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Serotonin and aversive processing in affective and social decision-making

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The effects of the neuromodulator serotonin on affect and behavior are so diverse and wide-ranging that characterizing its function has faced substantial challenges. Here we review recent work investigating how serotonin shapes affective and social decision-making in humans, focusing in particular on serotonin's influence on aversive processing. We consider the evidence that serotonin plays a key role in linking so-called Pavlovian aversive predictions with behavioral inhibition, a proposal derived from computational models of value-based decision-making. We evaluate the extent to which a core mechanism connecting serotonin with Pavlovian inhibition can explain diverse effects of serotonin on affective and social decision-making and highlight critical questions for future research.

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Introduction

Neuromodulators such as serotonin and dopamine serve a crucial function in shaping decision-making to adaptively fit the current environmental context. These systems have diffuse ramifications throughout cortical and subcortical regions that enable them to exert a global influence on brain function, but complicate the discovery of precise behavioral functions. In the case of dopamine, notable progress has been made in the last few decades, with insights coming from ground-breaking electrophysiological studies in nonhuman primates [1] and major advances in theoretical modeling implicating phasic dopamine signaling in reward-guided learning [2]. Like dopamine, serotonin has long been implicated in reinforcement learning and decision making. However, unlike dopamine, there is no similarly well-developed theoretical framework for guiding and interpreting empirical research. Perhaps the most popular contemporary ideas about serotonin come from Dayan, Daw, Huys, *et al.* [3••,4•,5,6], who have revived earlier ideas from, among others, Deakin *et al.* [7], to suggest that serotonin serves as a motivational opponent to dopamine with, on the one hand, dopamine neurons coding an appetitive prediction error, important for learning about reward, and on the other hand, serotonin neurons coding an aversive prediction error, important for learning about punishment [8•] (but see for an alternative proposal [9]).

This general idea concurs with observations that serotonin is implicated in disorders that are characterized by abnormal aversive processing, such as impulsive aggression [10], anxiety, and depression [11]. However, these clinical implications also highlight the paradoxical nature of the relationship between serotonin and aversive processing. On the one hand, low serotonin is associated with impulsive, disinhibited behavior, which is characterized by a failure to take into account the negative consequences of behaviors. On the other hand, low serotonin is also implicated in depression and anxiety, which are accompanied by negative biases in behavior and cognition that can be conceptualized as reflecting an enhanced impact of punishment [12]. How can the same neurotransmitter protect against both impulsive disinhibition and depression, which seem to be associated with a reduced versus enhanced impact of punishment, respectively? Here we review recent work on serotonin's role in aversive processing in affective and social decision-making, while recognizing explicitly that accumulating evidence implicates serotonin in the domains of appetitive processing [13] as well as waiting for reward [14].

Our aim is to identify and evaluate core mechanisms that may connect serotonin's common contribution to both affective and social decision-making. In particular, we consider the possibility that serotonin plays a key role in linking aversive predictions with behavioral inhibition — a so-called 'Pavlovian' mechanism that has been argued to underlie a range of anomalies in decision-making [15]. The basic idea is that evolution has endowed even simple organisms with powerful, pre-specified behavioral programs whereby predictions of rewards and punishments elicit innate, preparatory approach and avoidance responses, respectively. Such Pavlovian responses serve a useful function by preparing the organism to interact optimally with its environment, but can also lead to self-defeating behaviors

[16•]. Here we consider the extent to which a serotonergic modulation of Pavlovian aversive behaviors can unify its influence on social and affective decision-making and help to resolve its paradoxical involvement in both impulsive disinhibition and depression.

Serotonin and affective decision-making

To begin assessing the effects of serotonin on human learning and decision-making, Cools *et al.* have employed a probabilistic reversal learning paradigm [17]. In this task, participants have to learn by trial and error to choose the usually rewarded stimulus, and to avoid the usually punished stimulus. This paradigm enables separate assessment of sensitivity to reward and sensitivity to punishment, by assessing the degree to which participants stay with the same option after receiving reward, on win-stay trials, versus the degree to which they shift to the other option after receiving punishment, on lose-shift trials. The proportion of lose-shift trials is a particularly sensitive measure in this task. For example, Sahakian *et al.* have used this task to show that clinical depression is accompanied by an enhanced proportion of lose-shift trials [18]. Evidence for a role for serotonin specifically in lose-shift behavior comes from recent work investigating the sensitivity of probabilistic reversal learning to a common genetic polymorphism in the serotonin-transporter-linked promoter region, the 5HTTLPR, in SLC6A4, the gene that codes for the serotonin transporter [19•]. Using a large sample ($n > 700$) den Ouden *et al.* [19•] found that participants who are homozygous for that long allele, putatively associated with higher serotonin transporter density, exhibited more lose-shift behavior than did carriers of the short allele. As in the studies with depression, there were no effects on win-stay behavior. Furthermore, the effect of the serotonin transporter polymorphism doubly dissociated from that of the dopamine transporter polymorphism, which did not affect lose-shifting, while it did significantly affect perseveration following reversal [19•]. Together these studies substantiate a disproportionate role for serotonin in punishment-related behavior, although we recognize also the existence of several studies suggesting a potential role of serotonin in appetitive processing [20–22].

To assess more directly the hypothesis that low serotonin levels are associated with poor punishment prediction learning [8•], Cools, Robinson, *et al.* adopted the acute tryptophan depletion procedure [23] and a deterministic reversal learning paradigm where participants had to learn to predict whether a highlighted pattern would be followed by reward or punishment. The reward/punishment contingencies reversed regularly, thus ensuring high demands for learning. Lowering serotonin levels with acute tryptophan depletion [23] improved punishment prediction learning in this task, while leaving unaffected reward learning, in two independent studies [24,25]. This finding is generally consistent with serotonin's implication in clinical depression. However, it did not follow obviously from the theoretical proposal that lowering (phasic) serotonin should rather *attenuate* aversive prediction errors [8•]. According to this work, learning to predict punishment might depend on a learning-dependent transfer of a high-amplitude phasic serotonin response from an aversive outcome to a conditioned stimulus that predicts it. How can we reconcile this with our observation that lowering serotonin actually enhanced punishment prediction? One possibility, albeit speculative, is that tryptophan depletion reduced only the 'background' levels of serotonin, thus indirectly increasing the dynamic range and impact of phasic serotonin. In other words, tryptophan depletion might have shifted the system from a tonic mode of neurotransmission to a phasic mode of neurotransmission [26].

A different though not mutually exclusive possibility is that effects of serotonin might be understood not just in aversive terms, but also in terms of a Pavlovian inhibition of behavior in the face of aversive predictions — an idea consistent with very early studies of serotonin and punishment [27,28]. The crucial observation here is that predictions of future aversive outcomes often lead to behavioral inhibition, and serotonin might not just be involved in the learning of these aversive predictions and the inhibitory consequences that ensue, but also in the causal relationship between aversive Pavlovian processing and behavioral inhibition. Consistent with this idea, researchers have shown that predictions of punishment typically lead to behavioral inhibition, indexed by a slowing of response times and a bias against responses that lead to punishment, and tryptophan depletion abolishes this punishment-induced behavioral inhibition [29,30]. Furthermore, the effect of tryptophan depletion on punishment-induced behavioral inhibition appears to be driven by Pavlovian aversive predictions linking stimuli and punishments irrespective of response, rather than instrumental aversive predictions linking stimuli, responses, and punishments [30]. According to this account, decreasing serotonin does not enhance the impact of punishment on learning, but rather reduces the impact of Pavlovian punishment predictions on behavioral inhibition. This bias also has implications for economic choices, such as those where larger delayed rewards lurk behind smaller immediate losses [31,32••].

A recent study tested the aversive Pavlovian inhibition hypothesis of serotonin directly using a Pavlovian to instrumental transfer (PIT) paradigm in conjunction with acute tryptophan depletion [33••]. Here, participants are asked to perform instrumental tasks (e.g. pressing a lever for food) and separately undergo classical conditioning. The PIT effect consists in these task-irrelevant Pavlovian stimuli modulating the instrumental responses (in extinction), with positively and negatively valued stimuli, respectively, increasing and decreasing responding for

reward [34]. Under placebo, instrumental responding was inhibited in the presence of aversive Pavlovian conditioned stimuli, evidencing a classic aversive PIT or conditioned suppression effect. Strikingly, this effect was abolished, if anything reversed, after acute tryptophan depletion. Thus depletion of central serotonin elicited aversive Pavlovian disinhibition [33••] (but see [35]).

We began this review by highlighting that reductions in serotonin transmission have been associated with both ends of an apparent continuum of neuropsychiatric disorders, ranging from impulsive aggression (e.g. violent offenders) to anxiety and depression. Recent work has investigated whether these distinct disturbances, given their associations with low serotonin, might also *both* be accompanied by impaired Pavlovian aversive (inhibitory) responses to aversive cues.

One line of work has investigated the interaction between aversion and behavioral inhibition in healthy participants who were high or low in trait social avoidance, as measured with the Liebowietz Social Anxiety Scale. Participants completed a task in which they were presented with appetitive happy faces and aversive angry faces. For each face, they had to learn whether to make a Go or NoGo response. Aversive inhibition was quantified as the degree to which participants exhibited a greater tendency to make NoGo responses for the angry versus the happy faces. Such a NoGo bias was indeed present in the low-avoidant participants. Intriguingly, this aversive inhibition effect was completely abolished in highly avoidant participants [36].

Another line of work has focused on aversive Pavlovian inhibition in violent offenders with psychopathy. Psychopaths are typically not affected by emotional distress cues that would normally discourage instrumentally aggressive acts [37]. In keeping with these characteristics, we found that the instrumental choices of violent offenders with psychopathic traits were unaffected by angry emotional faces. Specifically, violent offenders showed reduced instrumental avoidance in the context of aversive (versus appetitive) faces relative to non-criminal controls [70]. Thus, psychopathic tendencies were accompanied by deficient transfer of Pavlovian value to systems that control instrumental action. This general finding was replicated in a separate study using a different paradigm, which revealed that increased psychopathic severity was associated with reduced aversive PIT [71]. Thus, aversive Pavlovian inhibition is disrupted both in violent offenders and as a function of social anxiety traits, raising the possibility that antisocial aggression and social anxiety represent distinct expressions of a common underlying deficit.

In summary, accumulating evidence suggests that central serotonin depletion attenuates the coupling between aversive Pavlovian predictions and behavioral inhibition. Critically, aversive Pavlovian disinhibition might represent a core feature of a continuum of serotonin-related neuropsychiatric disorders, ranging from antisocial, impulsive aggression to social avoidance. As such, aversive Pavlovian biases might well contribute critically to adaptive social behavior. In the next section we examine this possibility in further detail.

Serotonin and social decision-making

The observations reviewed so far concur with decades of research linking reduced serotonin function to antisocial and aggressive behavior [10,38,39•]. More recent work has used neuroeconomics methods to identify how serotonin modulates social decision-making in particular. For example, lowering serotonin with tryptophan depletion decreased cooperation in a repeated prisoner's dilemma [40] and a repeated common pool dilemma [41]. However, the repeated interactions in these settings obscure somewhat the underlying mechanism. Serotonin could influence cooperative behavior by modulating *beliefs* about others, other-regarding *preferences* for fair versus purely self-serving outcomes, or both.

Later work pinpointed a role for serotonin in shaping other-regarding preferences specifically. In a series of experiments, Crockett *et al.* manipulated serotonin function in participants playing the role of responder in one-shot ultimatum games, where a proposer offers a portion of a shared pie to the responder. The responder can either accept the offer in which case both players are paid accordingly, or reject the offer, which results in neither receiving any payment. Responders typically reject offers of less than about 30% of the pie, a behavior thought to reflect a desire to punish proposers who violate a social norm of fairness [42]. Depleting central serotonin made responders more likely to punish unfair behavior [43,44], while enhancing serotonin neurotransmission with the selective serotonin reuptake inhibitor (SSRI) citalopram reduced punishment [45]. Consistent with these findings, a PET study demonstrated that low serotonin levels in the dorsal raphé nuclei were associated with increased rejection rates in the ultimatum game [46]. This demonstrates that serotonin influences preferences about others' outcomes in addition to its role in shaping decisions about one's own outcomes, as reviewed above.

Neuroimaging work provides clues about the underlying mechanism. Previous studies had shown that punishing unfair behavior is associated with increased activation in the dorsal striatum [47,48], a region implicated in representing the value of instrumental goals [49]. Acute tryptophan depletion increased dorsal striatal responses during rejection of unfair offers, and the extent to which depletion affected striatal responses was correlated with the extent to which depletion affected choices [43]. These findings suggest that serotonin depletion increased

the instrumental goal value of punishing others. This goal value could arise from a desire to enforce social norms, or alternatively, a desire to harm people who violate those norms. Two recent studies suggest the latter motive constitutes a driving force in punishment behavior by showing that people are willing to (financially) harm unfair actors even in the absence of opportunities for norm enforcement. Researchers compared punishment of unfair behavior under two conditions. In the 'open' condition, the target of punishment both lost money and also learned that he had been punished; 'open' punishment therefore satisfies both a motive to harm and a motive to enforce social norms. In the 'hidden' condition, however, the target of punishment lost money but never learned that he had been punished. Thus, 'hidden' punishment satisfies only a motive to harm. Results showed that people used hidden punishment nearly as much as open punishment, suggesting that a motive to harm norm violators explains most of the variance in punishment behavior [50,51], an idea that is consistent with the observation of increased punishment behavior in psychopaths [52]. This suggests that serotonin's effects on punishment may stem from a modulation of the valuation of harming others, with impairments in serotonin function resulting in people placing a less negative value on harming others, and vice versa. More generally this could reflect a positive relationship between serotonin function and concern for others' welfare [38]. Recent studies provide additional support for this idea, showing that enhancing serotonin neurotransmission (with tryptophan supplementation or MDMA) makes people more generous and cooperative [53–56].

Taken together, these findings support a role for serotonin in *harm aversion*, or a preference to avoid harming others [57,58]. Consistent with this idea, violent, and aggressive behavior is linked to reduced serotonin function [39•,59]. Patients with borderline personality disorder, characterized by unstable social relationships, impulsive aggression, and self-harm, show reduced serotonin metabolism in the prefrontal cortex [60]. In healthy people, deciding whether to harm others engages the amgydala, anterior cingulate cortex and insula [61], regions densely innervated by serotonin [62], and functionally abnormal in antisocial behavior [63]. Enhancing serotonin neurotransmission with SSRIs reduces the expression of aggression [64,65] and amplifies the influence of harm aversion in hypothetical moral dilemmas [45].

How might serotonin modulate harm aversion? One possibility, following from the Pavlovian aversive inhibition mechanism outlined above, is that aversive social stimuli such as distress cues inhibit the performance of harmful behaviors. Indeed, this idea aligns with early work on harm aversion, which proposed a *violence inhibition mechanism* whereby distress cues suppress the behavioral expression of aggression [66]. Thus, reduced serotonin function could facilitate aggressive, harmful behavior by reducing the inhibitory impact of Pavlovian aversive predictions (in this case, bad outcomes to others) on the *implementation* of harmful behaviors. Alternatively, serotonin might influence harmful behavior by impacting the *valuation* of harmful decisions. The studies reviewed so far cannot readily distinguish between these two mechanisms, as they did not explicitly separate action requirements from choice values.

A recent study investigated directly how serotonin modulates both the valuation and implementation of harmful decisions for oneself and others. Participants were invited to trade off profits for themselves against painful electric shocks for either themselves or another person. Computational models of choice quantified individuals' harm aversion as the exchange rate between money and pain. Initial studies showed that in this setting harm aversion for others was greater than harm aversion for oneself, with participants willing to pay nearly twice as much money to prevent pain to others than themselves, probably reflecting moral concerns [58]. Subsequent work combined this paradigm with a pharmacological manipulation of serotonin to investigate the effects of enhancing serotonin neurotransmission on harm aversion for self and others. Crucially, on half the trials participants could avoid harming themselves or others by withholding a motor response, and on the other half of trials participants could avoid harming themselves or others by making a motor response. Participants given a single dose of the selective serotonin reuptake inhibitor citalopram were willing to pay nearly twice as much money to prevent pain to both themselves and others, and this effect was evident regardless of action requirements [67•]. As with the work on probabilistic reversal learning [19•], the effects of manipulating serotonin were doubly dissociable from the effects of manipulating dopamine with levodopa, which abolished people's tendency to avoid harming others more than themselves. Thus, enhancing serotonin transmission had a general effect on increasing the avoidance of harm, regardless of the target of that harm and regardless of whether harm avoidance occurred via an active or passive motor response, and these effects were selective to serotonin manipulation. The findings suggest that serotonin influences social behavior through a non-social effect on aversive processing, consistent with serotonin's role in affective decision-making. However, notably, these findings argue against the possibility that serotonin modulates harm aversion via Pavlovian-induced behavioral inhibition of action. If serotonin increases harm aversion via an inhibitory effect of Pavlovian aversive predictions on the *implementation* of harmful actions, then citalopram would have increased harm aversion only in trials where harm occurred via an active motor response. The fact that citalopram increased harm aversion regardless of action requirements instead suggests a serotonergic modulation of the *valuation* of harmful decisions themselves.

Conclusion

The diversity of experimental findings linking serotonin function with various aspects of decision-making is a testament to the complexity of the serotonin system and its multifarious behavioral functions. Nevertheless, a few common themes emerge. Some of the social effects of serotonin can be understood as reflecting non-social affective processes concerning the valuation of aversive outcomes. Serotonin appears to play a critical role in situations where appetitive and aversive values must be integrated to produce an appropriate behavioral response, for example when making instrumental responses to gain rewards in the presence of punishment cues (as in PIT), or when making tradeoffs between profit and pain for oneself and others. In the affective domain, converging evidence points to a role for serotonin linking aversive Pavlovian predictions with behavioral inhibition, an idea already present in very early theories of serotonin function [7]. However, this hypothesis seems less suitable for organizing the effects of serotonin on social decision-making, where serotonin appears to be more involved in modulating the valuation of decisions rather than the behavioral implementation of those decisions.

Recent work employing computational models that link decisions and response times has revealed an intimate relationship between valuation and vigor: smaller differences in subjective value between choice options are associated with slower decisions [68,69]. Thus, serotonergic effects on value could masquerade as effects on motor responses in experiments where value is not explicitly measured but only inferred indirectly through observation of behavioral responses. An open question, therefore, concerns the extent to which serotonin modulates the valuation of appetitive and aversive outcomes themselves, the valuation of actions that lead to those outcomes, or the influence of appetitive and aversive predictions on action selection. The fact that these factors are so often correlated in behavioral paradigms has so far eluded a straightforward picture of results. Future work in this area therefore crucially depends on the development of paradigms that can convincingly disentangle these components of decision-making in both affective and social contexts.

Conflict of interest statement

Nothing declared.

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