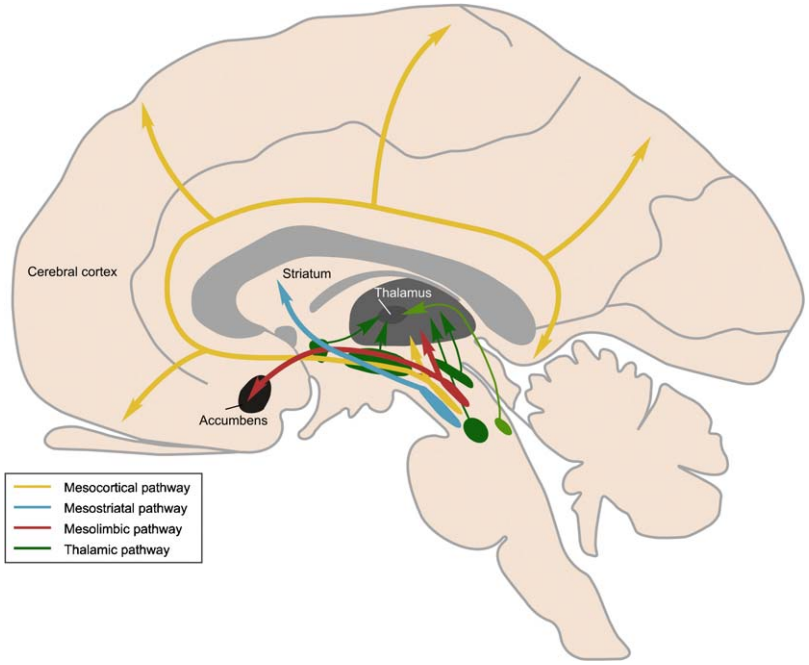

Fig. 2. A schematic diagram of the major dopaminergic pathways in the brain (adapted from Li et al., 2009 with permission; copyright Oxford University Press).

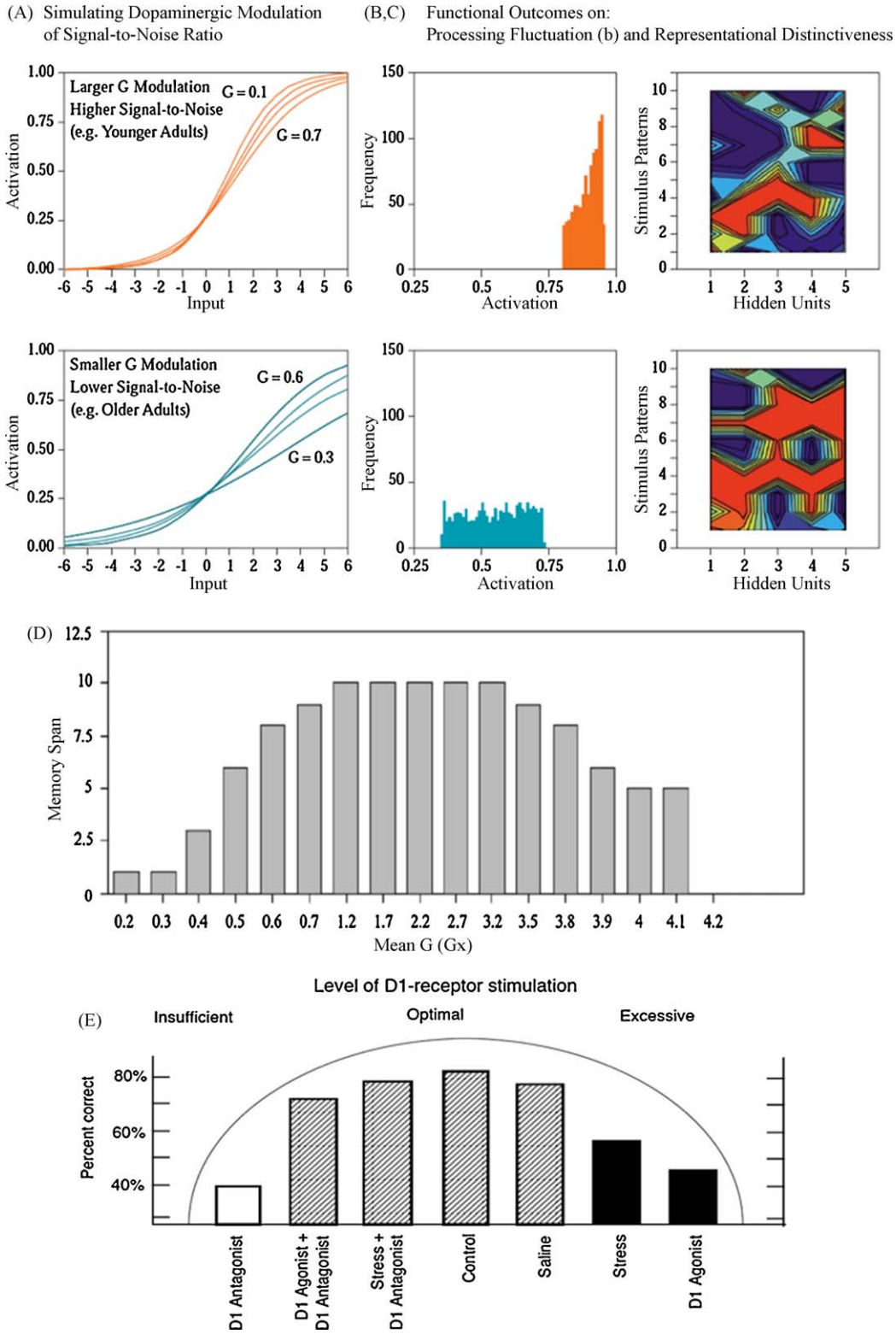

Fig. 3. (A–C) Dopaminergic modulation of neuronal noise and representation distinctiveness. The role of DA in affecting neuronal signal-to-noise ratio can be modeled by the gain (G) parameter of the sigmoidal activation function (Li et al., 2001; Servan-Schreiber et al., 1990). (A) The neuronal input-response mapping functions of individuals with suboptimal DA modulation because of aging (or disadvantageous genotypes) are captured by less steep activation functions with lower G and signal-to-noise ratio. (B) G modulation of signal-to-noise ratio affects random activation variability and (C) the representational distinctiveness of activation patterns. (D) G modulation of processing noise and representational distinctiveness capture the inverted-U function relating DA modulation and working memory. Extremely small or large G values result in reduced memory capacity (adapted from Li et al., 2001; Li and Sikström, 2002 with permission; copyright Elsevier). (E) Empirical evidence of insufficient or excessive D1 receptor stimulation on spatial working memory performance (adapted from Arnsten, 1998, with permission; copyright Elsevier).

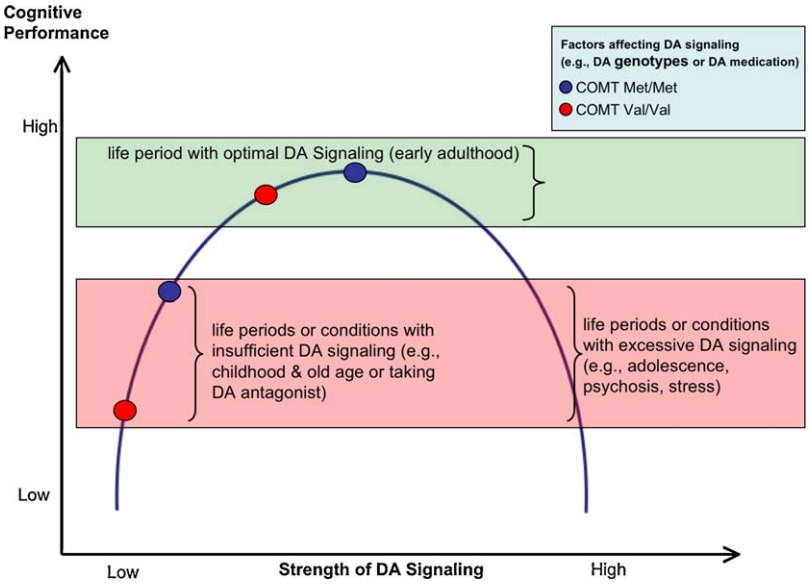

Fig. 4. Lifespan age differences in DA modulation as well as other factors, such as genotype, medication, stress and psychosis that lead to insufficient or excessive DA signaling affect the extent and pattern of DA effects on cognition (cf. Lindenberger et al., 2008; Nagel et al., 2008).

2006). Other models focus on DA's general computational role in affecting the signal-to-noise ratio of neuronal signal transduction (e.g., Cohen and Svervan-Schreiber, 1992; Li et al., 2001) or outcome-based valuation in reinforcement learning (see Montague et al., 2004, for review).

Though the various computational approaches differ in level of analysis and biophysical specificity, most of them share the basic assumption that dopaminergic modulation influences the properties of neuronal representations of perceptual and cognitive events. For instance, a two-stage model of dopaminergic modulation of working memory aims at capturing the dynamic interactions between DA and NMDA receptors in affecting the neuronal representations of memory items in the prefrontal cortex (Durstewitz et al., 2000). Specifically, when D2 receptor modulation predominates during the first stage, the PFC network is supposed to be in an exploratory state with multiple weak representations. However, when D1 receptor modulation predominates in a second stage, heightened inhibitory mechanisms weed out weaker representations and enhance the representation of the stronger inputs (Seamans and Yang, 2004). These patterns are nicely paralleled by results from other models aiming at explicating the computational effects of dopaminergic modulation on the signal-to-noise ratio of information processing at a more molar level (Li et al., 2001; Cohen and Svervan-Schreiber, 1992). When the gain parameter of a neural network's activation function is attenuated or increased to mimic deficient or excessive dopaminergic modulation, random fluctuations in activation increase and subsequently reduce the distinctiveness of internal presentations of stored memory items (see Fig. 3, panels A–C). Less distinctive representations result in reduced memory span and account for the inverted-U function relating DA signaling to working memory performance (Li and Sikström, 2002; see Fig. 3D). These simulation results are consistent with empirical studies demonstrating that medication and other factors such as stress or allelic variations in DA-relevant genotypes result in insufficient or excessive DA signaling and poorer working memory performance (see Fig. 3E; Arnsten, 1998; Goldman-Rakic et al., 2000; Mattay et al., 2003).

3. Lifespan development and the inverted-U function of DA modulation

The strength of DA signaling is also affected by age. The late maturation of dopaminergic modulation during childhood and adolescence (Andersen et al., 1997; Rosenberg and Lewis, 1994; for review, see Benes, 2001) constraints developmental changes in attention and other frontal executive functions (e.g., Diamond, 1996, 2002; Diamond et al., 2004; Liotti et al., 2005). In later life, dopaminergic modulation declines markedly, and this senescent decline has been linked to age-related deficits in processing speed, processing robustness, episodic memory, working memory, cognitive control and fluid intelligence (Bäckman et al., 2000; Volkow et al., 2000; see also Bäckman et al., 2006, in press; Li et al., 2009 for reviews).

The inverted-U function relating dopamine signaling to performance is well suited to capture the effects of age-graded differences in DA signaling on cognition. At the same time, this function also predicts that the influence of other factors (e.g., genetic differences) should be magnified at dopamine signaling recedes from the apex of the function, reflecting either not fully mature DA signaling, as in childhood, or depleted DA signaling, as in old age (see Fig. 4; cf. Lindenberger et al., 2008). A recent study by Nagel et al. (2008) provided direct empirical support for the hypothesis that normal aging magnifies the effects of a DA-relevant gene on cognition. Specifically, allelic variations in the Catechol-O-Methyltransferase (COMT) gene, which regulates DA signaling in PFC, were associated with greater differences in working memory performance among older adults than among younger adults. Thus, lifespan age differences in DA modulation are an important ontogenetic factor affecting the extent and pattern of DA effects on cognition.

4. Overview of this special issue

We deeply appreciate the input from all contributors to this special issue, who also presented on related topics in a symposium at the 2008 International Congress of Psychology held in Berlin, Germany. The seven articles included in this volume were selected

to represent a wide range of approaches including cognitive, behavioral genetics, genomic imaging, pharmacological and computational studies. Furthermore, empirical findings reviewed here draw on data collected from adolescents, younger adults, older adults and patient groups, with the aim to cover dopaminergic modulation across the lifespan in a broad range of cognitive functions.

The paper by Wahlstrom and colleagues reviews evidence of overactive DA signaling during adolescence and relates this to increased behavioral and emotional lability in adolescents. The article by Ullsperger reviews recent genomic imaging research on dopaminergic modulation of reward-related learning in adulthood. In light of findings showing that DA activity originating from the midbrain enhances hippocampal synaptic plasticity for novel events, the Düzel et al. article proposes that DA signals may enhance episodic memory via an energizing motivational process triggered by novelty. Focusing on old age, the paper by Bäckman et al. reviews recent findings that relate deficient DA modulation in aging to older adults' increased performance variability and reduced cognitive plasticity, both in terms of response to increasing task demands and cognitive training. Addressing more specifically the topic of DA modulation of reward-related decision making, the paper by Mohr et al. reviews recent findings on dopaminergic and serotonergic modulation of three key aspects of economic decisions (i.e., amount of reward, extent of risk and the time delay of reward), and highlights the implications of aging-related decline in both transmitter systems for economic decisions. Turning to pathology, the paper by Tost et al. reviews findings from recent genomic imaging studies on the relation between chaotic and stimulus-independent DA signaling and psychosis. Lastly, the paper by Hazy et al. discusses recent progress in computational models that formalize the relations between reward-predictive firing properties of midbrain dopamine neurons and reward-related learning, as well as their interactions with working memory and stimulus novelty.

Finally, we would like to thank Dr. Verity Brown and Dr. Linda Porrino, the chief editors of Neuroscience and Biobehavioral Reviews, who welcomed our initial exposé for the special issue. We also thank the Elsevier production editors, who assisted us in all practical matters related to publishing it.

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