Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Neuromodulation and aging: implications of aging neuronal gain control on cognition

Shu-Chen Li[1,2] and Anna Rieckmann[3,4]

The efficacy of various transmitter systems declines with advancing age. Of particular interest, various pre-synaptic and post-synaptic components of the dopaminergic system change across the human lifespan; impairments in these components play important roles in cognitive deficits commonly observed in the elderly. Here, we review evidence from recent multimodal neuroimaging, pharmacological and genetic studies that have provided new insights for the associations among dopamine functions, aging, functional brain activations and behavioral performance across key cognitive functions, ranging from working memory and episodic memory to goal-directed learning and decision making. Specifically, we discuss these empirical findings in the context of an established neurocomputational theory of aging neuronal gain control. We also highlight gaps in the current understanding of dopamine neuromodulation and aging brain functions and suggest avenues for future research.

Addresses
[1] Lifespan Developmental Neuroscience, Department of Psychology, TU Dresden Zellescher Weg 17, Dresden D-01062, Germany
[2] Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallee 94, Berlin D-14195, Germany
[3] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129, USA
[4] Department of Radiation Sciences, Diagnostic Radiology, Umeå University, Umea 901 87, Sweden

Corresponding author: Li, Shu-Chen (shu-chen.li@tu-dresden.de)

Current Opinion in Neurobiology 2014, **29**:148–158

This review comes from a themed issue on **Neuromodulation**

Edited by **David McCormick** and **Michael P Nusbaum**

For a complete overview see the Issue and the Editorial

Available online 26th July 2014

http://dx.doi.org/10.1016/j.conb.2014.07.009

Global aging

According to the United Nation's 2011 report on world population prospects, the number of people aged 65 or older will outnumber children under age 5 before 2020 [1]. This unprecedented demographic shift is jointly driven by reduced fertility rates and an increase in life expectancy. In most developed countries the average life expectancy at birth has increased from about 45 years in 1840 to above 75 years in 2000 [2,3]. This remarkable 30-year gain in physical health is, however, not necessarily accompanied by cognitive fitness and mental well-being into old age. Faced with the rapid growth of aging populations worldwide and an ever-expanding prevalence of dementia, understanding brain aging and aging-related cognitive declines has become a key challenge for neuroscience and psychology in the 21st century.

Brain aging is characterized by multiple neurobiological changes including losses of white matter integrity, cortical thickness and grey matter volumes, metabolic activity, and neurotransmitter functions (e.g. see [4•] for an overview). The focus of the current review will be on aging-related declines in neurotransmitter functions and the associated implications for cognitive functioning. The emphasis will be on recent studies that have linked declines in various markers of the dopamine system to information processing fidelity, memory functions as well as reward-based learning and decision-making in old age.

Aging-related declines of neurotransmitter systems

Neurons contain and release a large number of neurotransmitters, which regulate signal transmissions between neurons [5]. Several transmitter systems, such as the catecholamines — dopamine, serotonin, and norepinephrine — and acetylcholine, originate from the brain stem (e.g. subtantia nigra, ventral tegmental area, raphe nucleus) and broadly innervate various neural circuitries throughout the brain. In contrast to faster transient effects on local synaptic neurotransmission, these transmitter systems also exert lasting long-range neuromodulatory effects in various brain regions throughout striatum and the cortex that play central roles in key aspects of cognition and behavior.

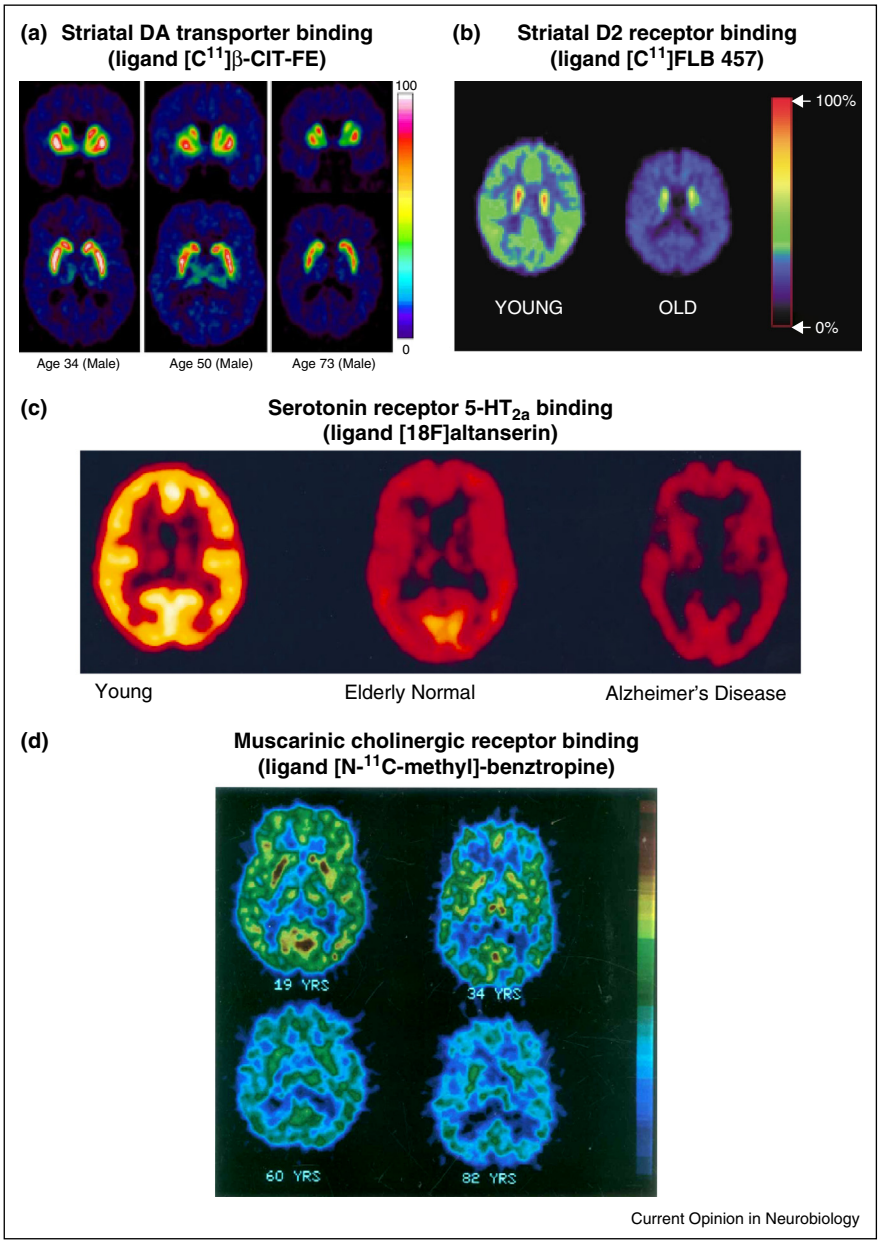
Primate and human positron emission tomography (PET) studies in the 1980s [6–9] first suggested aging-related losses of neurotransmitter functions. By now, there is general consensus that brain aging takes tolls on these transmitter systems, and a large number of studies have started to explore the functional implications of neurotransmitter losses, in particular those of the neurotransmitter dopamine.

In vivo PET receptor imaging studies in healthy elderly populations show extensive evidence for gradual but pervasive declines in different markers of the dopamine system: the binding potential of pre-synaptic dopamine transporter [10] and D2 [11] receptor in the striatum show

clear aging-related declines (Figure 1a, b). The binding potential of a PET ligand is an index of the density of receptors or transporters in the given region of interest. Similar to striatal receptor densities, D1 [12] and D2 [13•] receptor densities in the frontal regions are negatively affected by aging. Collectively, the evidence based on cross-sectional imaging studies in humans indicates density losses in extrastriatal and striatal presynaptic and postsynaptic markers of the dopamine system of up to 10% per decade, starting around the beginning of the third decade of life [13•,14,15,16•].

Although a large portion of the literature on neurotransmitter functions in old age has focused on dopamine, it should be noted that cross-sectional estimates of serotonin receptor availability (e.g. 5-HT_{2a} in Figure 1c; [8,17–19]) as well as markers of the acetylcholine system, including muscarinic receptors (Figure 1d, [20]) and the

Figure 1



Evidence from PET receptor imaging studies showing aging-related declines in receptor binding potentials in three transmitter systems. **(a)** Striatal dopamine transporter binding potential (data adapted from [10] with permission, copyright 2005 Elsevier). **(b)** Striatal D2 receptor binding potential (data adapted from [11] with permission, copyright 2002 Elsevier). **(c)** Serotonin receptor 5-HT_{2a} binding potential (data adapted from [18] with permission, copyright 1998 Elsevier). **(d)** Muscarinic cholinergic receptor binding potential (data adapted from [20] with permission, copyright 1990 Wiley).

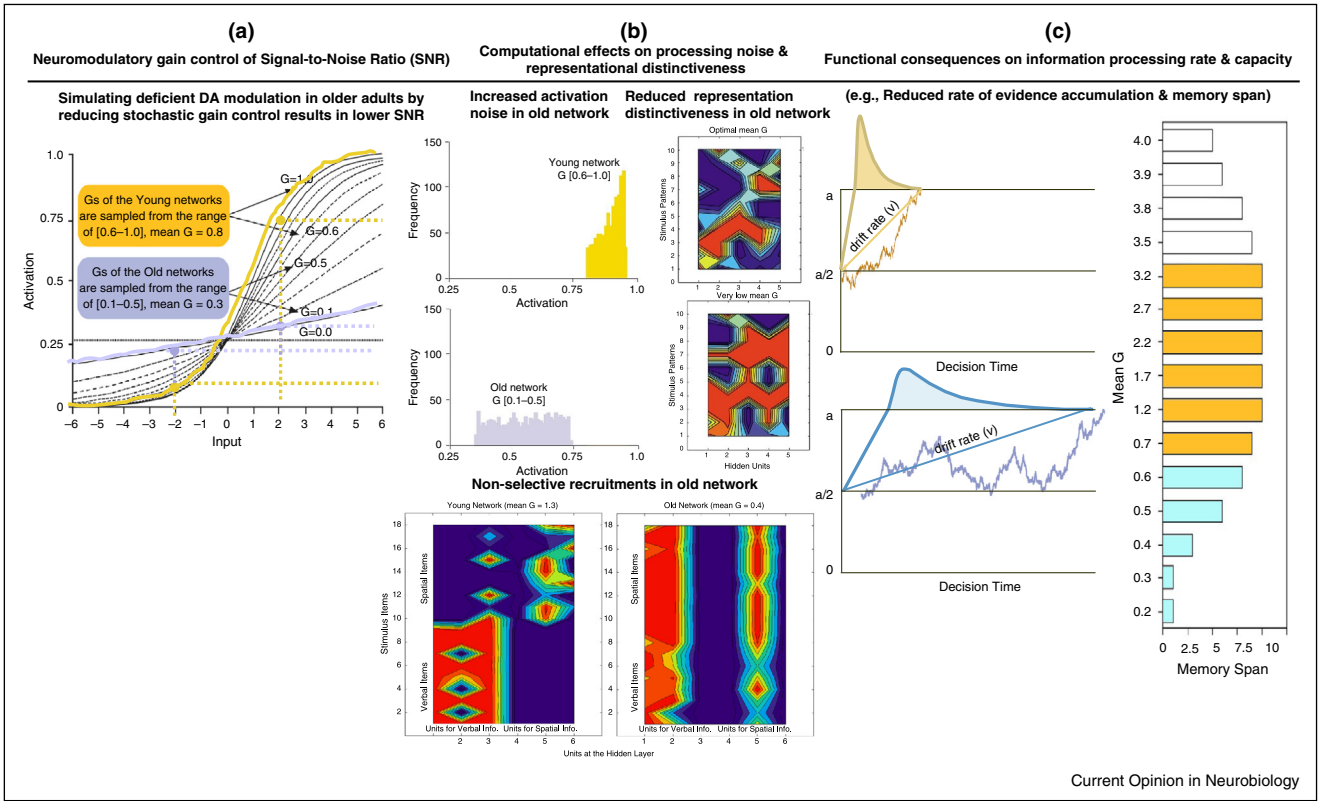
nicotinic acetylcholine receptor (β_2-nAChR), also show significant declines with advancing age in various brain regions, including the striatum, parietal, frontal, and temporal regions [21] (see also [22,23]).

Aging neuronal gain control

Over the past two decades, computational neuroscience has contributed to understanding the mechanisms through which dopamine [24–27], serotonin [28], norepinephrine [29] and acetylcholine [30] regulate the dynamics of neural information propagation within and between brain circuitries. The roles of neuromodulators have been modeled at different levels of analysis as well as with respect to different functionalities (e.g. attention, memory as well as reward and affective processing). Diversities in the specifics of modeling aside, a key role of neuromodulation that is subscribed by most computational approaches is neuronal gain control, be it in the forms of tuning the signal-noise-ratio (SNR) of synaptic signal transmission or gating information transfers between cortical networks [24–32].

Extending an early computational model of cognitive symptoms in schizophrenia that implicated suboptimal dopamine modulation of the SNR of neural information processing in the prefrontal cortex [25], over a decade ago the stochastic gain tuning model of aging [31] explicated a sequence of computational effects that link deficient dopamine modulation in the aging brain with impairments in cognitive processes and behavior. Specifically, this model captures aging-related decline in dopaminergic neuromodulation by stochastically attenuating the gain (G) parameter of the sigmoidal activation function, which models presynaptic to postsynaptic input-response transfer (Figure 2a). Reducing gain control reduces the slope of the activation function and the SNR of information transmission, which yields a sequence of subsequent effects that are suboptimal for neurocomputation in the simulated 'old' network (Figure 2b): increased random processing activations (noise), reduced representation distinctiveness of activation patterns, non-selective recruitment of presumably independent processing modules [32]. In terms of functional consequences,

Figure 2



Dopamine's computational role as neuronal gain control with computational effects on processing noise and representational distinctiveness as well as functional consequences on processing rate and capacity. **(a)** Simulating deficient dopamine modulation in older adults by reducing stochastic gain control reduces the signal-to-noise ratio of information processing. **(b)** Attenuated gain control increases random activation noise as well as reduces representational distinctiveness and processing specificity of different processing modules (e.g. greater co-activation of the simulated spatial and verbal processing modules). **(c)** Less distinctive representations reduces processing rate and memory capacity (adapted from [31,32] with permission. Copyright 2001, 2002 Elsevier).

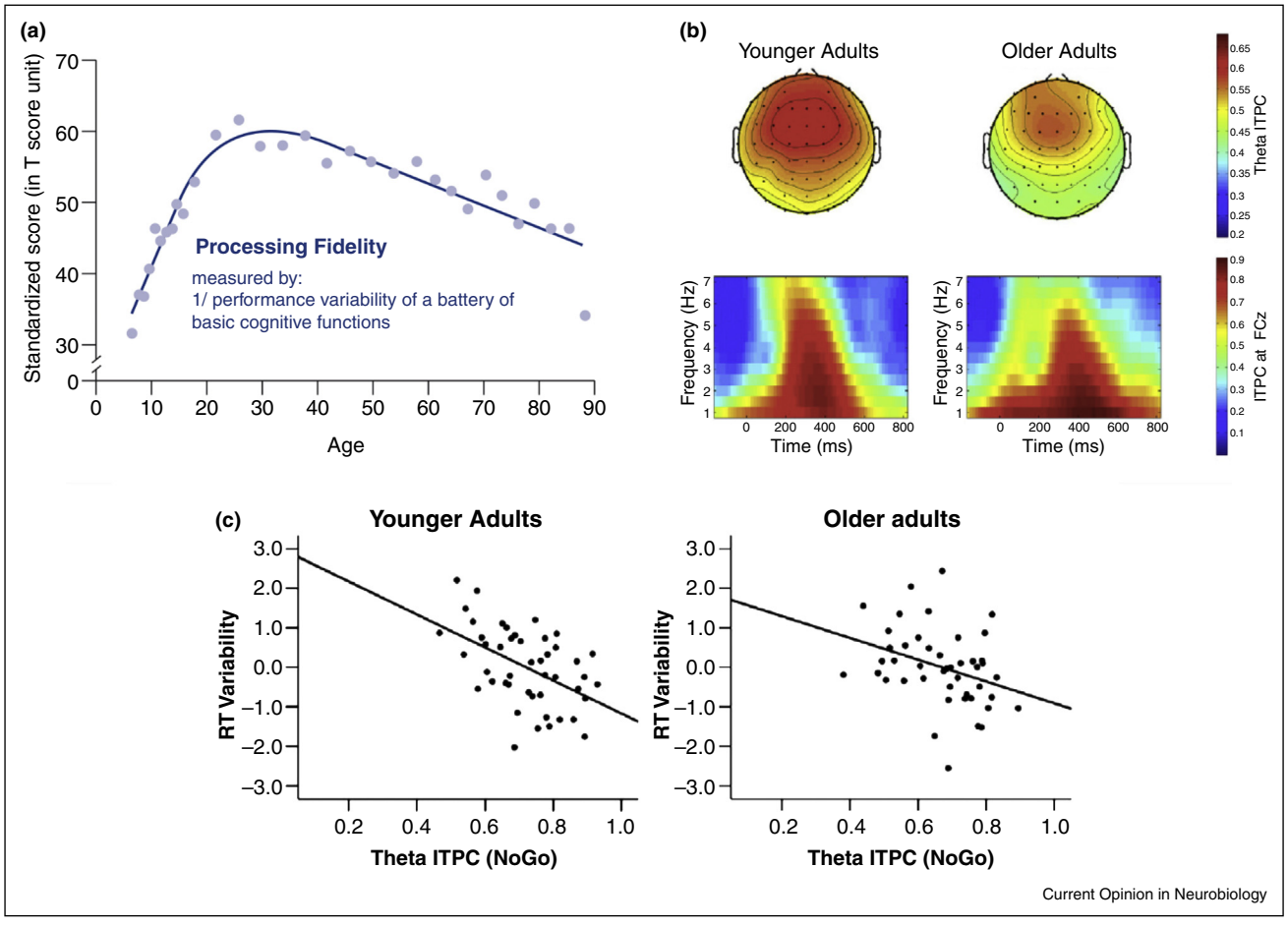
these suboptimal neurocomputational properties have negative implications for information processing (Figure 2c), for instance in terms of reduced rate of evidence accumulation (i.e. slower drift rate as modeled in diffusion/sequential sampling models [33]) and memory capacity [32]. The stochastic gain tuning model also yields an inverted-U function that relates DA signaling and cognition ([32], Figure 2c), which is in good agreement with empirical findings from animal [34] and clinical [35] research (see also [36,37] for reviews).

Over the last decade, genetic, psychophysiological, and brain imaging studies have shown that dopamine functions in the aging brain contribute to the elderly's impairments in various aspects of cognitions and behavior. The following sections will review recent studies that have implicated suboptimal dopamine modulation in the aging of information processing fidelity, memory functions and goal-directed learning and decision making.

Aging of information processing fidelity

At the behavioral level, information processing fidelity can be indexed by the inverse of within-person trial-to-trial reaction time (RT) variability. Higher levels of within-person behavioral variability when performing sensorimotor, perceptual, and cognitive tasks reflect a lack of processing fidelity and is indicative of suboptimal processing associated with pathology or aging [38]. Across the lifespan, information processing fidelity increases substantially during childhood in a various cognitive functions, reaches a maximum in early adulthood and then declines considerably with advancing age [39] (Figure 3a). When cognitive processes are modeled as a diffusion process, decreased information processing fidelity in older adults is reflected in increased trial-to-trial variability in the rate of evidence accumulation (drift rate) and reduced drift rates for performance in source memory [40], semantic and perceptual discrimination tasks [41]. Of particular clinical relevance, older adults

Figure 3



(a) Lifespan differences in processing robustness/fidelity (indexed by the inverse of within-person trial-by-trial variability; data adapted from [39] with permission, copyright 2004, Association for Psychological Science/Sage Journals). **(b)** Adult age differences in EEG inter-trial phase coherence. Lower inter-trial phase coherence reflects greater trial-by-trial variability of EEG signals in the theta range in older adults. **(c)** Theta inter-trial coherence correlates negatively with intraindividual trial-by-trial RT variability in young and older adults (data adapted from [44] with permission, copyright 2013 Elsevier).

who exhibited more short-term moment-to-moment RT fluctuations showed steeper longitudinal declines over 13 years in the category fluency task that, in part, demands executive control [42]. Moreover, psychophysiological measures of neuronal variability during executive control that are derived from electroencephalogram (EEG), such as greater amplitude variability of the P300 evoked brain potential [43] or lower theta inter-trial phase coherence [44], showed increased variability in older adults and AD patients as compared to healthy controls. A lower level of EEG phase coherence across trials partly reflects temporal 'jitters' in neuronal activity, which is in turn associated with higher trial-to-trial RT fluctuation at the performance level (Figure 3c).

Of interest to the current review is the effect of deficient dopamine modulation on random performance and neuronal variability. An early animal study had shown that dopamine receptor reductions as observed during aging not only slow down the animal's performance but also increase performance variability [45]. Prefrontal broadband noise derived from EEG is also increased in patients with schizophrenia, a pathological condition marked by dysfunctional dopaminergic neuromodulation [46]. Furthermore, recent neuroimaging studies indicate that individual and aging-related differences in dopamine receptor density are associated with cognitive processing fidelity. Lower dopamine receptor binding potentials (measured by PET) in the cortex have been found to be associated with lower processing fidelity (higher within-person trial-by-trial RT fluctuations) in middle aged adults during episodic memory and executive control task [47,48••,49]. These studies are in line with the theoretical link between dopaminergic modulation of SNR of synaptic signal transmission, neuronal noise, and fluctuations in performance.

Aging of memory functions

In his autobiography (1924, Haper & Brothers Publishers), Mark Twain wrote about his memory problems at old age: ''When I was younger, I could remember anything, whether it had happened or not; but my faculties are decaying now and soon I shall be so that I cannot remember any but the things that never happened.'' Twain's personal lamentation voiced a core issue of human conditions that most people experience with advancing age: the problem of less reliable memory. Aging-related declines in the anatomical, neurochemical, and functional integrities of the frontal-hippocampal-striatal circuitry contribute to age-related impairments in memory functions, including working memory, episodic memory and source memory [49]. Here, we will selectively highlight recent evidence from behavioral genetic and brain imaging studies that have suggested associations between deficient dopamine modulation and memory functions supported by the frontal-hippocampal-striatal circuitry.

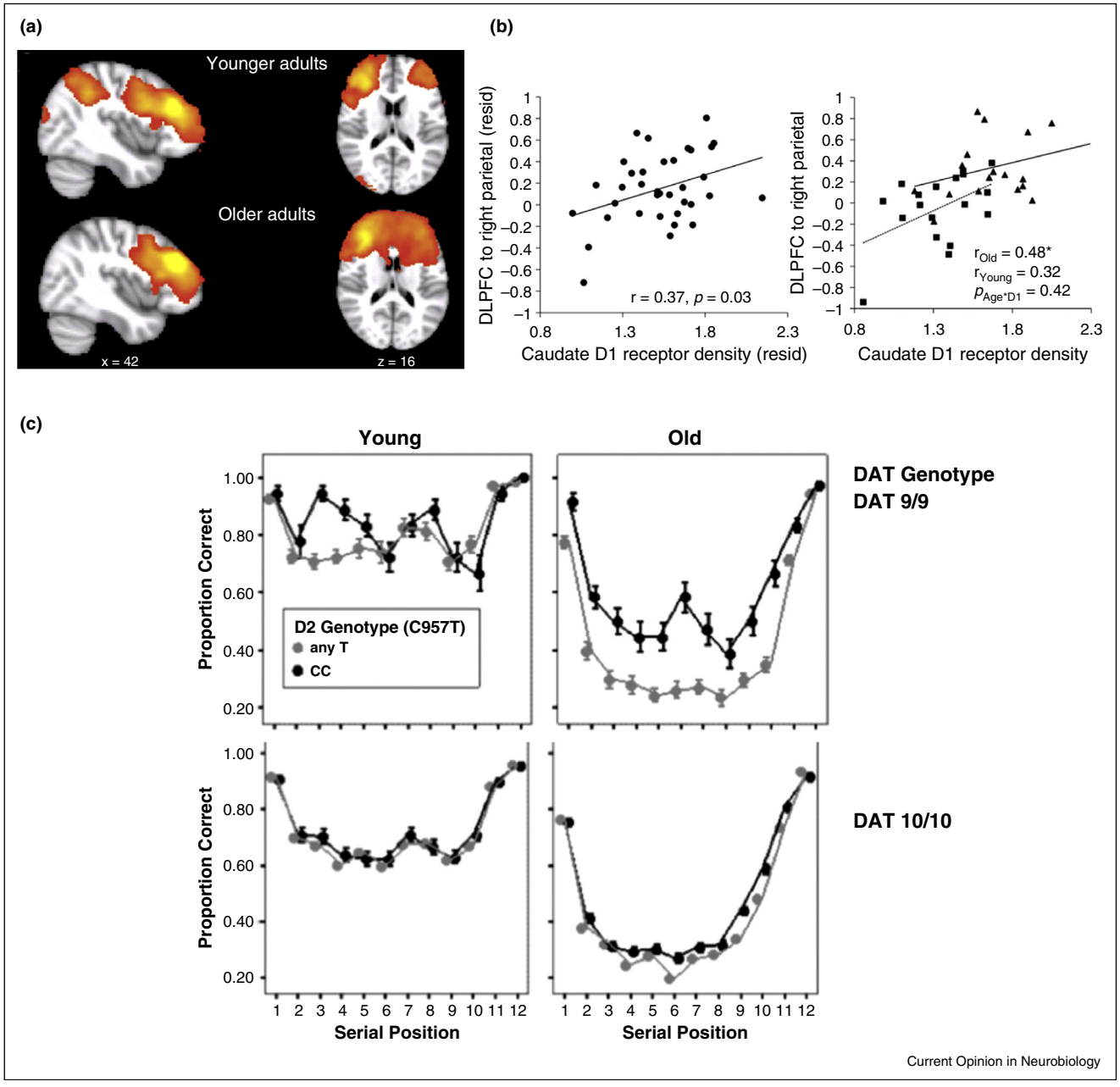
PET studies in healthy young adults suggest that better working memory performance is associated with higher capacity of dopamine synthesis in caudate [50] and greater extrastriatal dopamine release [51]. Extending this line of research, evidence from multimodal imaging studies combining MRI and PET show that in older adults PET markers of the DA system are associated with fMRI activity in prefrontal and parietal cortex during working memory [52,53] as well as the functional connectivity between striatum and prefrontal cortex [54], an index of optimal neuronal coupling that is reduced in older adults. Relatedly, another study [55] showed that the functional connectivity between the prefrontal and parietal cortex, key regions in the fronto-parietal control network that underlies working memory, was reduced in older compared to younger adults (Figure 4a). Importantly, in this study interindividual differences in the frontal-parietal connectivity correlated positively with striatal caudate D1 receptor density (Figure 4b), suggesting that age-related losses in striatal DA receptors partly explain age-related decline in fronto-parietal network strength and working memory.

A promising line of research that is gaining in popularity are genetic behavioral and imaging studies that make use of genetic predispositions that are associated with individual differences in dopamine functioning. In line with the multi-modal imaging studies reviewed above, a recent imaging genetics study showed that older adults who are of a specific genotype, associated with higher frontal dopamine signaling, that is, Met carriers of the catechol-O-methyltransferase (*COMT*) gene, showed patterns of brain activation during working memory that resembled the patterns of young adults. Carriers of the genotype associated with reduced frontal dopamine (*COMT* Val carriers) exhibited the patterns of inefficient prefrontal activation associated with aging [56••].

In addition to a limited working memory capacity, advancing age is also characterized by reduced working memory plasticity following cognitive training [57]. Receptor imaging studies with younger adults showed that extensive working memory training alters the binding potentials of cortical dopamine D1 receptor [58•] (measured with [^{11}C]SCH23390), striatal dopamine release [59•] (inferred by [^{11}C] raclopride displacement) and striatal activation [60•]. Considering that training-related transfer following cognitive intervention appears to be mediated by striatal dopamine functions [60•], it is plausible that aging-related decline in striatal dopamine signaling is one factor that limits training-related memory improvements in the elderly.

Episodic memory — memory for experienced events — is multifaceted. For instance, the memory about an old conversation includes the content of the conversation, the persons involved as well as the time and place at which

Figure 4



(a) Frontal–parietal functional connectivity during working memory is reduced in older adults. **(b)** Caudate D1 receptor density correlates with the frontal-parietal connectivity particularly in older adults (data adapted from [55] with permission, copyright 2011, Society of Neuroscience). **(c)** Dopamine transporter genotype (*DAT1*) and D2 receptor genotype (*DRD2*) interactively affect backward serial memory, particularly in older adults (data adapted from [70] with permission, copyright 2013 Elsevier).

the conversation took place. Associative mechanisms are required to bind different aspects of an experience into an integrated episode in long-term memory. The frontal-hippocampal circuitry has been implicated in the strategic organization and elaboration of memory materials during encoding, the binding of different features and consolidation of memory episodes, as well as pattern completion and monitoring processes during retrieval [61]. Compared to memory for specific facts or knowledge (item and semantic memory), the elderly are particularly impaired in episodic strategic organization and elaboration [62,64] that are subserved by the frontal network [40,59•,60•] as well as associative mechanisms that implicate the hippocampus [65–67].

Evidence from animal research indicates that midbrain dopamine modulation of the hippocampus plays an important role in stabilizing and maintaining encoded memory associations in long-term memory [68]. In humans, a recent pharmacological imaging study showed that a pharmacological dopamine agonist (levodopa) enhanced episodic memory and brain activation in older adults [69••]. Recent behavioral genetic evidence shows that genetic predispositions of dopamine transporter (*DAT1*) and receptor (*DRD2*) genes are associated with individual differences in serial memory (Figure 4b, [70•]) and long-term episodic memory forgetting [71], particularly in older adults. The magnification of genotype effects in old age can be computationally derived from the non-linear neuronal gain control function [31], which results in an inverted-U function relating levels of dopamine signaling and memory performance [32] that is in line with empirical evidence [34–37]. Effects of genetic predispositions can thus be expected to be larger in individuals whose efficacy of dopamine modulation is further away from the optimal level [72], that is, the top portion of the inverted-U function [32].

Finally, non-selective functional recruitments of additional brain regions during both episodic and working memory are common observations in fMRI experiment in older adults [see [73] for an early review]. For instance, during episodic encoding older adults tend to under-recruit left frontal cortex, while at the same time non-selectively recruiting right frontal regions that are usually not recruited in younger adults for the same process [63,74]. Non-selective recruitment in older adults has also been demonstrated during retrieval. Whereas brain activation in left prefrontal cortex and the hippocampus are selectively modulated by the demand of associative binding during retrieval in younger adults, the activities of the frontal-hippocampal network seem not sensitive to the associative demands in older adults [75]. The stochastic gain tuning model predicts general non-efficient over activation and non-selective recruitment of presumably independent processing pathways (Figure 2b, [32]), suggesting that non-selective fMRI activation of brain regions in aging across a variety of tasks might, in part, be a reflection of reduced dopamine functions in older age. This notion has to date not been comprehensively investigated but was supported by genomic imaging studies [35,56] showing that Val homozygotes of the *COMT* gene exhibited non-efficient over activation in prefrontal areas during working memory. Amphetamine, which temporarily increases synaptic dopamine level, reduced the over-activation and improved performance [35].

Aging of goal-directed learning and decision-making

Midbrain dopamine neurons are critically involved in modulating reward processing [76]. Reward anticipation has been shown to enhance long-term memory formation through stronger coupling between the striatal and hippocampal activities during encoding [77]. Thus, interactions between striatal dopamine release and hippocampal memory processes may, on the one hand, bias memory for events with higher reward or motivational significance and, on the other hand, provide a mean for forming integrated memory representations that guide future actions [78,79].

Given aging-related declines in various aspects of frontal and striatal dopamine modulation (see Figure 1), accumulating evidence indicates adult age differences in reward-based learning and decision-making. Findings from studies using probabilistic reinforcement learning or incentive delay tasks that compare striatal activations in younger and older adults indicate that striatal signaling of reward or outcome valence per se may not be affected by aging [80,81]. However, complex integration of reward values with outcome expectations for reward prediction, which depends on prefrontal outcome monitoring and hippocampal memory processes that integrate expectation-action-outcome contingencies, is impaired in aging [81,82,83•,84–87]. Several studies have indicated a link between fMRI activation in key areas of the dopamine system and performance of older adults during tasks involving reward-related processes. For instance, the greater temporal variability in mesolimbic activity assessed during a financial decision task seems to mediate older adults' suboptimal choices [83•]. Furthermore, in comparison to younger adults, healthy older adults and unmedicated Parkinson's patients under-recruited mesolimbic activity for learning the predictive value of rewards, while showing preserved responses to the reward outcome itself [84]. In inter-temporal choice tasks, where individuals are presented with the choice options of immediate or delayed rewards of different magnitudes, older adults tend to discount delayed reward less than younger adults. This behavioral effect is paralleled by a reduced sensitivity of striatal activities to immediate or delayed rewards [85–87]. That said, further research is necessary to better understand age-related differences in decisions about future rewards, as current findings are still mixed, depending on delay durations and task types.

Although a considerable number of studies exists linking striatal fMRI signal and reward expectation in younger samples, PET studies, genetic imaging and behavioral studies that could link individual differences in dopamine modulation to reward processing and decision making in older adults are still rare. A notable exception is a recent pharmacological imaging study, which shows that L-DOPA can restore the striatal activity and improve decision performance in some older adults [88••].

Outlook: enhancing neuronal gain control via cognitive training and non-invasive brain stimulation

If reduced neuronal gain control is at the heart of dopamine-related cognitive decline in aging, how could

neuronal gain control be enhanced in older adults? In the future, pharmacological intervention might be a viable approach for restoring neuromodulatory functions in regulating the processing fidelity of synaptic signal transmission or gating information transfers between cortical networks. To date, however, cognitive enhancer drugs that are suitable for the non-clinical elderly populations are not readily available, and bear a great risk for side effects that likely outweighs the benefits. Cognitive interventions and non-invasive brain stimulations that may be able to target the dopamine system constitute interesting alternatives to pharmaceuticals.

In younger adults, working memory training across five weeks was found to be associated with changes in cortical dopamine D1 receptor binding potential in the prefrontal and parietal cortices [58•] and in striatal dopamine D2 receptor binding potential [59•]. Although there is little evidence to date that similar intervention successes could be achieved in older adults, understanding the neural circuitry that underlies reduced gain control in older adults may open up future avenues for the development of cognitive interventions that target specific functional brain circuitries (e.g. the frontal-hippocampal-striatal network) innervated by the major transmitter pathways.

Related to the development of non-invasive cognitive interventions that are designed to target specific brain pathways in order to enhance older adults' performance, one other approach is non-invasive brain stimulations. Studies using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) that were applied to the fronto-parietal network revealed cognitive enhancing effects in young adults, clinical samples [see [89] for review]. Very recently, a few explorative studies have begun to use non-invasive brain stimulations in older adults. Some preliminary success in terms of ameliorating cognitive aging deficits could be demonstrated. For instance, anodal tDCS applied over the left inferior frontal gyrus improved performance in a semantic word generation task that implicates frontal cognitive control and working memory in old adults. Moreover, anodal tDCS also reduced the non-specific recruitment of the right prefrontal regions in older adults observed with fMRI, and modified functional brain activity of older adults to resemble those observed in younger adults [90•]. Of note, TMS applied to the prefrontal cortex has been shown to elicit dopamine release in striatum [91], to perturb functional connectivity of the striatum [92], activate the midbrain [93], and to interact with baseline dopamine level [94]. Thus, non-invasive brain stimulations might, in part, exert their effects through dopaminergic modulation. Together, these findings demonstrate reciprocal interplays between environmental supports in the form of cognitive training or non-invasive brain stimulation and dopamine modulation in vivo and hint at possible new avenues for buffering the aging population's cognitive vitality by sharpening neuronal gain control. In light of the recent evidence suggesting that an attenuated transfer effect of working memory training in older adults maybe associated with the under-recruitment of striatal activation [60•], combining frontal tDCS or TMS simulations with cognitive training might be a viable mean to enhance the intervention benefits in old adults. The initial progress notwithstanding, further research is needed for better understandings about the underlying mechanisms of tDCS and TMS, their long-term effects and potential risks, in order to develop appropriate protocols for gerontological applications.

Conclusions

Computational models have suggested that suboptimal dopamine modulation attenuates neuronal gain control, which yields a sequence of suboptimal neurocompuational effects that (Figure 2) may underlie deficits in older adults' cognition and behavior across multiple domains. Over the last decade, neuroimaging, genetic and pharmacological manipulation studies have accumulated and provided compelling evidence for a link between deficient dopamine modulation in the aging brain and the elderly's limitations in (i) information processing fidelity, (ii) working memory and episodic memory, and (ii) goal-directed learning and decision making. Where available, we have focused on imaging studies that linked dopamine functions (in terms of PET, genetics, or pharmacological manipulation) to both behavioral performance and patterns of fMRI activations that are common in aging. We have also highlighted existing gaps in the literature. For example, the association between deficient dopamine modulation and non-selective overactivation in aging is still insufficiently explored. Moreover, although animal and human studies suggest a strong involvement of dopamine functions in reward-related processes, relative to evidence on dopamine's role in memory deficits, knowledge about how deficient dopamine modulation in aging may limit goal-directed learning and decision making in old age is still scarce. Finally, we have briefly reviewed recent findings from cognitive training and non-invasive transcranial stimulations, which suggest cognitive-enhancing interventions, be it training or brain stimulation, that target the frontal-striatal circuitry and neuromodulation may be a promising avenue for future aging research.

Acknowledgements

Shu-Chen Li's research has been supported by fundings from the Max Planck Society (1996–2012), German Science Foundation (DFG LI 878/12-2), and the Ministry for Education and Research (BMBF 0Q0913, 01GQ1313). She gives special thanks to all collaborators in the Neuromodulation of Lifespan Cognition Project, which was sponsored by the Max Planck Institute for Human Development (2005–2012; M.FE.A.BILD0005). Anna Rieckmann was supported by a Marie Curie International Outgoing Fellowship from the European Commission.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. WHO (Ed): *Global health and aging*. 2011 . NIH Publication no. 11-7737 *http://who.int/ageing/publications/global_health/en/*.

2. Oeppen J, Vaupel JW: **Broken limits to life expectancy**. *Science* 2002, **296**:1029-1031.

3. Christensen K, Rau R, Vaupel JW: **The challenges ahead**. *Lancet* 2009, **375**:1196-1208 Additional information and discussion can be found at the Human Mortality Database (http://www.mortality.org).

4. • Jagust W, D'Espositio M (Eds): *Imaging the Aging Brain*. New York: Oxford University Press; 2009.
This edited volume provides a comprehensive collection of imaging studies of brain aging at the anatomical, neurochemical, and functional levels.

5. Lajtha A, Vizi SE (Eds): *Handbook of Neurochemistry and Molecular Neurobiology: Neurotransmitter Systems*, edn 3. New York: Springer; 2008.

6. Goldman-Rakic PS, Brown RM: **Regional changes of monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys**. *Neuroscience* 1981, **6**:177-187.

7. Wenk GL, Pierce DJ, Struble RG, Price DL, Cork LC: **Age-related changes in multiple neurotransmitter systems in the monkey brain**. *Neurobiol Aging* 1989, **10**:11-19.

8. Wong DF, Wagner HN, Dannals RF, Links JM, Frost JJ, Ravert HT *et al.*: **Effects of age on dopamine and serotonin receptors measured by positron tomography in the living brain**. *Science* 1984, **226**:1393-1396.

9. Bartus RT, Dean RL, Beer B, Lippa AS: **The cholinergic hypothesis of geriatric memory dysfunction**. *Science* 1982, **217**:408-417.

10. Erixon-Lindroth N, Farde L, Robins Wahlin TB, Sovago J, Halldin C, Bäckman L: **The role of the striatal dopamine transporter in cognitive aging**. *Psychiatry Res Neuroimag* 2005, **138**:1-12.

11. Kaasinen V, Rinne JO: **Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease**. *Neurosci Biobehav Rev* 2002, **26**:785-793.

12. Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, Tateno Y: **Age-related changes in human D1 dopamine receptors measured by positron emission tomography**. *Psychopharmacology* 1991, **103**:41-45.

13. • Kaasinen V, Vilkman H, Hietala J, Någren J, Helenius H, Olsson H *et al.*: **Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain**. *Neurobiol Aging* 2000, **21**:683-688.
This PET imaging study shows cross-sectional age differences (20–75 years) in dopamine D2/D2 receptor binding potentials (measured by [^{11}C]FLB 457) in frontal cortex, anterior cingulate cortex, lateral temporal cortex, medial temporal cortex, lateral and medial thalamus.

14. Inoue M, Suhara T, Sudo Y, Okubo Y, Yasuno F, Kishimoto T, Yoshikawa K, Tanada S: **Age-related reduction of extrastriatal dopamine D_2 receptor measured by PET**. *Life Sci* 2001, **69**:1079-1084.

15. Bäckman L, Nyberg L, Lindenberger U, Li SC, Farde L: **The correlative triad among aging, dopamine, and cognition: status and future prospects**. *Neurosci Biobehav Rev* 2006, **30**:791-807.

16. • Rieckmann A, Karlsson S, Karlsson P, Brehmer Y, Fischer H, Farde L, Nyberg L, Bäckman L: **Dopamine D1 receptor associations within and between dopamine pathways in younger and elderly adults: link to cognitive performance**. *Cerebral Cortex* 2011, **21**:2023-2032.
A recent study found that D1 receptor densities (measured by radioligand [^{11}C]SCH23390) were uniformly reduced across striatal and cortical regions in older adults relative to younger adults. Of note, however, intercorrelations between D1 receptor densities in striatal and extrastriatal areas were weak in older adults, suggesting individual differences in the relative losses of striatal and extrastriatal DA receptors.

17. Yamamoto M, Suhara T, Okubo Y, Ichimiya T, Sudo Y, Inoue M *et al.*: **Age-related decline of serotonin transporters in living human brain of healthy males**. *Life Sci* 2002, **71**:751-757.

18. Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY *et al.*: **Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging**. *Neuropsychophamacology* 1998, **18**:407-430.

19. Eppinger B, Hämmerer D, Li SC: **Neuromodulation of reward-based learning and decision making in human aging**. *Ann N Y Acad Sci* 2011, **1325**:1-17.

20. Dewey SL, Volkow ND, Logan RR, MacGregor JS, Fowler DJ, Schlyer DJ *et al.*: **Age-related decreases in muscarinic cholinergic receptor binding in the human brain measured with positron emission tomography (PET)**. *J Neurosci Res* 1990, **27**:569-675.

21. Mitsis EM, Cosgrove KP, Staley JK, Bois F, Frohlich EB, Tamagnan GD *et al.*: **Age-related decline in nicotinic receptor availability with [^{123}I]5-IA-85380 SPECT**. *Neurobiol Aging* 2009, **30**:1490-1497.

22. Terry AV, Buccafusco JJ: **The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development**. *Perspect Pharmacol* 2003, **306**:821-827.

23. Haense C, Kalbe E, Herholz K, Hohmann C, Neumaier B, Krais R, Heiss WD: **Cholinergic system function and cognition in mild cognitive impairment**. *Neurobiol Aging* 2012, **33**:867-877.

24. Montague PR, Hyman SE, Cohen JD: **Computational roles for dopamine in behavioral control**. *Nature* 2004, **431**:760-767.

25. Servan-Schreiber D, Printz HW, Cohen JD: **A network model of catecholamine effects: gain, signal-to-noise ratio and behavior**. *Science* 1990, **249**:892-895.

26. Braver TS, Cohen JD: **On the control of control: the role of dopamine in regulating prefrontal function and working memory**. In *Attention and Performance XVIII*. Edited by Monsell S, Driver J. Cambridge, MA: MIT Press; 2000:713-737.

27. Frank MJ: **Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and non-medicated Parkinsonism**. *J Cogn Neurosci* 2005, **17**:51-72.

28. Dayan P, Huys QJM: **Serotonin in affective control**. *Annu Rev Neurosci* 2009, **32**:95-126.

29. Aston-Jones G, Cohen JD: **An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance**. *Annu Rev Neurosci* 2005, **28**:403-450.

30. Stiefel KM, Gutkin BS, Sejnowski TJ: Cholinergic neuromodulation changes phase response curve shape and type in cortical pyramidal neurons. *PLoS One* 2008, 3 e3947:1-7.

31. Li SC, Lindenberger U, Sikström S: **Aging cognition: from neuromodulation to representation**. *Trends Cogn Sci* 2001, **5**:479-486.

32. Li SC, Sikström S: **Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation**. *Neurosci Biobehav Rev* 2006, **26**:795-808.

33. Smith PL, Ratcliff R: **Psychology and neurobiology of simple decisions**. *Trends Neurosci* 2004, **27**:161-168.

34. Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten A: **Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory**. *Nat Neurosci* 2007, **10**:376-384.

35. Mattay VS, Goldberg TE, Fera FH, Tessitore A, Egan ME, Kolachana B, Callicott JH, Weinberger DR: **Catechol-O-methyltransferase Val_{158}Met genotype and individual variation in the brain responses to amphetamine**. *Proc Natl Acad Sci* 2003, **100**:6186-6191.

36. Arnsten AFT: **Catecholamine modulation of prefrontal cortical cognitive function**. *Trends Cogn Sci* 1998, **2**:436-446.

37. Cools R, D'Espositio M: **Inverted-U shaped dopamine actions on human working memory and cognitive control**. *Biol Psychiatry* 2011, **69**:e113-e125.

38. MacDonald SWS, Nyberg L, Bäckman L: **Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity**. *Trends Neurosci* 2006, **29**:475-480.

39. Li SC, Lindenberger U, Hommel B, Aschersleben G, Prinz W, Baltes PB: **Lifespan transformations in the couplings of mental abilities and underlying cognitive processes**. *Psychol Sci* 2004, **15**:155-163.

40. Spaniol J, Grady CL: **Aging and the neural correlates of scource memory: over-recruitment and functional reorganization**. *Neurobiol Aging* 2012, **33** e3-425e18.

41. Ratcliff R, Thapar A, McKoon G: **Aging and individual differences in rapid two-choice decision**. *Psychon Bull Rev* 2006, **13**:626-635.

42. Lövdén M, Li SC, Shing YL, Lindenberger U: **Within-person trial-by-trial variability precedes and predicts cognitive decline in old and very old age: longitudinal data from the Berlin Aging Study**. *Neuropsychologia* 2007, **45**:2827-2838.

43. Hogan MJ, Carolan L, Roche RAP, Dockree PM, Kaiser J, Bunting BP, Roberstson IH *et al.*: **Electrophysiological and information processing variability predicts memory decrements associated with normal age-related cognitive decline and Alzheimer's disease (AD)**. *Brain Res* 2006, **1119**:215-226.

44. Papenberg G, Hämmerer D, Müller V, Lindenberger U, Li S-C: **Lower theta inter-trial phase coherence during performance monitoring is related to higher reaction time variability: A lifespan study**. *NeuroImage* 2013, **83**:912-920.

45. MacRae PC, Spirduso WW, Wilcox RE: **Reaction time and nigrostriatal dopamine function: the effects of age and practice**. *Brain Res* 1988, **451**:139-146.

46. Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR: **Prefrontal broadband noise, working memory, and genetic risk for schizophrenia**. *Am J Psychiatry* 2004, **161**:490-500.

47. MacDonald SWS, Cervenka S, Farde L, Nyberg L, Bäckman L: **Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning**. *Neuropsychologia* 2009, **47**:2299-2304.

48. •• MacDonald SWS, Karlsson S, Rieckmann A, Nyberg L, Bäckman L: **Aging-related increases in behavioral variability: relations to losses of dopamine D1 receptors**. *J Neurosci* 2012, **32**:8186-8191.

A recent study showing that lower dopamine D1 receptor binding potentials (measured by radioligand [^{11}C]SCH23390) in the dorsal prefrontal cortex, anterior cingular gyrus and parietal cortex are associated with greater processing fluctuations when the elderly performed a task that demands executive control.

49. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L: **Memory aging and brain maintenance**. *Trends Cogn Sci* 2012, **16**:292-305.

50. Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M: **Working memory capacity predicts dopamine synthesis capacity in human striatum**. *J Neurosci* 2008, **28**:1208-1212.

51. Aalto S, Brück A, Laine M, Någren K, Rinne JO: **Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D_2 receptor ligand [^{11}C]FLB 457**. *J Neurosci* 2005, **25**:2471-2477.

52. Landau SM, Lal Rayhan, O'Neil JP, Baker S, Jagust WJ: **Striatal dopamine and working memory**. *Cereb Cortex* 2009, **19**:445-454.

53. Bäckman L, Karlsson S, Fischer H, Karlsson P, Brehmer V, Rieckmann A *et al.*: **Dopamine D_1 receptors and age differences in brain activation during working memory**. *Neurobiol Aging* 2011, **32**:849-1856.

54. Klostermann EC, Braskie MN, Landau SM, O'Neil JP, Jagust WJ: **Dopamine and frontostriatal networks in cognitive aging**. *Neurobiol Aging* 2012, **33** 623.e15–623.e24.

55. Rieckmann A, Karlsson S, Fischer H, Bäckman L: **Caudate dopamine D1 receptor density is associated with individual differences in frontoparietal connectivity during working memory**. *J Neurosci* 2011, **31**:14284-14290.

56. •• Nyberg L, Andersson M, Kauppi K, Lundquist A, Persson J, Pudas S, Nilsson L-G: **Age-related and genetic modulation of frontal cortex efficiency**. *J Cogn Neurosci* 2014, **26**:746-754.

A recent study in a large sample of younger and older adults which showed that the same patterns of differences in dorsolateral prefrontal activation that characterized old versus young subjects during performance of a working memory task could be seen within the group of older subjects based on their catechol-O-methyltransferase (COMT) Val^{158}Met status. Older Met carriers, associated with higher synaptic dopamine tone, were more similar to younger adults in their patterns of activation than older Val carriers, suggesting an important role for dopamine tone in optimal recruitment of DLPFC during working memory.

57. Li SC, Schmiedek F, Huxhold O, Röcke C, Smith J, Lindenberger U: **Working memory plasticity in old age: practice gain, maintenance and transfer**. *Psychol Aging* 2008, **23**:731-742.

58. • McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, Klingberg T: **Changes in cortical dopamine D1 receptor binding associated with cognitive training**. *Science* 2009, **323**:800-802.

A recent study showing that D1 receptor binding potential (measured by radioligand [^{11}C]SCH23390) in prefrontal and parietal cortex is sensitive to 5-week working memory training in a young adult sample.

59. • Bäckman L, Nyberg L, Soveri A, Johansson J, Andersson M, Dahlin E, Neely AS *et al.*: **Effects of working-memory training on striatal dopamine release**. *Science* 2011, **333**:718.

A recent study showing that striatal D2 receptor binding (measured by raclopride) is also sensitive to working memory training in young adults.

60. • Dahlin E, Neely AS, Larsson A, Bäckman L, Nyberg L: **Transfer of learning after updating training mediated by the striatum**. *Science* 2008, **320**:1510-1512.

This age-comparative functional imaging study showed that striatal activity mediates training-related transfer effect. In comparison to younger adults, no training-related recruitment of striatal activity was found in older adults nor did they transfer effect.

61. Simons JS, Spiers HJ: **Prefrontal and medial temporal lobe interactions in long-term memory**. *Nat Rev Neurosci* 2003, **4**:637-648.

62. Shing YL, Werkle-Bergner M, Li SC, Lindenberger U: **Associative and strategic components of episodic memory: A lifespan comparison**. *J Exp Psychol Gen* 2008, **137**:495-513.

63. Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL: **Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging**. *Neuron* 2002, **33**:827-840.

64. Jacques PL St, Rubin DC, Cabeza R: **Age-related effects on the neural correlates of autobiographic memory retrieval**. *Neurobiol Aging* 2012, **33**:1298-1310.

65. Chalfonte BL, Johnson MK: **Feature memory and binding in young and older adults**. *Mem Cogn* 1996, **24**:403-416.

66. Old SR, Naveh-Benjamin M: **Differential effects of age on item and associative measures of memory: a meta-analysis**. *Psychol Aging* 2008, **23**:104-118.

67. Li SC, Naveh-Benjamin M, Lindenberger U: **Aging neuromodulation impairs associative binding: a neurocomputational account**. *Psychol Sci* 2005, **16**:445-450.

68. Lisman JE, Grace AA: **The hippocampal-VTA loop: controlling the entry of information into long-term memory**. *Neuron* 2005, **46**:703-713.

69. •• Chowdhury R, Guitart-Masip M, Bunzeck N, Dolan RJ, Düzel E: **Dopamine modulates episodic memory persistence in old age**. *J Neurosci* 2012, **32**:14193-14204.

A recent pharmacological imaging study in older adults that showed that the dopamine precursor levodopa (L-DOPA) delayed (six hours) episodic

memory retrieval and suppressed non-specific hippocampal activity. Moreover the effect of L-DOPA followed an inverted-U shaped dose–response function.

70. • Li SC, Papenberg G, Nagel IE, Preuschhof C, Schröder J, Nietfeld W, Bertram L *et al.*: **Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory**. *Neurobiol Aging* 2013, **34** e1-358.e10.
Together with Ref. [69••], this study provides empirical evidence that the dopamine genotype effects on episodic memory in older adults are in line with the non-linear inverted-U function relating dopamine signaling and cognition. Accordingly, genotype effects on cognitive phenotypes may be more apparent when the intermediated brain phenotypes, that is, the efficacy of dopamine modulation in this case, function suboptimally.

71. Papenberg G, Bäckman L, Nagel IE, Nietfeld W, Schröder J, Bertram L, Heekeren HR *et al.*: **Dopaminergic gene polymorphisms affect long-term forgetting in old age: further support from the magnification hypothesis**. *J Cogn Neurosci* 2013, **25**:571-579.

72. Lindenberger U, Nagel IE, Chicherio C, Li SC, Heekeren HR, Bäckman L: **Age-related decline in brain resources modulates genetic effects on cognitive functioning**. *Front Neurosci* 2008, **2**:234-244.

73. Reuter-Lorenz PA: **New visions of the aging mind and brain**. *Trends Cogn Sci* 2002, **6**:394-400.

74. Leshikar ED, Gutchess AH, Hebrank AC, Sutton BP, Park DC: **The impact of increased relational encoding demands on frontal and hippocampal function in older adults**. *Cortex* 2010, **46**:507-521.

75. Giovanello KS, Schacter DL: **Reduced specificity of hippocampal and posterior ventrolateral prefrontal activity during relational retrieval in normal aging**. *J Cogn Neurosci* 2011, **24**:159-170.

76. Schultz W: **Updating dopamine reward signals**. *Curr Opin Neurobiol* 2013, **23**:229-238.

77. Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabriele JDE: **Reward-motivated learning: mesolimbic activation precedes memory formation**. *Neuron* 2006, **50**:507-517.

78. Shohamy D, Adcock RA: **Dopamine and adaptive memory**. *Trends Cogn Sci* 2010, **14**:464-472.

79. Shohamy D, Wagner AD: **Integrating memories in the human brain: hippocampal-midbrain encoding of overlapping events**. *Neuron* 2008, **60**:378-389.

80. Samanez-Larkin GR, Gibbs SEB, Khanna K, Nielsen L, Carstensen LL, Knutson B: **Anticipation of monetary gain but not loss in healthy older adults**. *Nat Neurosci* 2007, **10**:787-791.

81. Cox KM, Aizenstein HJ, Fiez JA: **Striatal outcome processing in healthy aging**. *Cogn Affect Behav Neurosci* 2008, **8**:304-317.

82. Mell T, Wartenburger I, Marschner A, Villringer A, Reischies FM, Heekeren HR: **Altered function of ventral striatum during reward-based decision making in old age**. *Front Hum Neurosci* 2009, **3** Article 34.

83. • Samanez-Larkin GR, Kuhnen CM, Yoo DJ, Knutson B: **Variability in nucleus accumbens activity mediates age-related suboptimal financial risk task**. *J Neurosci* 2010, **30**:1426-1434.
This age-comparative functional brain imaging study showed that temporal variability (measured by mean square successive difference) in BOLD signals in the nucleus accumbens mediated age differences in risk-seeking mistakes in an investment decision task.

84. Schott NH, Niehaus L, Wittmann BC, Schütze H, Seidenbecher CI, Heinze HJ, Düzel E: **Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing**. *Brain* 2007, **130**:2412.

85. Samanez-Larkin GR, Mata R, Radu PT, Ballard IC, Carstensen LL, McClure SM: **Age differences in striatal delay sensitivity during intertemporal choice in healthy adults**. *Front Neurosci* 2011, **5**:126.

86. Eppinger B, Nystrom LE, Cohen JD: **Reduced sensitivity to immediate reward during decision making**. *PLoS ONE* 2012, **7**:e36953.

87. Eppinger B, Schuck NW, Nystrom LE, Cohen JD: **Reduced striatal responses to reward prediction errors in older compared to younger adults**. *J Neurosci* 2013, **33**:9905-9912.

88. •• Chowdhury R, Guitart-Masip M, Lambert C, Dayan P, Huys Q, Düzel E, Dolan RJ: **Dopamine restores reward prediction errors in old age**. *Nat Neurosci* 2013, **16**:649-654.
A recent pharmacological imaging study that provides a direct link between deficient dopamine modulation and weakened striatal prediction signal by showing that L-DOPA can restore the striatal activity and improve decision performance in some older adults.

89. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Lenoe A: **Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders?** *Neuropharmacology* 2013, **64**:566-578.

90. • Meinzer M, Lindenberg R, Antonenko A, Flaisch T, Flöel A: **Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes**. *J Neurosci* 2013, **33**:12470-12478.
This study shows that atDCS stimulation over the left ventral inferior gyrus in older adults improved performance in a semantic work generation task, reduced non-selective recruitments of right ventral inferior gyrus and medial frontal gyrus, as well as increased functional frontal–parietal connectivity.

91. Strafella AP, Paus T, Barrett J, Dagher A: **Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus**. *J Neurosci* 2001, **21**:1-4.

92. van Schouwenburg MR, O'Shea J, Mars RB, Rushworth MFS, Cools R: **Controlling human striatal cognitive function via the frontal cortex**. *J Neurosci* 2012, **32**:5631-5637.

93. Chib VS, Yun K, Takahashi H, Shimojo S: **Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex**. *Transl Psychiatry* 2013, **3**:e268.

94. Monte-Silva K, Kuo M-F, Thirugnanasambandam N, Liebetanz D, Paulus W, Nitsche MA: **Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans**. *J Neurosci* 2009, **29**:6124-6131.