NOW vs LATER brain circuits: implications for obesity and addiction

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Balancing behaviors that provide a reward NOW versus behaviors that provide an advantage LATER is critical for survival. We propose a model in which dopamine (DA) can favor NOW processes through phasic signaling in reward circuits or LATER processes through tonic signaling in control circuits. At the same time, through its modulation of the orbitofrontal cortex, which processes salience attribution, DA also enables shifting from NOW to LATER, while its modulation of the insula, which processes interoceptive information, influences the probability of selecting NOW vs LATER actions on the basis of an individual's physiological state. Disruptions along these circuits contribute to diverse pathologies, including obesity and addiction.

Delayed gratification: a basic feature of self-control

How do we decide when to do a behavior now versus leaving it for later? Such decisions are influenced by the context, the nature of the behavior, and the probability of its occurrence. For behaviors that have a reward outcome, a premium will be applied to choosing it 'now', whereas for behaviors that have an aversive outcome or that involve exerting effort, the 'later' option will tend to be more appealing. The evolutionarily optimized balance in NOW vs LATER behavioral choices increases the chances of fulfilling immediate needs as well as those that are better served by behaviors designed to attain longer-term goals.

Delay discounting (DD) (see Glossary) is an algorithm that quantifies an individual's propensity toward seeking immediate rewards or avoiding aversive commodities, even if later rewarding ones are larger or immediate aversive ones are smaller. To be certain, there are several forms of ‘discounting’, such as those based on probability [1], and a discount is also applied as a function of how much cognitive or physical effort will be demanded by alternative rewards [2]. However, we focus here on DD because it displays significant test validity, with adverse changes having been associated with several unhealthy behaviors and markers of health status [3], including prepotent responses [4], maladaptive lifestyle choices [5], and a range of psychiatric disorders, including addiction [6–10]. Many factors contribute to or can influence DD rates, including the context, prior experience with the stimulus, physiological states, choice presentation, and previously conditioned responses. The DD literature is vast and fascinating and many of these factors have been extensively described in prior reviews [11–13].

The neurobiology of NOW vs LATER

Decisions involving intertemporal, sustained-effort, probabilistic, and risk-aversion choices rely on overlapping circuits. While much of the neuroanatomical and neurophysiological details that distinguish one function from another remains to be elucidated, it is clear that they are all strongly dependent on DA signaling [14]. Here we focus almost exclusively on the NOW vs LATER (or intertemporal) decision paradigm as it relates to reward choice since this is the aspect that has been most thoroughly investigated. Similarly, the regulatory influence of neurotransmitter systems other than DA on the various components of impulsivity that contribute to DD [15], including lack of premeditation (failure to reflect on consequences), lack of perseverance (inability to remain focused on a task that requires energy expenditure or is distressful), urgency (tendency to act on strong impulses), and sensation seeking (tendency to seek novel and exciting activities) [16], have been reported in the literature [17–21] and are outside the scope of this opinion article.

NOW vs LATER processes are differentially modulated by DA: LATER processes require steady DA signaling in striatal and prefrontal regions to sustain effort as achieved by tonic DA firing, whereas NOW processes are predominately driven by fast, sharp bursts of DA as achieved by phasic DA firing that drive attention to the salient stimulus. In humans, brain imaging studies have revealed that stimuli that result in fast DA increases in ventral and dorsal striatal regions are experienced as rewarding and generate the desire to attain the stimulus [22] whereas stimuli that trigger slow and steady DA increases do not [23,24]. By contrast, steady DA increases are associated with increases in the ability to exert sustained (i.e., cognitive) effort and to experience the task or stimulus as motivating and interesting [25]. Moreover, these results

Glossary

Delay or intertemporal discounting (DD): the devaluing of a reward as a function of the delay of its delivery.
Effort discounting: the devaluing of a reward as a function of the effort demanded to achieve it.
Probabilistic discounting: the devaluing of a reward as a function of the chances that the reward has of materializing.
also seem to ascribe a differential role of DA signaling within striatal subregions, the caudate being implicated in inhibitory control of cognitive operations, the ventral striatum (VS) in reward and impulsive choices [26,27], and the putamen in habits and routines [28]. Similarly, within the prefrontal cortex (PFC) the dorsolateral PFC (dlPFC) is associated with improved sustainability of effort [29,30] whereas activity in the ventral PFC (vPFC) is more consistent with temporal discounting of subjective value, and preferentially so in impulsive individuals [31], a differential role consistent with the predominance of their striatal projections from the caudate and the VS, respectively [32].

Additionally, neuroimaging evidence supports the existence of dynamic communication between cortical (including but not limited to the PFC) and basal ganglia regions (including but not limited to the striatum) whenever there is a need to make ‘NOW vs LATER’ decisions, a system that carries valuation signals not only for appetitive or goal-related stimuli but also for aversive stimuli and for invested effort [33], including responses to economic conflict, moral dilemma, physical pain, and visceral (e.g., moral) disgust [34].

According to a widely accepted model, one of these systems hinges on the preferential activation of high-level deliberative/cognitive processes [e.g., dlPFC, dorsal anterior cingulate cortex (dACC), posterior parietal cortical (PFC) areas] [35] to assess the subjective value of future outcomes and allow people to contemplate or simulate their consequences [36,37]. The second system, which revolves around limbic and paralimbic cortical structures [e.g., ventromedial PFC (vmPFC), VS, hippocampus, amygdala, insula] helps integrate complex appetitive and aversive predictions to coordinate behavior [38] and weigh in whenever there is an opportunity for instant gratification. However, a more holistic model has also been proposed according to which the system as a whole calculates (discounts) the saliency value of a given reward as a function of how soon it will become available [39].

Whatever neurocomputational model of DD turns out to provide the best account of its complex outputs, there is consensus that DA modulates how timing is incorporated into the value of a reward [40]. Indeed, the prediction error signal conveyed by DA neurons includes the predicted time for the reward to materialize. There is also universal consensus that the PFC and striatum [including the nucleus accumbens (NAc)] play crucial roles in cost/benefit analyses of the kinds that underlie NOW vs LATER decisions. In these regions, stimuli and events that induce or predict reward, as well as unexpected or omitted rewards, can trigger rapid changes of DA neuron activity at sub-second to second timescales [41,42]. The modulation of phasic DA firing is regulated by several afferents, of which the most prominent are glutamatergic projections from the PFC, thalamus, amygdala, ventral hippocampus, and brainstem [43–45].

Researchers have uncovered important details about how the PFC and NAc influence DD. In the prelimbic medial PFC (mPFC), DA changes (measured with microdialysis) facilitate shifts in choice bias (important for cognitive flexibility) by conveying information about reward availability, whereas DA changes in the NAc convey information about the magnitude and relative value of a reward in a way that biases choice toward larger, uncertain rewards [46]. Overall, studies indicate that lower DA levels in the PFC contribute to steeper discounting of future rewards by impairing corticostriatal function [47,48]. For example, higher DD rates are observed not only when the executive attention control network [dlPFC, dorsomedial PFC (dmPFC), inferior parietal cortex, cingulate ACC, and precuneus] was less engaged but also when the ‘bottom-up’ reward valuation network (including the amygdala, hippocampus, insula, and vmPFC) was less deactivated [48]. Similarly, volitional downregulation of drug craving hinges on opposite patterns of activation in the NAc (reduced) versus the dlPFC (increased) [49,50].

The differential influence of DA along striatocortical pathways is partly explained by the subtype of DA receptor being activated. Animal studies indicate that DA receptors have different, albeit complementary, roles in risk-based decision making (for a review see [51]). Specifically, in the mPFC preferential activation of D1 and D2 receptors (D1R and D2R) tips the balance toward or against riskier options, respectively [52]. In the NAc, D1Rs appear to optimize decision making in such a way that their stimulation can increase risky choices (large/uncertain options) when advantageous but shift choice toward small/certain options when their utility declines. By contrast, the stimulation of D3Rs in the NAc appears to decrease the sensitivity to rewards and reduce riskier options, whereas stimulation of D2Rs does not alter choice behaviors associated with risky reward choices [53]. However, D2Rs in the NAc might mediate behavioral choices that result in aversive consequences [54]. Similarly, receptor subtypes mediate reward seeking behaviors: striatal neurons containing predominantly D1Rs promote while those expressing primarily D2Rs inhibit reward-seeking behaviors [55]. Additionally, a subset of neurons expressing D1Rs in the VS (the location of the NAc) are modulated by D3Rs and their activation favors reward seeking [56]. Interestingly, there are D4Rs that modulate the function of D2Rs on the terminals of glutamatergic corticostrial neurons, and decreased D4R signaling has been implicated in novelty seeking [57,58]. The role of D5Rs in reward has been much less investigated. Finally, impulsivity and sustainability of effort toward a reward have also been shown to be differentially associated with receptor subtype, with distinct modulatory effects in the PFC compared with the NAc [59].

It is likely that the differential impact of various target-area receptor configurations on NOW vs LATER decisions will be predicated on differences in neuronal activation patterns. Although cue-evoked DA bursts in the NAc reflect the value of future rewards, and are clearly involved in reward learning and decision making [60], the DA transients that result from phasic activation of DA neurons are probably not very suitable for the orchestration of behaviors geared toward achieving goals in long time frames. Such calculations are likely to rely on more protracted modes of DA signaling [61,62] that are likely to be more adept at encoding the valence of distant rewards or of sustaining effort. Using fast-scan cyclic voltammetry, a previously unknown, not phasic nor tonic but extendedly
ramping (up or down) mode of DA signaling was recorded in the striatum of rats as they toiled to reach a distant goal that appears particularly well suited to sustaining protracted motivational drive [61]. Perhaps D2Rs, which have high affinity for DA [63] and feature a second, more protracted wave of response during slow synaptic transmission [64], play a more predominant role in this mode of signaling and in orchestrating behaviors to resist the urge for an immediate reward and sustain this resistance as well as maintaining the effort necessary to achieve a long-term goal.

**Shifting between NOW vs LATER**

The external context and internal state of the individual during the making of NOW vs LATER decisions will modulate proclivity to favor one over the other. The impact of the external context is influenced by prior experience with the stimulus through learned and conditioned responses that rely on brain regions classically associated with memory and expectation (hippocampus, amygdala) and those associated with failed expectation (i.e., the habenula) [65]. Memory of past experience, partly encoded in the hippocampus, allows us to ‘imagine’ various potential outcomes some time into the future and influences the value that an individual assigns to a simulated option [66]. The amygdala, through its role in processing emotionally laden stimuli [67], also affects impulsivity, DD rates, and goal-directed behaviors [19,68]. Patients with lesions in the basolateral nucleus of the amygdala (BLA) make ‘riskier’ choices, opting for large rewards NOW even at the expense of significant losses LATER. Additionally, the habenula provides inhibitory tone to DA neurons that project to the NAc when a predicted reward does not materialize or a stimulus is perceived as aversive [69]. Conversely, lateral habenula neurons are inhibited by rewarding stimuli [70], which is likely to remove tonic inhibitory influence on the PFC and NAc [71].

The decision of NOW vs LATER is also influenced by computing the available options on the basis of their intrinsic values, which relies on the orbitofrontal cortex (OFC) and the ACC [72]. The OFC processes salience attribution and is essential for changing the weighted value of a reward as a function of alternative reinforcers and the physiological state of the individual. For example, when starved the salience value of food is much greater than when satiated and this shifting value is conveyed to the NAc through the OFC [73]. Similarly, the OFC will modulate alternative choices to stimuli, such that more rewarding stimuli will be preferred over smaller ones [74] based, among others, on the subjective hedonic value of the reward [75]. Consistent with this role, lesions in the OFC are associated with repetitive behaviors that are not influenced by context or physiological state (i.e., compulsive eating or drug taking) [76]. The ACC plays a central role in error processing and conflict monitoring [77], a contribution that hinges on a form of learning that is driven by outcomes that do not match the prediction [78]. By conveying this conflict-related information to inhibitory circuits, the ACC enables inhibitory learning and facilitates impulse control [79].

Finally, the awareness of the internal state, as it relates to need, desires, or sensations and which relies on the insula [80], also modulates NOW vs LATER decisions. The insula has an overarching role across various modes of self-control, including motor impulsivity as well as reactive aggression [81].

**Model of NOW vs LATER circuits**

Based on the updated information described above we propose an integrated, albeit simplified model of the complex circuitry that instantiates NOW vs LATER decisions (Figure 1). Computational units within this broad circuit can be generally ascribed to one of three classes depending on whether they facilitate immediate or delayed responses or enable the shifting between them whenever appropriate (coded as green, red, and orange boxes in Figure 1). According to this model, the initial salience of a reward correlates with fast and large elevations of synaptic DA within the NAc [82]. The vmPFC appears to enhance reward salience calculations through its involvement in the processing of the outcome value of that reward. The OFC is critically involved in salience attribution; its main contribution is to offer predictive information about alternative options and outcomes, which is essential for shifting between NOW and LATER rewards. Meanwhile, the ACC enables inhibitory learning by keeping tabs on conflicts between predicted and actual outcomes and conveying that information to executive control/inhibitory circuits orchestrated by the dIPFC and dorsal striatal regions (caudate).

![Figure 1. Proposed model of delay discounting (DD) decisions as the result of computations performed within a circuit core that includes cortical (including the dorsolateral prefrontal cortex (dIPFC), medial PFC (mPFC), ventromedial PFC (vmPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC)) and subcortical (including the caudate and nucleus accumbens (NAc) in the dorsal and ventral striatum, respectively) regions. Additional regions and structures modulate DD computations in the core by providing interoceptive information (the somatosensory cortex (SSC) and insula), emotional states (amygdala), reward-associated memories (hippocampus), and input about reward omissions (lateral habenula). Core computations are strongly affected by tonic dopamine (DA) signals that have a strong influence on the dIPFC and favor LATER rewards. Conversely, they are also influenced by phasic DA signaling, which tends to drive the vmPFC/NAc to favor choosing a reward NOW. To ensure optimal choice, these computations are influenced by a broad array of additional, interacting modules that convey critical information about the reward itself, internal states, past experiences, and current conditions, including alternative options and the probability of occurrences. Regions that mediate immediate responses are depicted in green. Regions that mediate delayed responses are depicted in red. Regions that enable a behavioral shift between now and later responses are depicted in orange.](image-url)
This inhibitory arm of the decision-making process is facilitated in turn by tonic DA signaling sustaining activity in the dIPFC. Together with the insular cortex, which provides key information about the physiological state of the individual, the ACC also allows the circuit to estimate the level of uncertainty involved in choosing among alternative options. Finally, the amygdala, hippocampus, and lateral habenula, which provide information about emotional salience, past experience, and pertinent reward-overflow events, respectively, can all contribute to lower DD rates and an ability to shift from NOW to LATER rewards \[66,83,84\].

**Disordered NOW vs LATER processes: addiction and obesity**

Repeated exposure to instantly gratifying rewards (like drugs, instant lotteries, or junk food) can trigger or exacerbate preexisting deficits within NOW vs LATER circuits. These disruptions, which can display significant overlaps when probed in disorders such as addiction, gambling, or obesity [85–87], include: (i) decreased signaling through striatal D2Rs (leading to reduced inhibition by DA of the indirect striatocortical pathway), which is associated with reduced activity in frontal regions involved with self-control (dmPFC, dIPFC, and inferior frontal cortex), error monitoring (ACC), and salience attribution (OFC); (ii) increased sensitivity and influence from the amygdala and hippocampus toward stressful stimuli and reward-associated cues; (iii) enhanced interoceptive awareness of desire states that implicate increased activity of the insula and stronger connectivity with the default mode network (DMN), which modulates attention to inner processes; and (iv) increased expectation of reward associated with cues that relate to food (obesity) or to drugs (addiction) with a paradoxical decline in sensitivity to the actual consumption of the reward. This discrepancy between the expected versus the actual experience of consuming the reward is likely to drive the motivation to persist in the NOW behavior until the expected outcome is achieved [22].

The activity of circuits involved with NOW vs LATER processes are likely to be influenced by genetic, developmental, and environmental factors (Box 1), all of which could modulate a person's tendency to make unhealthy choices [3,88] or manifest psychiatric disorders [6,89,90] (right-side arm of Figure 2). There is strong converging evidence to propose DD to be a common core impairment across many disorders characterized by behavioral dyscontrol.

**NOW vs LATER circuitry: the linchpin of universal prevention**

DD has been suggested to represent a trans-disease process [91], which one could argue reflects an example of ‘bow-tie’ architecture. This regulatory motif, identifiable in many other complex adaptive systems [92,93], is the result of an evolutionarily optimized organization whereby a narrowing funnel of many potential inputs converges onto one or more master core processes before fanning out again into a great diversity of outputs.

A bow-tie architecture provides an economical and satisfactory heuristic model for conceptualizing NOW vs LATER decisions (Figure 2). It also has clinical implications, for it suggests that interventions focused on either protecting or strengthening the ability to delay gratification (improve self-control, reduce DD rates, reduce various components of impulsivity) could help better prevent a wide range of negative behavioral health outcomes. Supporting this is the evidence that early self-control is a robust predictor of long-term physical and behavioral health [94–96]. Moreover, several evidence-based behavioral and/or environmental interventions to strengthen various components of the ‘self-control’ network could be incorporated into resiliency-building programs [97,98].

**NOW vs LATER circuitry: treatment implications**

A better understanding of the circuits that underlie NOW vs LATER decisions could lead to significant translational benefits. A recent study, for example, has found that high discounting rates among substance-use disorder (SUD) patients in an inpatient detoxification program were predictive of shorter treatment retention [99]. On the other side of the equation, recent evidence suggests that treatment for anorexia nervosa may help restore normal rates of DD [100]. Moreover, examples of successful manipulation of DD rates for therapeutic purposes are beginning to appear in the scientific literature [101]. This general approach may be especially relevant in light of therapeutic and other technological advances that may allow us to purposefully enhance our ability to access hidden layers of cognition and help counteract operational DD deficits. A wide range of strategies to improve human decision making could hinge on largely subconsciously operating reward-substitution interventions [102], environmental context manipulations [103], and novel brain exercise paradigms like reward training [104], mindful meditation [105], or episodic future thinking, all of which have been shown to enhance PFC control function and thus a person’s
ability to generate more future-minded choice behaviors. Other areas ripe for research include better understanding and harnessing of the phenomenon of self-control depletion [106,107] and/or the systematic investigation of how the mere reframing of a reward can enhance self-control without necessarily depleting willpower [108].

The involvement of a dysfunctional insula in DD deficits provides an opportunity to test the hypothesized therapeutic potential of making implicit processes explicit. For example, it has been suggested [109] that a deficit in interoception could be responsible for impaired anticipatory behavior when an environmental situation calls for cognitive flexibility (e.g., when an abstinent cocaine addict is exposed to drug-associated cues). If this is indeed the case, it may be warranted to follow up on the evidence that contemplative practices (e.g., mindfulness) [110] or intense exercise [111] can modulate insular activation patterns and improve interoceptive function [112]. Similar techniques may also be helpful for morbidly obese individuals who may have an impaired ability to tap into such visceral data to more accurately estimate the impact of future negative consequences.

It is worth noting that easing the transfer from implicit to explicit is the hallmark of very different kinds of therapeutic approaches such as neurofeedback [113], 12-step programs [114], cognitive behavioral treatment (CBT) [115,116], and mindfulness training [117]. In the future, we might also be able to complement behavioral or lifestyle change strategies with electric or magnetic stimulation interventions targeting control or interoceptive circuits [118]. For example, repetitive transcranial magnetic stimulation (rTMS) has been successfully used in healthy human volunteers to transiently activate the dmPFC and reduce DD for delayed rewards, an effect that was associated with enhanced DA release in the dorsal striatum whereas there were no DA changes in the NAc [119]. However, these studies have been limited to the evaluation of immediate responses to acute rTMS administration; further studies are required to evaluate the permanence of rTMS-induced changes in DD and in DA release. Also, in the future, access to stimulation devices (magnetic or electrical) that can target specific PFC and ACC regions (or other cortical relevant regions such as the anterior insula) will allow investigators to more precisely modulate neuronal networks through stimulation (high frequency) or inhibition (low frequency) that optimizes behavioral choices. For example, devices that can be used to target more ventral PFC regions and use of rTMS at slow frequencies might result in reduced DA release in the ventral striatum that, when coupled with high-frequency rTMS of the dIPFC, might further reduce impulsive choices.

**Concluding remarks: policy implications**

Human health and well-being are contingent not only on the state of the NOW vs LATER circuitry but also on that of many other regulatory networks in the brain. Yet, a sharper focus on DD appears justified if we consider not only its potential benefits for universal prevention and behavioral and/or lifestyle interventions (i.e., individual policy) but also its implications vis-à-vis public policy.

**Box 1. Outstanding questions**

- Which genes influence the various components of impulsivity that contribute to DD and what are the mechanisms involved? For example, variants in the COMT gene (Val158 allele) have been associated with impulsivity and studies in transgenic mice carrying the human COMT variant have related this to increased DA release [131]. However, it is likely that many other genes make different contributions to distinct components of impulsivity.

- What are the neuronal circuits underlying the various components of impulsivity that contribute to DD (i.e., urgency, lack of perseverance, sensation seeking, and disinhibition)? While much work links impaired function of the PFC with a tendency toward impulsive behaviors and indicates the role of executive control networks in sustaining top-down control as necessary for self-regulation, the details of these interactions are not well understood [132].

- DA is recognized to play a central role in action selection between rewards of different values and probabilities. However, recent findings also show that DA signaling in the NAc correlates with behavioral preferences when the benefits overshadow the costs but not when the costs outweigh the benefits [133]. This suggests the existence of different mechanisms underlying behavioral choices for rewarding options versus those requiring sustained effort.

- What are the policy implications of emerging neurobiological data that clarify how environmental stimuli influence our proclivity toward immediate rewards or how they can facilitate sustained effort?

- What are the ethical considerations that emerge as we learn to manipulate neuronal circuits to optimize certain behaviors that are deemed to be more socially appropriate? What are the consequences for human behavioral diversity?

More specifically, gaining a better understanding of the impact of various environmental factors on NOW vs LATER behavioral choices could be an important priority area for policy research. The Construal Level Theory (CLT) of psychological distance offers an interesting perspective from which to explore this idea.

According to the CLT, as objects move from closer to distant relative to a person, the thinking about that object tends to shift from concrete (low level) to abstract (high level). Thus, it can be argued that a growing number of environmental factors have had the unintended (or intended) effect of promoting low-level while impeding high-level construal. Since this effect is bound to display vast interindividual differences, one way to try to manage the consequences of this shift would be to classify [120] and/or intervene [121] based on an individual’s construal of self-control dilemmas. For example, we could envision traits such as neuroticism and conscientiousness being investigated for their validity as construal characterization tools since they have been associated with relatively greater preferences for immediate and delayed rewards, respectively [75].

NOW vs LATER processes are relevant for public health, including the redesigning of policies and environments known to be detrimental to human well-being. For example the widespread availability of highly rewarding and affordable food with high caloric but low nutritional value facilitates inappropriate NOW choices at the expense of adverse health consequences that emerge LATER. Since such foods tend to be much more affordable than healthy foods, those in lower socioeconomic strata are more negatively affected by them. However, this negative impact is
not only influenced by cost, for the mere feeling of being poor negatively affects intertemporal choice [122]. This finding is likely to underlie a host of worrisome public health consequences. For example, overall debt and ratios of debt to income and debt to assets have all been associated with a tendency to forego medical or dental care [123]. Some have even suggested [124] that the exaggerated temporal discounting displayed by individuals with conduct disorder could ‘reflect an adaptation to chronic exposure to psychosocial insecurity during development’ [125]. Preclinical research even shows that adverse circumstances early in life can perturb the balance between D1Rs and D2Rs in the prelimbic PFC [126] and the expression of plasticity markers in the NAc [127], setting the stage for later problems with NOW (concrete) vs LATER (abstract) decisions [128,129]. Fortunately, our growing knowledge of NOW vs LATER circuitry opens new opportunities for the design of smarter environments that promote healthier behaviors. For example, and taking a cue from the successful marketing strategies that trigger automatic, emotion-based decisions, it should now be possible to design food labels that engage the same implicit mechanisms and nudge us to make better choices [103,130].

Our natural tendency to discount rewards that are less than immediate, harder to achieve, or less likely to materialize should be harnessed to make our world healthier even when it might be costly NOW, for this will be offset by much greater savings from averted health costs LATER.

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