Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Review

Resources, costs and long-term value: an integrative perspective on serotonin and meta-decision making☆

Renée S Koolschijn[1,*], Bertalan Polner[1,2,*], Julie M Hoomans[1], Roshan Cools[1,3], Eliana Vassena[1,4,*] and Hanneke EM den Ouden[1,*]

Serotonin has been associated with a wide range of neural computations and behaviours, yet an overarching function of this neurotransmitter has been hard to pinpoint. Here, we combine recent theories and findings on serotonin and propose a framework where serotonin integrates information on resource availability and state value to represent a cost–benefit trade-off at the neural level. Critically, this framework supports meta-decision making, that is, the flexible allocation of resources to decision-making. We highlight a computational and neural implementation of this framework, and through this novel, lens interpret empirical findings in the domains of controllability and persistence.

Addresses
[1] Radboud University, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands
[2] Institute of Psychology, ELTE, Eötvös Loránd University, Budapest, Hungary
[3] Radboud University Medical Center, Department of Psychiatry, the Netherlands
[4] Radboud University, Behavioural Science Institute, Nijmegen, the Netherlands

Corresponding author: den Ouden, Hanneke EM (hanneke.denouden@donders.ru.nl)
* Equal contribution.

Current Opinion in Behavioral Sciences 2024, **60**:101453

This review comes from a themed issue on **Cognitive Flexibility**

Edited by **Roshan Cools** and **Lucina Uddin**

For complete overview of the section, please refer to the article collection, "Cognitive Flexibility (2024)"

Available online 4 October 2024

Received: 14 June 2024; Revised: 13 September 2024; Accepted: 13 September 2024

https://doi.org/10.1016/j.cobeha.2024.101453

Introduction

The major ascending modulatory neurotransmitters (dopamine, serotonin, noradrenaline, and acetylcholine) share their characteristic structural organisation, with a single brain stem 'source' that projects widely throughout the cortex and subcortical structures. The diffuse 'broadcasting' nature of these signals make them perfectly placed to signal important, global computational variables to shape behaviour. Of these modulatory neurotransmitters, serotonin remains the most elusive in terms of our thinking of such a putative 'global' function. Rather, serotonin has been implicated in a wide and sometimes seemingly contradictory range of cognitive and affective functions [1–11]. Medications acting on the serotonin system are the first-line treatment in a similarly wide range of mental health disorders [12]. Serotonin's elusive nature has at least two sources. One factor is the complexity of the serotonergic system, with no fewer than 14 known receptor subtypes in the brain, compared with, for example, 'only' five dopamine receptor subtypes. To further complicate matters, distinct dorsal raphe nucleus (DRN) populations (the primary source of serotonergic projections) appear to project to distinct cortical and subcortical regions, with different or even opponent functional characteristics [13]. Indeed, the spatial distribution of different serotonin receptor subtypes is associated with distinct cognitive processes, including impulsivity and negative biases [14]. Furthermore, activity evoked by DRN stimulation has been suggested to reflect functional rather than direct anatomical connectivity in anaesthetised animals [15]. However, in awake animals, the effects of DRN stimulation do map more closely onto anatomical connections [16,17]. To further complicate matters, distinct DRN populations appear to project to distinct cortical and subcortical regions, with different or even opponent functional characteristics [14]. A second, and perhaps even more important factor, is that until relatively recently, our tools to measure and manipulate serotonin

☆ Guest Editor, Roshan Cools had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Lucina Uddin.

with high specificity have been limited, hampering its functional characterisation. It is only in recent years that reliable measures of serotonin release and activity have become readily available, such as optogenetic techniques that allow for reliable tagging and stimulation of serotonin neurons and voltammetry measurements to track release in animals [18] and humans [19]. These advances have lent great momentum to serotonin research, with over 65 000 published papers in the last decade (source: PubMed). In this abundance of empirical data, serotonin has been associated with aversive processing, behavioural inhibition [6,8], patience for rewards [20], reward signalling [21], prediction error coding [22], uncertainty [11], and recently, tracking average reward over extended period [23]. A major and persistent challenge has been to synthesise this long list of seemingly divergent findings under a single theoretical framework based on a shared underlying computational principle.

In this review, we build on previous proposals for unifying serotonergic function [10,18,24–28] and present a novel integrative explanation of serotonin's function in meta-decision-making. Meta-decision-making refers to the optimisation of *how* we select and integrate information to come to our decisions, that is, decisions about how decisions are made. Thus, meta-decisions involve the evaluation of the costs and benefits of a particular decision strategy [29] and imply decisions about whether to stick to a decision policy or switch to a different one. We discuss our framework in a high-level, conceptual manner and do not commit to one particular mathematical formalisation of the meta-decision construct but instead recognise that there are multiple alternative formal accounts of how serotonin regulates meta-decision-making. Thus, we focus on the broad scope of the meta-decision account of serotonin and raise various qualitative (rather than quantitative) predictions for effects of serotonin.

Through this lens, a variety of the prior findings on serotonin function can be interpreted as tracking of costs (delay, uncertainty, punishment, cognitive, and physical effort) or benefits (momentary rewards, rewards over an extended period), leading to the idea that serotonin may support meta-decision-making by signalling the integration of costs and benefits over extended time scales. In this view, serotonin may modulate arbitration between more frugal versus more resource-intensive decision styles and discourage or promote persistence. Such meta-decisions require not only the tracking of rewards and punishments over time but also of statistical features of the environment such as its controllability [30] and environmental richness and the individual differences in goals and skills that impact these quantities. Notably, these parameters thus represent subjective estimates, affected by the individual's beliefs, prior experiences, and mood [28,31], rather than being objective quantities.

We first review key prior evidence demonstrating a role of serotonin in resource cost and reward signalling and discuss two recent theories that aim to unify serotonergic function [18,24]. We integrate these theories with recent evidence suggesting serotonin is involved in the representation of average environmental 'richness' and propose serotonin represents a cost–benefit integration over time that informs meta-decisions. We then discuss a possible neurocomputational mechanism underlying this cost–benefit integration [27] and conclude by defining the scope of this novel meta-decision account of serotonin, highlighting future avenues of investigation in the domains of controllability and persistence.

Aversive processing, anticipatory responding, and resource investment

Serotonin has long been hypothesised to play a key role in aversive processing and inhibitory responding. For instance, earlier accounts have linked serotonergic signalling to anticipatory responses to threat [1], behavioural inhibition [32], waiting for reward [33], punishment prediction errors (as a dopamine opponent) [34], or average punishment rates [35]. Other accounts have attempted to reconcile these different explanations by considering serotonin in light of hardwired coupling between punishment prediction errors and behavioural inhibition [4,36,37]. This hypothesis has been incorporated into theories where serotonin is proposed to act as an opponent to dopamine [4,5,35]. Over the years, ample evidence supporting the aversive processing/inhibition account for serotonergic function has come from studies in both humans and animal models [7–9,36]. A second line of research, primarily in rodents and nonhuman primates, has emphasised the role of serotonin in anticipation [21] and anticipatory responding in the context of rewards, specifically active waiting and patience for reward [2,20,33]. For example, activation of DRN serotonin afferents both promotes and is necessary for successful waiting for a reward [33,38,39], while low levels of serotonin promote impulsive responding when rewards or punishments are at stake [6]. These observations related to patience can be considered a particular example of aversive inhibitory responding, as outlined previously [35]. Within this framework, serotonin decreases the (aversive) cost of time, that is, the time that is spent exerting patience whilst choosing to withhold a response.

Distilling from these observations, with particular emphasis on the robust finding that serotonin increases preparedness to wait, thus reducing sensitivity to the opportunity cost of time, Doya et al. propose that the unifying function of serotonin is to signal the availability of time and resources. In doing so, higher serotonin levels promote the willingness to 'spend' time or other resources [18]. This framework accommodates observations beyond anticipatory responding to aversive and

rewarding stimuli; for example, a signal of increased availability of resources could favour more exploration and learning, explaining serotonin's role in cognitive flexibility [22], promote the willingness to exert physical effort [40], and the tendency for deliberation [41]. Within this framework, less serotonin would favour more shallow search strategies and the pruning of decision trees [4] and freezing rather than active coping responses when presented with acute threat [17,42]. We note, however, that a potential alternative hypothesis is that high reward environments could instead favour a low-cost Pavlovian strategy, as 'errors' do not lead to loss of a rare opportunity.

Reward and long-range average value

While the above 'time and resource availability' account can account for a wide range of observations related to serotonin [18], it does not address findings implicating serotonin in the representation of reward and punishment in the absence of variability in costs or resource investment. Numerous studies demonstrate serotonin's involvement in the processing of rewards and the learning of value, that is, the average of rewards and punishments over a longer timescale [10,43]. For instance, DRN neuron activity in both rodents and macaques is modulated by the value of expected and received rewards [21,44] and DRN serotonin neuron activity covaries with both positive and negative reward prediction errors in the context of reversal learning [22]. In macaques, functional Magnetic Resonance Imaging (fMRI)-derived DRN activity was found to track recent reward history or reward state [45], and similarly, in humans, serotonin levels in substantia nigra tracked offer value in social decision-making [19]. Finally, serotonergic signalling in response to punishment [7,22] could in some cases be interpreted as the rewarding properties of relief from an aversive stimulus [24,46,47].

Based on these findings implying serotonin in processing reward on both longer and shorter timescales, it has been suggested that serotonin signals a long-running value signal. Harkin et al. recently formalised this hypothesis in a biologically constrained neurocomputational model of DRN firing, where serotonin encodes state value, quantified as the temporally discounted average of future expected rewards and punishments, approximated from past experience [24]. In other words, in this model, DRN serotonin signalling keeps track of the reward state of the environment, that is, how good the current environment is. This model reproduces several characteristic activity patterns of DRN, including phasic responses to rewards, reward-predicting cues, and imminent relief of punishment [24]. Furthermore, the model also captures tonic serotonin dynamics over longer timescales across periods of rewards or punishments. As we shall see, such a, putatively serotonergic, state value signal might provide a heuristic for deciding on effort or resource investment [48].

In summary, the 'time and resource availability' and 'state value' theories each capture important aspects of serotonin function. Doya et al. present a high-level conceptual framework that aims to explain a wide range of relevant behaviours but does not provide specifics regarding the neural computations [18]. In contrast, Harkin et al. provide a precise model of DRN serotonin firing and the computations this embodies in the context of trace conditioning experiments but remain agnostic about how this expected value signal might influence learning and decision-making behaviour more broadly [24]. While it is possible that the suggested 'resource availability' and 'state value' accounts are indeed separate aspects of serotonin signalling subserved by different neural circuits, we believe that there is explanatory merit in integrating these ideas, as we will set out below.

Integrating serotonin theories of resource availability and state value

We propose that the theories discussed above embody two aspects of serotonergic function that can be combined into a single model of serotonin that *integrates* these quantities of resource availability and state value into a cost-benefit trade-off to inform flexible allocation of resources to decision-making, that is, meta-decisions [29,48,49]. From psychology to economics, the overarching consensus is that choice is not a unitary process. Rather, efficient decision-making requires a 'meta-optimisation' that accounts for the benefits and costs of the internal processes. This meta-optimisation involves the arbitration between different behavioural strategies at any timescale, each associated with their respective benefits of obtaining a potential reward, pitted against the internal and external resources and opportunity costs [29].

A first hint that serotonin could be crucial to such meta-decision processes is its apparent role in the evaluation of the value of a current offer relative to the average, long-term reward value or 'richness' of the environment. This evaluation approximates *opportunity cost*, that is, how worthwhile it is to invest in the current opportunity, knowing that it will make one miss out on other opportunities [48,50]. Recordings from rodents and non-human primates show that DRN neurons signal not only various features of the reward on offer, like value or uncertainty [11,20,51], but also the average reward rate, that is, richness, of the environment [51]. In another study, fMRI-derived DRN activity related to the value of an offer relative to the environment, and the average richness of the environment influenced the willingness to invest time to obtain rewards [23]. In addition, changes in the value of the environment are tracked by DRN, and DRN activity relates to transitions in

motivational states [52]. Finally, when DRN activity is disrupted, sensitivity to the richness of the environment decreases. Taken together, these findings make a case for DRN to guide decisions to invest resources or not [23] or to engage or disengage in the task at hand.

The work by Khalighinejad et al. [23] provides two further important pieces of evidence in support of serotonin's involvement in resource allocation. First, DRN tracked the intertrial interval (ITI), which related to the relative scarcity of reward. Then, when serotonin was modulated through semi-chronic administration of a selective serotonin reuptake inhibitor (SSRI), subjects became more willing to invest time to obtain reward, particularly when opportunities to obtain benefits were scarcer. This role of serotonin appears to extend to allocation of cognitive resources, as pharmacological manipulations of serotonin in rats changed decision boundaries for cognitive effort allocation [53]. These findings suggest that serotonin signals integrated information on costs, benefits, reward history, and environment to guide resource allocation, thus supporting meta-decision making.

Neurobiological implementation

In line with the idea that the allocation of resources — such as time and effort — is optimised depending on the expected return [49,54,55], we here propose that the underlying computational principle of serotonergic function is the long-term integration of cost and benefits to support meta-decisions. This requires optimising decision-relevant variables, such as reward prediction (combining reward value and uncertainty) and required effort [20,51,56] at the momentary time scale while optimising the appropriate meta-level decision-policy, influencing decisions at the temporally extended time scale. This dynamic momentary optimisation regulates short-term decisions to allocate resources (e.g. cognitive and physical effort, time), while the meta-level optimisation controls the overall resource allocation policy depending on the extended context (e.g. how much of these resources should be allocated on average), arbitrating between a more frugal and a more generous allocation policy, depending on the expected benefit.

Notably, momentary decisions have been associated with dopamine and noradrenaline release [57–59] in concert with the dorsal anterior cingulate cortex (dACC) [49,56,60,61]. A recent computational framework implemented this theoretical view through a neurobiologically plausible architecture, proposing reinforcement meta-learning as the critical computation linking momentary and extended timescales [54,55]. This model captures cost–benefit computations at the momentary level through catecholamine action, while serotonin embodies the critical link between momentary and extended timescales by modulating catecholamine release at a longer timescale [27]. In this model, higher serotonin levels mitigate the cost of spending resources (via catecholamine release). Concretely, lower serotonin levels lead to an overall more frugal catecholaminergic management policy compared to when serotonin levels are high. Such a frugal policy results in increased cost of releasing catecholamines, leading to reduced exertion. For further details on the model, including some critical predictions, see Box 1. We note that the algorithmic implementation of this particular model is discussed elsewhere [27,55], whilst here we will restrict ourselves to a brief conceptual description. Compellingly, the notion that serotonin acts on more extended timescales generally concurs with the proposal linking serotonin, mood, and decision-making [28], and the finding that serotonin mediates the interaction between mood and reward [31].

In sum, serotonin may act as a high-level neuromodulator of meta-level optimisation of the integration of all relevant momentary variables, thus supporting meta-decisions. This way, dynamic momentary integration leads to long-term emergence of temporally extended behaviours that can be shifted toward more resource-heavy or frugal policies in terms of cost–benefit running average. While noradrenaline and dopamine are critical for short-sighted incentive-driven responding and invigoration, serotonin may promote far-sighted meta-level integration and decisions to pay a higher resource cost and persist despite the costs over a longer timescale. Such meta-decisions to persist/invest versus give up/reject then result from a combination of information about cognitive, energetic and time resources, and features of the environment such as environmental richness. As such, shifts in modes of decision-making become an emergent property of the system, without postulating an additional control or 'meta-decision' homunculus.

Interpreting serotonin's role in controllability and persistence through the lens of meta-decision making

We have introduced an integrative proposal for serotonergic function in meta-decision making by building on theoretical and empirical accounts in the domains of aversive processing, anticipatory responding, reward learning, and resource investment. We now highlight two other topical cognitive domains where serotonin is suggested to play an important role and for which the proposed framework yields testable predictions.

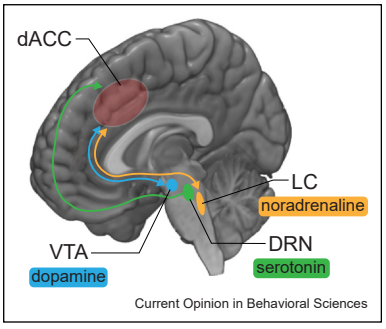
A factor that should normatively influence whether to invest resources in a particular action is whether that

Box 1 The Reinforcement Meta-Learner (RML) model.

The neurobiologically plausible RML model performs dynamic tracking of multiple external (i.e. environmental) and internal variables, such as reward expected value, temporal expectations, volatility, information value, and required effort [55,78]. This dynamic momentary optimisation regulates short-term decisions to allocate resources, such as cognitive and physical effort or time, when engaging in a specific task. Based on this multivariate and dynamic optimisation of momentary variables, the meta-learning architecture leads to the emergence of a temporally extended decision policy consistent with the proposed meta-decision process. Importantly, in this model, momentary optimisation relies on bidirectional signalling of relevant variables (such as reward, punishments, volatility) via input of dopamine and noradrenaline, from the ventral tegmental area and locus coeruleus, respectively, to the dACC [55], and in turn dACC top-down control of noradrenaline and dopamine release (Figure 1). Hereby, serotonin may provide the critical link between momentary and meta-level timescales through the modulation of dopamine and noradrenaline release at a slower timescale [27].

Qualitative simulations of this computational framework show that depletion of a putative serotonergic meta-parameter leads to reduced willingness to exert effort for rewards [27]. These simulations match evidence of reduced willingness to exert effort for reward in patients with major depressive disorder [79,80] — where serotonergic medication typically alleviates symptoms — and mirrors evidence of increased willingness to exert effort after chronic serotonin reuptake inhibition in healthy individuals [40].

Figure 1



Schematic overview of the RML model (Figure adapted from Ref. [55] with author permission).

action is going to matter for obtaining the desired outcome [29,62]. Therefore, meta-decisions should factor in whether an agent can control its environment [63]. The well-documented role of serotonin in the phenomenon of learned helplessness suggests that serotonin may indeed play a role in signalling environmental controllability [64–66]. Within the framework outlined here, an increase in serotonin should boost investments of resources in environments with high controllability. Indeed, there is long-standing evidence showing that learned helplessness can be reversed with chronic SSRI administration [67]. However, this is at odds with experimental data showing that uncontrollable stress in fact *increases* DRN serotonin release [64,68]. Future studies could investigate this discrepancy at the microcircuit level [18] using computational and empirical frameworks that disentangle controllability from uncertainty and environmental reward richness [30,63]. An interesting prediction of the framework would be that serotonin modulates the reward richness experienced by an individual and that this in turn modulates one's sense of controllability (rather than directly modulating estimated controllability). Another important question to be addressed is whether serotonin primarily promotes exploratory action necessary for the detection of control or rather mediates the effects of controllability estimates on the recruitment of different decision strategies [69].

The idea that serotonin integrates information about benefits and costs toward a long-term goal also implies an important role of serotonin in effortful persistence. Most rewarding outcomes are obtained with effort, a quantity considered as a cost to be minimised in most models of motivated control [49,55]. Serotonin may mitigate these momentary costs of effort and sustain a costly behavioural policy when justified by the rewards on the long-term horizon (c.f. [27]). Importantly, this dynamic may emerge from the interplay of momentary catecholamine exertion and sustained serotonin levels, balancing between strategies (higher willingness to pay, resulting in more persistence and higher effort, but also more cognitively effortful decision-making strategies). An open question is whether tonic serotonin levels indeed orchestrate the balance between different decision strategies and to what extent momentary DRN firing contributes to triggering shifts in such strategies.

A critical prediction of the framework is that serotonin would not boost persistence per se. Rather, it mediates effortful persistence or resource-intensive decision strategies, as a function of the expected value of effort that itself depends on meta-decision parameters like individual representations of environmental richness and controllability. Precisely how serotonin affects this computation warrants further research; one possibility is that serotonergic signalling reduces the cost parameter in the cost–benefit evaluation (as proposed by Ref. [27]) in line with empirical evidence that serotonergic medication promotes effort exertion [40]. Another possibility is that serotonin does not mediate effortful persistence itself but boosts (cognitively) frugal strategies as a function of the cost parameter, in line with previous theorising [4] and the observation that uncontrollable stress induces serotonin release [68]. According to this account, serotonin release would inhibit effortful

decision strategies in anticipation of aversive outcomes, instead promoting low-cost, in particular, aversive Pavlovian, strategies, but only when effort costs are high, for example, because the current environment is uncontrollable. Indeed, optogenetic activation of serotonin neurons led to increased effortful reward exploitation in a foraging task [70] and serotonergic medication given to patients with obsessive-compulsive disorder improved effortful switching in a deterministic reversal learning task [71]. This prediction could be tested in experiments where both required (cognitive) effort or resource investment and reward richness are manipulated independently, and combining such a study design with a serotonergic manipulation, for example, optogenetic stimulation in rodents or SSRI administration in humans. Another phenomenon that similarly stretches across momentary and long-term timescales is fatigue [72]. Considering the link with effort exertion and the fact that fatigue can be regarded both as a momentary cost as well as a long-term build-up, future studies could investigate whether DRN dynamics impact experienced fatigue, and whether this could be accounted for by the proposed meta-decision integrative function for serotonin.

Final considerations

In this brief review, we have focused on the cognitive and computational role of serotonin in motivated decision-making. While we did not discuss the large literature on serotonin and social cognition and behaviour [73,74], the meta-decision processes proposed here may well generalise to social decision-making. Indeed, a recent voltammetry study in humans shows tantalising evidence that serotonin release in substantia nigra tracks social context as well as value signals during economic exchange games [19]. We have also not addressed the role of serotonin in brain development and plasticity, nor discussed ensuing long-term effects on behaviour and cognition [75,76]. However, we believe that this is another fruitful avenue to investigate, as these long-term effects on e.g. resilience likely interact with the meta-decision making framework proposed here [77]. Finally, we want to conclude by once again acknowledging the complexity of the serotonergic neuromodulatory system and emphasise that considering the functional role of differentially spatially distributed serotonin receptor networks [13] will be necessary to further finetune the proposed framework. We hope that despite its necessary omissions, this updated proposal for serotonergic function will spark further investigations and theorising toward an overarching computational role for serotonin.

Funding

This work was supported by an European Research Council Advanced Grant, Brussels Belgium (CHEMCONTROL 101054532) to RC, a Dutch Research Council Open Competition Xs grant (NWO 406. XS.04.129) to EV and a Dutch Research Council 'Vidi' grant (NWO 016.175.450) to HdO.

CRediT authorship contribution statement

Renée Koolschijn: Writing – original draft, Writing – review & editing; **Bertalan Polner:** Writing – original Draft, Writing – review & editing; **Julie Hoomans:** Writing – review & editing**; Roshan Cools:** Conceptualization, Writing – review & editing, Funding acquisition**; Eliana Vassena:** Conceptualisation, Writing – original draft, Writing – review & editing, Funding acquisition; **Hanneke den Ouden:** Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

RC serves as a consultant for Roche LtD but does not hold any shares. All other authors have no conflicts of interest to report.

Acknowledgements

We would like to thank all members of the Stress & Control meeting at the Donders Institute for our inspiring and helpful discussions.

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. Deakin J, Graeff FG: **5-HT and mechanisms of defence**. *J Psychopharmacol* 1991, **5**:305-315.
2. Doya K: **Metalearning and neuromodulation**. *Neural Netw* 2002, **15**:495-506.
3. Cools R, Roberts AC, Robbins TW: **Serotoninergic regulation of emotional and behavioural control processes**. *Trends Cogn Sci* 2008, **12**:31-40.
4. Dayan P, Huys QJM: **Serotonin, inhibition, and negative mood**. *PLoS Comput Biol* 2008, **4**:e4.
5. Boureau Y-L, Dayan P: **Opponency revisited: competition and cooperation between dopamine and serotonin**. *Neuropsychopharmacology* 2011, **36**:74-97.
6. Faulkner P, Deakin JFW: **The role of serotonin in reward, punishment and behavioural inhibition in humans: insights from studies with acute tryptophan depletion**. *Neurosci Biobehav Rev* 2014, **46**:365-378.
7. Cohen JY, Amoroso MW, Uchida N: **Serotonergic neurons signal reward and punishment on multiple timescales**. *eLife* 2015, **4**:e06346.
8. Crockett M, Cools R: **Serotonin and aversive processing in affective and social decision-making**. *Curr Opin Behav Sci* 2015, **5**:64-70.
9. den Ouden HEM, Swart JC, Schmidt K, Fekkes D, Geurts DEM, Cools R: **Acute serotonin depletion releases motivated inhibition of response vigour**. *Psychopharmacol* 2015, **232**:1303-1312.
10. • Liu Z, Lin R, Luo M: **Reward contributions to serotonergic functions**. *Annu Rev Neurosci* 2020, **43**:141-162.

Comprehensive review of experimental data on DRN serotonin activity, reward processing, and behaviour and integrates these findings with theory proposing that serotonin signals 'beneficialness' (Luo et al., 2016) with experimental findings.

11. • Grossman CD, Bari BA, Cohen JY: **Serotonin neurons modulate learning rate through uncertainty**. *Curr Biol* 2022, **32**:586-599 e7.
In a foraging task, activity of DRN serotonin neurons related to expected and unexpected uncertainty. Inhibition of serotonin neurons modulated choice behaviour and computational modelling suggested this was due to disruption of meta-learning.

12. Gosmann NP, Costa M de A, Jaeger M de B, Motta LS, Frozi J, Spanemberg L, Manfro GG, Cuijpers P, Pine DS, Salum GA: **Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive, and stress disorders: a 3-level network meta-analysis**. *PLoS Med* 2021, **18**:e1003664.

13. Ren J, Friedmann D, Xiong J, Liu CD, Ferguson BR, Weerakkody T, DeLoach KE, Ran C, Pun A, Sun Y, *et al*.: **Anatomically defined and functionally distinct dorsal raphe serotonin sub-systems**. *Cell* 2018, **175**:472-487 e20.

14. • Salvan P, Fonseca M, Winkler AM, Beauchamp A, Lerch JP, Johansen-Berg H: **Serotonin regulation of behavior via large-scale neuromodulation of serotonin receptor networks**. *Nat Neurosci* 2023, **26**:53-63.
This study shows that activation of dorsal raphe serotonin neurons differentially modulates the functional connectivity of different receptor networks. In humans, these networks were separately associated with serotonin effects on impulsivity and negative biases, suggesting that heterogeneous effects of serotonin regulating multiple aspects of human behaviour may occur through modulation of different receptor networks.

15. Grandjean J, Corcoba A, Kahn MC, Upton AL, Deneris ES, Seifritz E, Helmchen F, Mansuy IM, Mann EO, Rudin M, *et al*.: **A brain-wide functional map of the serotonergic responses to acute stress and fluoxetine**. *Nat Commun* 2019, **10**:350.

16. • Hamada HT, Abe Y, Takata N, Taira M, Tanaka KF, Doya K: **Optogenetic activation of dorsal raphe serotonin neurons induces brain-wide activation**. *Nat Commun* 2024, **15**:4152.
In awake mice, optogenetic stimulation of DRN serotonin neurons results in brain-wide activity that aligns with DRN projection topography, while in anaesthetised mice, brain-wide activity was decreased following the same stimulation protocol.

17. • Seo C, Guru A, Jin M, Ito B, Sleezer BJ, Ho Y-Y, Wang E, Boada C, Krupa NA, Kullakanda DS, *et al*.: **Intense threat switches dorsal raphe serotonin neurons to a paradoxical operational mode**. *Science* 2019, **363**:538-542.
Optogenetic activation of serotonin neurons in DRN has differential effects on movement depending on the level of threat associated with the environment, suggesting DRN mediates switching between behavioural strategies depending on context.

18. •• Doya K, Miyazaki KW, Miyazaki K: **Serotonergic modulation of cognitive computations**. *Curr Opin Behav Sci* 2021, **38**:116-123.
In this review, the authors take an evolutionary perspective and propose an integrative function for serotonin as signalling time and resource availability to support a wide range of findings relating serotonin to actions, perception, learning, and development.

19. • Batten SR, Bang D, Kopell BH, Davis AN, Heflin M, Fu Q, Perl O, Ziafat K, Hashemi A, Saez I, *et al*.: **Dopamine and serotonin in human substantia nigra track social context and value signals during economic exchange**. *Nat Hum Behav* 2024, **8**:718-728, https://doi.org/10.1038/s41562-024-01831-w.
Using newly developed voltammetry in patients with Parkinson's disease, the authors demonstrate that serotonin in substantia nigra tracks value during the ultimatum game. Provides evidence for the association between serotonin and value in humans with unprecedented temporal and spatial precision.

20. Miyazaki K, Miyazaki KW, Yamanaka A, Tokuda T, Tanaka KF, Doya K: **Reward probability and timing uncertainty alter the effect of dorsal raphe serotonin neurons on patience**. *Nat Commun* 2018, **9**:2048.

21. Nakamura K, Matsumoto M, Hikosaka O: **Reward-dependent modulation of neuronal activity in the primate dorsal raphe nucleus**. *J Neurosci J Soc Neurosci* 2008, **28**:5331-5343.

22. Matias S, Lottem E, Dugué GP, Mainen ZF: **Activity patterns of serotonin neurons underlying cognitive flexibility**. *eLife* 2017, **6**:e20552.

23. •• Khalighinejad N, Manohar S, Husain M, Rushworth MFS: **Complementary roles of serotonergic and cholinergic systems in decisions about when to act**. *Curr Biol* 2022, **32**:1150-1162 e7.
This study in macaques shows that the average value of the environment is tracked by DRN neuron firing and influences the amount of time macaques are willing to invest to obtain reward. Pharmacologically manipulating serotonin levels increased subjects' willingness to invest time in a relatively scare environment.

24. •• Harkin EF, Grossman CD, Cohen JY, Béïque J-C, Naud R: **Serotonin Predictively Encodes Value**; biorxiv; 2023..
The authors propose serotonergic activity serves 'value prediction' and present a biologically constrained neurocomputational model that incorporates reinforcement learning and prediction coding and captures characteristic firing patterns of the DRN measured in mice during trace conditioning experiments.

25. • Ligneul R, Mainen ZF: **Serotonin**. *Curr Biol* 2023, **33**:R1216-R1221.
In this primer, the authors present an overview of serotonin's neurophysiology and neuroanatomy and its role in pharmacological interventions. Within this context, they discuss theories of serotoninergic function and highlight open questions.

26. Luo M, Li Y, Zhong W: **Do dorsal raphe 5-HT neurons encode "beneficialness"?** *Neurobiol Learn Mem* 2016, **135**:40-49.

27. Silvetti M, Baldassarre G, Caligiore D: **A computational hypothesis on how serotonin regulates catecholamines in the pathogenesis of depressive apathy**. In *Multiscale Models of Brain Disorders*. Edited by Cutsuridis V. Springer International Publishing; 2019:127-134.

28. Eldar E, Rutledge RB, Dolan RJ, Niv Y: **Mood as representation of momentum**. *Trends Cogn Sci* 2016, **20**:15-24.

29. Boureau Y-L, Sokol-Hessner P, Daw ND: **Deciding how to decide: self-control and meta-decision making**. *Trends Cogn Sci* 2015, **19**:700-710.

30. Ligneul R: **Prediction or causation? Towards a redefinition of task controllability**. *Trends Cogn Sci* 2021, **25**:431-433.

31. •• Michely J, Eldar E, Martin IM, Dolan RJ: **A mechanistic account of serotonin's impact on mood**. *Nat Commun* 2020, **11**:2335.
SSRI-induced increased serotonin levels amplify the effect of mood on reward learning in humans. The authors apply a computational model on mood and reward (Eldar et al., 2016) to suggest that this effect is due to enhanced subjective reward perception induced by serotonin.

32. Soubrié P: **Reconciling the role of central serotonin neurons in human and animal behavior**. *Behav Brain Sci* 1986, **9**:319-335.

33. Miyazaki KW, Miyazaki K, Doya K: **Activation of dorsal raphe serotonin neurons is necessary for waiting for delayed rewards**. *J Neurosci* 2012, **32**:10451-10457.

34. Daw ND, Kakade S, Dayan P: **Opponent interactions between serotonin and dopamine**. *Neural Netw Off J Int Neural Netw Soc* 2002, **15**:603-616.

35. Cools R, Nakamura K, Daw ND: **Serotonin and dopamine: unifying affective, activational, and decision functions**. *Neuropsychopharmacology* 2011, **36**:98-113.

36. Geurts DEM, Huys QJM, Ouden HEM, den Ouden HEM, den Cools R: **Serotonin and aversive Pavlovian control of instrumental behavior in humans**. *J Neurosci* 2013, **33**:18932-18939.

37. Crockett MJ, Clark L, Robbins TW: **Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans**. *J Neurosci* 2009, **29**:11993-11999.

38. Fonseca MS, Murakami M, Mainen ZF: **Activation of dorsal raphe serotonergic neurons promotes waiting but is not reinforcing**. *Curr Biol* 2015, **25**:306-315.

39. Miyazaki KW, Miyazaki K, Tanaka KF, Yamanaka A, Takahashi A, Tabuchi S, Doya K: **Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards**. *Curr Biol* 2014, **24**:2033-2040.

40. Meyniel F, Goodwin GM, Deakin JW, Klinge C, MacFadyen C, Milligan H, Mullings E, Pessiglione M, Gaillard R: **A specific role for serotonin in overcoming effort cost**. *eLife* 2016, **5**:e17282.

41. Michely J, Martin IM, Dolan RJ, Hauser TU: **Boosting serotonin increases information gathering by reducing subjective cognitive costs**. *J Neurosci* 2023, **43**:5848-5855.

42. Cryan JF, Mombereau C, Vassout A: **The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice**. *Neurosci Biobehav Rev* 2005, **29**:571-625.

43. Luo Q, Kanen JW, Bari A, Skandali N, Langley C, Knudsen GM, Alsiö J, Phillips BU, Sahakian BJ, Cardinal RN, *et al.*: **Comparable roles for serotonin in rats and humans for computations underlying flexible decision-making**. *Neuropsychopharmacology* 2024, **49**:600-608.

44. Zhong W, Li Y, Feng Q, Luo M: **Learning and stress shape the reward response patterns of serotonin neurons**. *J Neurosci* 2017, **37**:8863-8875.

45. • Wittmann MK, Fouragnan E, Folloni D, Klein-Flügge MC, Chau BKH, Khamassi M, Rushworth MFS: **Global reward state affects learning and activity in raphe nucleus and anterior insula in monkeys**. *Nat Commun* 2020, **11**:3771.
First paper in a range of studies (see also Khalighinejad et al., 2022; Priestley et al., 2024) linking DRN activity to average value of the environment. Choice behaviour in macaques is influenced by estimates of environmental richness, which in turn correlate with DRN activity measured using fMRI.

46. Navratilova E, Porreca F: **Reward and motivation in pain and pain relief**. *Nat Neurosci* 2014, **17**:1304-1312.

47. Solomon RL, Corbit JD: **An opponent-process theory of motivation: I. Temporal dynamics of affect**. *Psychol Rev* 1974, **81**:119-145.

48. Niv Y, Daw ND, Joel D, Dayan P: **Tonic dopamine: opportunity costs and the control of response vigor**. *Psychopharmacol* 2007, **191**:507-520.

49. Shenhav A, Botvinick MM, Cohen JD: **The expected value of control: an integrative theory of anterior cingulate cortex function**. *Neuron* 2013, **79**:217-240.

50. Guitart-Masip M, Beierholm UR, Dolan R, Duzel E, Dayan P: **Vigor in the face of fluctuating rates of reward: an experimental examination**. *J Cogn Neurosci* 2011, **23**:3933-3938.

51. Feng Y-Y, Bromberg-Martin ES, Monosov IE: **Dorsal Raphe Neurons Signal Integrated Value During Multi-Attribute Decision-M`aking**; 2023, doi:⟨10.1101/2023.08.17.553745⟩.

52. Priestley L, Chiew M, Shahdloo M, Mahmoodi A, Cheng X, Cleveland R, Rushworth M, Khalighinejad N: **Dorsal Raphe Nucleus Controls Motivational State Transitions in Monkeys**; 2024, doi:⟨10.1101/2024.02.13.580224⟩.

53. Hales CA, Silveira MM, Calderhead L, Mortazavi L, Hathaway BA, Winstanley CA: **Insight into differing decision-making strategies that underlie cognitively effort-based decision making using computational modeling in rats**. *Psychopharmacol* 2024, **241**:947-962.

54. •• Silvestrini N, Musslick S, Berry AS, Vassena E: **An integrative effort: bridging motivational intensity theory and recent neurocomputational and neuronal models of effort and control allocation**. *Psychol Rev* 2023, **130**:1081-1103.
A critical comparison of the biologically plausible computational framework of RML to prominent theories of effort allocation during motivated behaviour.

55. Silvetti M, Vassena E, Abrahamse E, Verguts T: **Dorsal anterior cingulate-brainstem ensemble as a reinforcement meta-learner**. *PLoS Comput Biol* 2018, **14**:e1006370.

56. Chong TT-J, Apps M, Giehl K, Sillence A, Grima LL, Husain M: **Neurocomputational mechanisms underlying subjective valuation of effort costs**. *PLoS Biol* 2017, **15**.

57. Chong TT-J, Bonnelle V, Manohar S, Veromann K-R, Muhammed K, Tofaris GK, Hu M, Husain M: **Dopamine enhances willingness to exert effort for reward in Parkinson's disease**. *Cortex J Devoted Study Nerv Syst Behav* 2015, **69**:40-46.

58. Salamone JD, Correa M, Yohn S, Lopez Cruz L, San Miguel N, Alatorre L: **The pharmacology of effort-related choice behavior: dopamine, depression, and individual differences**. *Behav Process* 2016, **127**:3-17.

59. Varazzani C, San-Galli A, Gilardeau S, Bouret S: **Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys**. *J Neurosci* 2015, **35**:7866-7877.

60. Silvetti M, Seurinck R, Verguts T: **Value and prediction error estimation account for volatility effects in ACC: a model-based fMRI study**. *Cortex* 2013, **49**:1627-1635.

61. Vassena E, Holroyd CB, Alexander WH: **Computational models of anterior cingulate cortex: at the crossroads between prediction and effort**. *Front Neurosci* 2017, **11**:316.

62. Dorfman HM, Gershman SJ: **Controllability governs the balance between Pavlovian and instrumental action selection**. *Nat Commun* 2019, **10**:5826.

63. Ligneul R, Mainen ZF, Ly V, Cools R: **Stress-sensitive inference of task controllability**. *Nat Hum Behav* 2022, **6**:812-822.

64. Baratta MV, Seligman MEP, Maier SF: **From helplessness to controllability: toward a neuroscience of resilience**. *Front Psychiatry* 2023, **14**.

65. Christianson JP, Greenwood BN: **Stress-protective neural circuits: not all roads lead through the prefrontal cortex**. *Stress* 2014, **17**:1-12.

66. Maier SF, Seligman MEP: **Learned helplessness at fifty: insights from neuroscience**. *Psychol Rev* 2016, **123**:349-367.

67. Martin P, Soubrié P, Puech AJ: **Reversal of helpless behavior by serotonin uptake blockers in rats**. *Psychopharmacol* 1990, **101**:403-407.

68. Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF: **Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus**. *Nat Neurosci* 2005, **8**:365-371.

69. Cools R: **Chemistry of the adaptive mind: lessons from dopamine**. *Neuron* 2019, **104**:113-131.

70. Lottem E, Banerjee D, Vertechi P, Sarra D, Lohuis MO, Mainen ZF: **Activation of serotonin neurons promotes active persistence in a probabilistic foraging task**. *Nat Commun* 2018, **9**:1000.

71. Apergis-Schoute AM, van der Flier FE, Ip SHY, Kanen JW, Vaghi MM, Fineberg NA, Sahakian BJ, Cardinal RN, Robbins TW: **Perseveration and shifting in obsessive-compulsive disorder as a function of uncertainty, punishment, and serotonergic medication**. *Biol Psychiatry Glob Open Sci* 2024, **4**:326-335.

72. Müller T, Klein-Flügge MC, Manohar SG, Husain M, Apps MAJ: **Neural and computational mechanisms of momentary fatigue and persistence in effort-based choice**. *Nat Commun* 2021, **12**:4593.

73. Kiser D, SteemerS B, Branchi I, Homberg JR: **The reciprocal interaction between serotonin and social behaviour**. *Neurosci Biobehav Rev* 2012, **36**:786-798.

74. Roberts C, Sahakian BJ, Robbins TW: **Psychological mechanisms and functions of 5-HT and SSRIs in potential therapeutic change: lessons from the serotonergic modulation of action selection, learning, affect, and social cognition**. *Neurosci Biobehav Rev* 2020, **119**:138-167.

75. Homberg JR, Brivio P, Greven CU, Calabrese F: **Individuals being high in their sensitivity to the environment: are sensitive period changes in play?** *Neurosci Biobehav Rev* 2024, **159**:105605.

76. Kroes MC, Henckens MJ, Homberg JR: **How serotonin transporter gene variance affects defensive behaviours along the threat imminence continuum**. *Curr Opin Behav Sci* 2019, **26**:25-31.

77. Homberg JR, Jagiellowicz J: **A neural model of vulnerability and resilience to stress-related disorders linked to differential susceptibility**. *Mol Psychiatry* 2022, **27**:514-524.

78. Silvetti M, Lasaponara S, Daddaoua N, Horan M, Gottlieb J: **A reinforcement meta-learning framework of executive function and information demand**. *Neural Netw* 2023, **157**:103-113.

79. Berwian IM, Wenzel JG, Collins AGE, Seifritz E, Stephan KE, Walter H, Huys QJM: **Computational mechanisms of effort and reward decisions in patients with depression and their association with relapse after antidepressant discontinuation**. *JAMA Psychiatry* 2020, **77**:513-522.

80. Treadway MT, Bossaller NA, Shelton RC, Zald DH: **Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia**. *J Abnorm Psychol* 2012, **121**:553-558.