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Neuromodulation of reward-based learning and decision making in human aging

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In this paper, we review the current literature to highlight relations between age-associated declines in dopaminergic and serotonergic neuromodulation and adult age differences in adaptive goal-directed behavior. Specifically, we focus on evidence suggesting that deficits in neuromodulation contribute to older adults' behavioral disadvantages in learning and decision making. These deficits are particularly pronounced when reward information is uncertain or the task context requires flexible adaptations to changing stimulus–reward contingencies. Moreover, emerging evidence points to age-related differences in the sensitivity to rewarding and aversive outcomes during learning and decision making if the acquisition of behavior critically depends on outcome processing. These age-related asymmetries in outcome valuation may be explained by age differences in the interplay of dopaminergic and serotonergic neuromodulation. This hypothesis is based on recent neurocomputational and psychopharmacological approaches, which suggest that dopamine and serotonin serve opponent roles in regulating the balance between approach behavior and inhibitory control. Studying adaptive regulation of behavior across the adult life span may shed new light on how the aging brain changes functionally in response to its diminishing resources.

Keywords: aging; neuromodulation; motivation; cognitive control

Learning to choose adaptively between different behavioral options in order to reach goals is a pervasive task in life for individuals of all ages. We are often confronted with complex, uncertain situations that nonetheless require decisive actions to pursue our short- or long-term goals. On the one hand, achieving goals in and of itself is rewarding. On the other hand, monitoring of action outcomes is necessary for goal attainment. Adaptive behavior entails interactions between processes that monitor action–outcome relations and mechanisms that evaluate these relations with respect to goal relevance to modify future actions based on these evaluations.[1] These dynamics require close interplay between cognitive control of actions for the focused pursuit of goals and motivational processes for the evaluation and expectation of action outcomes. These mechanisms are subserved by frontostriatal networks, which are heavily innervated by the midbrain dopamine system as well as other transmitter systems, such as serotonin.[2,3]

As adults age, the efficacy of these functional brain circuitries, as well as neurotransmitter systems, decline. Thus, on the one hand, it is necessary to understand how functional changes in these networks contribute to adult age differences in reward-based learning and decision making. On the other hand, one might expect functional changes and strategic adaptations in response to constraints on cognitive resources due to aging. Studying adaptive behavioral control across different life periods may shed light on these adaptations.

This paper provides a selective review of the current literature to highlight relations between age-associated decline in dopaminergic and serotoninergic neuromodulation and adult age differences in adaptive goal-directed behavior. The first section presents an overview on the neural systems involved in adaptive decision making and learning and how they are modulated by dopamine and serotonin. After the overview, evidence on age-related changes in these neurotransmitter systems and how they may affect frontostriatal circuits is reviewed. In the second section, we focus on behavioral contexts that are particularly challenging with respect to older adults' limited cognitive and brain resources to illustrate the

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impacts of deficient neuromodulation in old age. Specifically, we review recent findings on adult age differences in three major aspects of learning and decision making: (1) the acquisition of goal-directed behavior under reward uncertainty, (2) the ability to flexibly abandon accustomed actions and learn new behavior during reversal learning, and (3) asymmetries in the valuation of rewarding and aversive outcomes during learning and decision making.

Adaptive behavioral control and neuromodulation of frontostriatal networks

The ability to adapt behavior to changes in the utility of action outcomes is supported by three interrelated brain networks: the substantia nigra (SN) and the ventral tegmental area (VTA) in the midbrain; the basal ganglia, most importantly the ventral and dorsal striatum; and parts of the frontal cortex, including the medial orbitofrontal cortex (OFC)/ventral medial prefrontal cortex (vmPFC), the dorsal anterior cingulate cortex (dACC), and the dorsal lateral prefrontal cortex (dlPFC). The diversity of the involved brain circuits may reflect the different component processes involved in adaptive control of goal-directed behavior.

Activity of midbrain dopaminergic neurons in SN/VTA is thought to contribute the motivation for acquiring behavior (see Ref. 4 for a review) and to code for reward prediction errors during learning.[3,5–7] Furthermore, phasic dopaminergic responses in the midbrain covary with the expected value of reward, presumably integrating factors, such as the magnitude, delay, and probability of outcomes.[8–10] The SN/VTA neurons are reciprocally connected with the striatum.[11–13] Given that the striatum itself receives a major part of its inputs from cortical areas, it might serve as a relay structure for transferring inputs from midbrain dopaminergic neurons to the cortex and vice versa. Furthermore, the nucleus accumbens has been proposed to regulate the balance between limbic and prefrontal contributions to goal-directed behavior.[14]

The corticostriatal connections are organized such that the majority of cortical inputs to the ventral striatum stem from regions that are mostly involved in the valuation of outcomes, that is, the vmPFC and medial OFC. In contrast, the majority of inputs to the dorsal striatum originate from cortical areas involved in executive control, such as the dACC and dlPFC.[11,15] This ventral to dorsal gradient is also observable in the connections from the striatum to the midbrain SN/VTA areas. The ventral striatum receives least of the midbrain inputs but targets the most extensive parts of the SN/VTA.[12,16] In contrast, the dorsal striatum receives most of the SN/VTA outputs but targets the SN/VTA less than the ventral striatum.[11,17]

In summary, two loops link cortical, striatal, and midbrain structures during reward-based learning. The two loops can be characterized as a reward loop that is involved in the valuation of outcomes (including the VTA/SN, ventral striatum, and vmPFC/medial OFC) and an executive control loop that consists of cognitive control and motor areas involved in action selection (such as the dlPFC, dACC, and dorsal striatum). The specific anatomical setup of these two frontostriatal loops suggests that they play a major role in linking outcome valuation to cognitive and action control and thereby subserve goal-directed behavior.

Other than being richly innervated by the dopaminergic system, these frontostriatal circuits are, in part, also innervated by the serotonergic system.[2,3,7,18] Recent findings from pharmacological studies suggest that serotonin plays a critical role in the adaptation to changes in stimulus–reward contingencies during learning as well as in avoidance learning and the regulation of impulsive behavior.[19–22] Work in animal models indicates that a region in the epithalamus, the lateral habenula, controls serotonergic neuromodulation in the raphe nucleus as well as dopaminergic neuromodulation in the midbrain.[23] The lateral habenula has also been implicated in avoidance learning and shows a preferential sensitivity to negative motivational events.[24–26] Although clearly more research is necessary to replicate these results and to clarify the habenulas' role in the midbrain dopamine system, the current findings suggest that activity in the lateral habenula to negative motivational cues may trigger serotonergic neuromodulation and lead to adjustments in behavioral control.

Age-related declines in neuromodulation of the frontostriatal-limbic network

Parallel to anatomical shrinkages of cortical and subcortical regions and age-related decline in the integrity of white matter connections,[27–29] the efficacy of various neurotransmitter systems are also compromised by aging. Other than dopaminergic

and serotoninergic modulation, cholinergic and noradrenergic receptor mechanisms show age-related declines.[30,31] Whereas the cholinergic system is known to play an important role in hippocampal memory functions (see Ref. 32 for a review), the noradrenergic system is involved in mediating arousal (e.g., Ref. 33) or, as proposed in a recent theory, in regulating the exploration–exploitation trade-off.[34]

In this review, we focus on dopamine and serotonin because these two systems have been shown to be critically involved in reward-based learning and decision making (e.g., Refs. 7 and 18). Furthermore, the age-related trajectories in these systems are somewhat better documented than is the case for acetylcholine or norepinephrine. Evidence from cross-sectional studies shows that across the adult life span, the dopaminergic and serotonergic systems undergo substantial declines (e.g., Ref. 35; see Tables 1 and 2 for summaries of studies showing cross-sectional estimates of percentage reduction per decade in dopamine D2 and serotonin transporter binding efficacy in various brain regions).

Thus far, very few studies have directly compared the extent of age-related declines in these two systems. In the rare cases where the aging-related declines in dopamine and serotonin presynaptic and postsynaptic components were investigated in identical samples, the degrees of declines seemed to be comparable in both systems.[42]

Much of the work on the relationship between aging and the dopaminergic system has focused on the caudate and the putamen, which receive dense dopaminergic innervations from the midbrain. There is clear evidence for age-related loss in pre- as well as post-synaptic biochemical markers of this system. Regarding presynaptic mechanisms, both positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies (e.g., Refs. 44 and 45) indicate age-related loss of the dopamine transporter (DAT) expression in the striatum (see Fig. 1A). For postsynaptic mechanisms, molecular imaging work reveals age-related loss of both striatal D1 and D2 receptor densities of comparable magnitude as found for the DAT (Refs. 46–50; see also Fig. 1B). The average decline ranges between 5% and 10% per decade from early to late adulthood (see Table 1). A similar downward age trajectory is seen for the mesocortical and mesolimbic dopaminergic pathways (see decline in D1 and D2 receptor binding in frontal cortex across the adult life span, as portrayed in Fig. 1C and D, respectively).

In the aging literature, less attention has been focused on serotonin than dopamine. However, available evidence also indicates age-related decline in the serotoninergic system. For instance, an early PET receptor imaging study reported an estimate of about 25% drop in frontal serotonin receptors in adults aged from 19 to 73 years,[35] amounting to a decline of approximately 5% per decade. More recent studies reported cross-sectional estimates of 2–11% decline per decade of serotonin receptors in various brain regions, including the hippocampus, midbrain, thalamus, and hypothalamus (see Table 2 for details). Similarly, the binding potential in key elements of the serotonergic system (such as limbic

Table 1. Cross-sectional longitudinal estimates of percentage of decade-by-decade decline in dopamine D2 receptor binding mechanisms in various extrastriatal regions in two independent samples

	Kaasinen et al.[36]	Inoue et al.[37]
Brain regions		
Frontal (%)	11	14
Temporal (%)	10	12
Parietal (%)		13
Occipital (%)		12
Hippocampus (%)	10	12
Amygdala (%)	7	
Thalamus (%)	5	5

Table 2. SPECT and PET in vivo studies on age-related declines in serotonin receptor availability

	Per decade change	Reference
Brain regions		
Frontal	4–6%	Costes et al.[38]
		Wong et al.[35]
Midbrain	2–11%	Hesse et al.[39]
		Kuikka et al.[40]
		Newberg et al.[41]
		Pirker et al.[42]
		Yamamoto et al.[43]
Thalamus	3–10%	Hesse et al.[39]
		Pirker et al.[42]
		Yamamoto et al.[43]

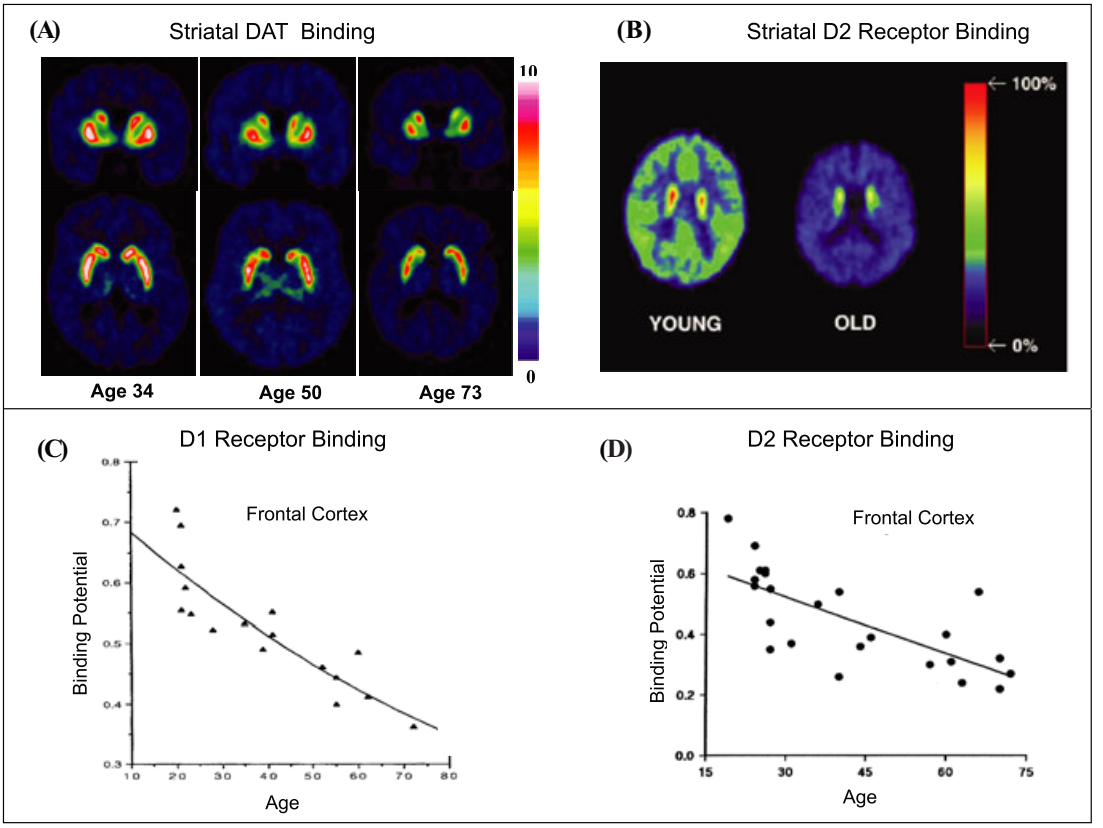

Figure 1. **Age-related decline in pre- and post-synaptic dopamine binding mechanisms. (A) Striatal DAT binding (adapted from Ref. 44 with permission from Elsevier Science). (B) Striatal D2 receptor binding (adapted from Ref. 49 with permission from Elsevier Science). (C) D1 receptor binding in frontal cortex (adapted from Ref. 46 with permission from Springer-Verlag). (D) D2 receptor binding in frontal cortex.[49]**

structures and raphe nuclei) has been suggested to decline with a rate of about 3–4% per decade in older adults.[51]

Age-related declines in neuromodulation as simulated in computational models

Various neurocomputational models have been proposed to link aging-related decline in dopamine modulation to behaviorally observed cognitive deficits. One of these models relates weakened phasic dopaminergic activity with older adults' deficits in monitoring-performance errors.[52] Another model focuses on capturing the relation between deficient dopaminergic modulation and older adults' compromised prefrontal cognitive control mechanisms.[53] Focusing on dopamine's role in the gain control (G) of neuronal signal-to-noise ratio, a third model has linked age-related increases in random processing fluctuations to less distinctive perceptual, memory, or goal representations in more general terms.[54,55] Specifically, this model captures aging-related decline in dopaminergic modulation by stochastically attenuating the G of the sigmoidal activation function that models dopaminergic modulation of presynaptic to postsynaptic input-response transfer (cf. Ref. 56). Reducing G decreases the slope of the activation function (Fig. 2A), which affects the signal-to-noise ratio of information transmission, and, subsequently, results in increased within-network random activation (Fig. 2B). This, in turn, leads to increased performance variability in a simulated aging neural network (Fig. 2C). If G is increased to excessive values, simulating increased dopaminergic modulation, the activation function becomes a step function, and activation variability depends critically on the amplitudes of inputs. In these cases, activation variability is markedly reduced with large

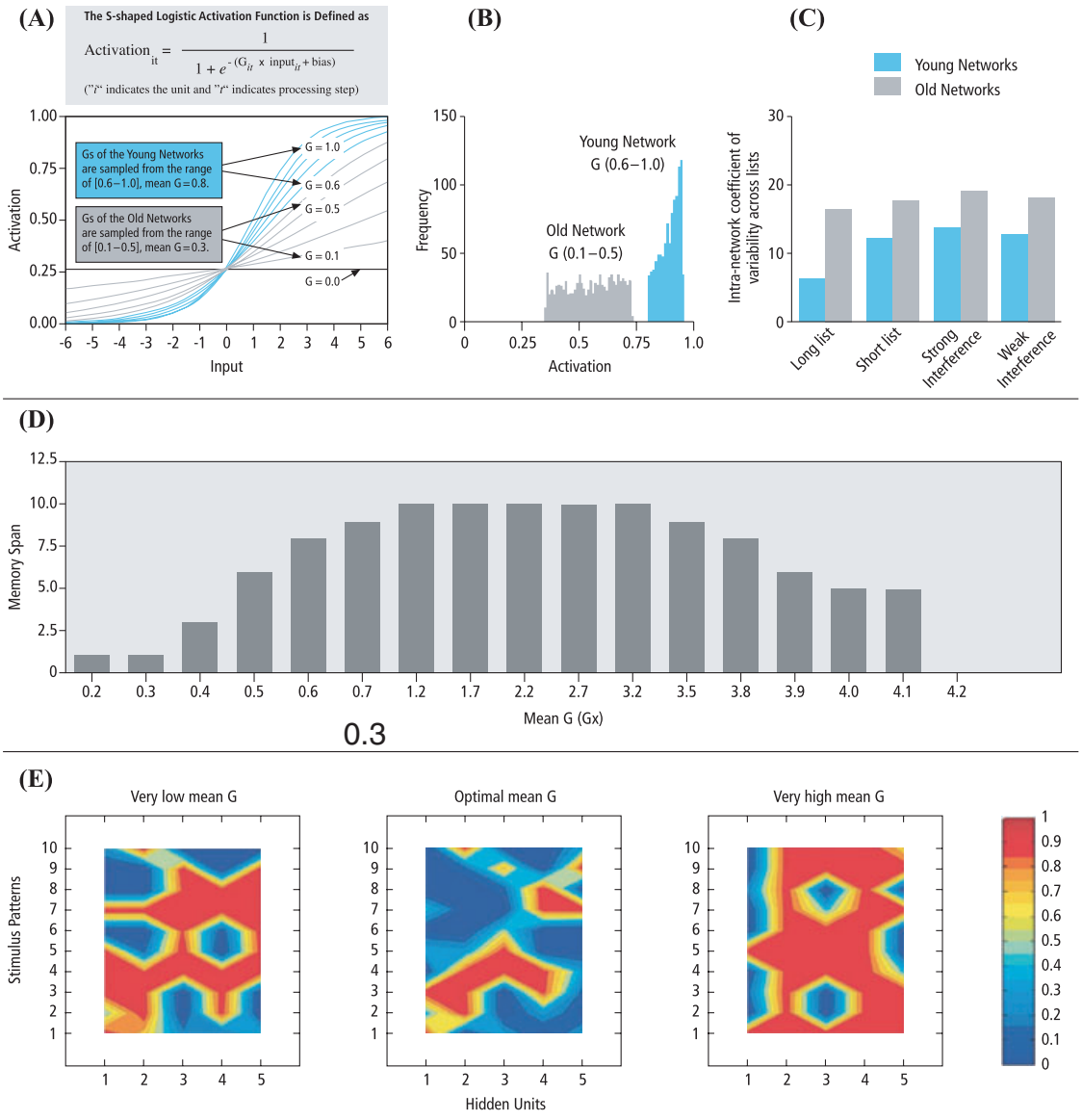

Figure 2. (A) Simulating aging-related DA modulation by reduction of stochastic gain tuning. Values of G parameters for younger networks were sampled from the range [0.6–1.0], with a mean of 0.9, whereas values for older networks were sampled from the range [0.1–0.5], with a mean of 0.3. (B) Reduced gain tuning increased random activation variability, indicated by activation distributions of one young network's and old network's responses to a noise stimulus across 1,000 trials. (C) Reduced gain tuning also increased within-network cross-trial performance variability in simulated old networks in four simulated episodic memory tasks (adapted with permission from Ref. 54 with permission from Elsevier Science). Stochastic gain tuning captures the inverted-U function relating DA modulation and functional outcomes of (D) memory performance and (E) distinctiveness of activation patterns.[54] To simulate the whole range of dopamine dysfunction from deficient to excessive signaling, mean G values from 0.2 to 4.1 were simulated. Activation patterns presented in (E) correspond to mean G of 0.3 (very low mean G), 1.7 (optimal mean G), and 4.0 (very high mean G).

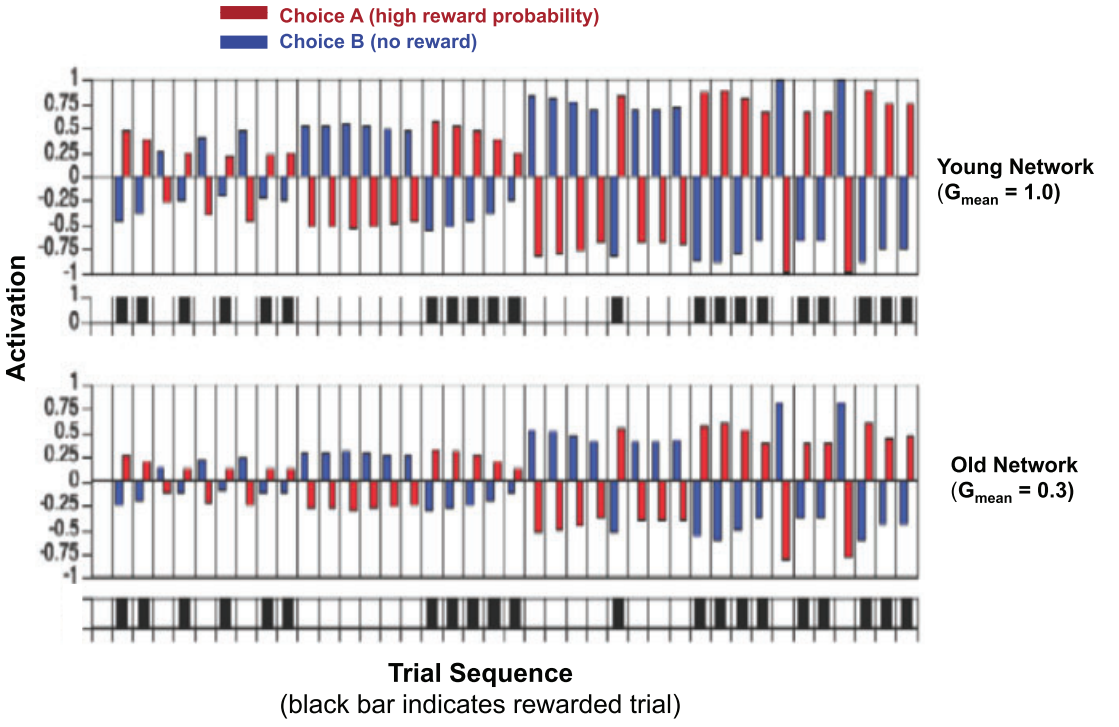

Figure 3. **Activation patterns of two choice options in the simulated prefrontal context module across learning in simulated young (mean G = 1.0) and old (mean gain = 0.3) networks. Across learning, activation levels for choice option with higher reward probability become more distinct from the choice option with no reward. This distinction is, however, less pronounced in the simulated old network.**

positive or negative inputs, and increased with intermediate inputs. These properties of stochastic G tuning predict an inverted-U function between the levels of dopamine modulation, representational distinctiveness, and working memory capacity (Fig. 2D and E). This inverted-U relation has been confirmed empirically in animal studies and more recently in human functional imaging (fMRI) research.[57–61] The noisier and less distinctive representations in older networks—as simulated in previous work on aging-related working memory and episodic memory deficits[54,55,62]—can, in principle, be extended to study the influences of deficient dopamine modulation on reward processing and decision making in old age.

Specifically, the probability of flexibly switching to other choice options, $P(\delta_t)$, may depend on the valuation of a given choice that is acquired during reinforcement learning. Outcome evaluation during learning involves a comparison of the obtained reward with the expected outcomes. In temporal difference models this is quantified by the prediction error (δ_t), which reflects the difference between a received reward and the expected reward.[3,63] Similar to previous accounts the probability of choice switch, $P(\delta_t)$, could be modeled by a sigmoidal function.[54,64] In this model, age-related decline in reward-based dopaminergic modulation of choice switches can be captured by attenuating the slope of the function for units in the simulated striatal network. The noisier processing of each choice, due to suboptimal G in simulated old networks, could accumulate during learning and result in less distinctive representations of reward expectations of the choice options. Furthermore, the thus computed $P(\delta_t)$, can be used to adapt the representations of choice options in a simulated prefrontal context module to guide (bias) subsequent choices. In the case of simulated old networks, the noisier representations of expectation–outcome contingencies and choice switches would thus also compromise prefrontal executive control of choices. Figure 3 shows the representation of two choice options (one with high reward probability and the other with no