Serotonin in Affective Control

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computational model, behavior, reward, punishment, opponency, dopamine

Abstract

Serotonin is a neuromodulator that is extensively entangled in fundamental aspects of brain function and behavior. We present a computational view of its involvement in the control of appetitively and aversively motivated actions. We first describe a range of its effects in invertebrates, endowing specific structurally fixed networks with plasticity at multiple spatial and temporal scales. We then consider its rather widespread distribution in the mammalian brain. We argue that this is associated with a more unified representational and functional role in aversive processing that is amenable to computational analyses with the kinds of reinforcement learning techniques that have helped elucidate dopamine's role in appetitive behavior. Finally, we suggest that it is only a partial reflection of dopamine because of essential asymmetries between the natural statistics of rewards and punishments.

Contents

INTRODUCTION

Serotonin is that most elusive of neurochemicals. Its fingerprints are on the scene of depression, anxiety, panic, aggression, dominance, obsessions, punishment, analgesia, behavioral inhibition, rhythmic motor activity, feeding, and more, in organisms from invertebrates to humans, and yet it has never quite been convincingly convicted of any single compelling influence. There are at least 17 different types and isoforms of serotonin receptor, mediating its wide range of diverse effects. These include pairs and multiples of receptors having mutually opposing influences on the release and action of serotonin itself and on other neuromodulators such as dopamine, thus realizing complex patterns of synergistic and opponent control as well as a great capacity for adaptivity. Divining levels of serotonin activity in vivo at timescales shorter than a few minutes is currently difficult because reliable extracellular signatures of serotonin neurons in electrophysiological recordings are hard to come by, and fast scan cyclic voltammetry is tricky because of low absolute concentrations of serotonin compared particularly with dopamine, which has a similar redox signature.

Our aim is to achieve a synthesis of the roles serotonin might play in affective control, that is in the adaptive choice of actions in the light of rewards and punishments. The synthesis is in the spirit of computational approaches that have been fruitful for other neuromodulators, notably dopamine, acetylcholine, and norepinephrine (Aston-Jones & Cohen 2005, Barto 1995, Bouret & Sara 2005, Cohen & Blum 2002, Dayan & Yu 2006, Doya 2002, Montague et al. 1996, Yu & Dayan 2005). It is intended to complement the multiple, excellent, accounts of many of the different aspects of serotonin (including Azmitia 2001, Cools et al. 2008, Cooper et al. 2002, Deakin 1983, Deakin & Graeff 1991, Hoyer et al. 1994, Jacobs & Fornal 1999, Lucki 1998, Soubrié 1986, Tecott 2007, Weiger 1997, together with the reviews that these reference). For reasons of space, we have had to leave to them a wealth of the complexities of serotonin, notably those coming from the multiple different types of serotonin receptors, and from psychiatry. Furthermore, there are as yet many unknowns, so we can only paint a rather impressionistic picture in places.

We adopt Marr's (1982) framework for the analysis and interpretation of neural systems, which has played an influential role in the understanding of dopamine's role in appetitive conditioning. This framework distinguishes three levels of analysis: computational, algorithmic/representational, and implementational. The implementational level is conceptually most straightforward, describing how computational procedures or algorithms are actually realized by aspects of the neural substrate. It speaks to the huge wealth of neurobiological data about serotonin's effects on the synaptic integration and plasticity properties of single cells, and thereby on the dynamics exhibited by the networks they comprise. Like other neuromodulators, it mediates structural and functional plasticity at a variety of spatial and temporal scales, providing a means for networks to escape some of the bounds of fixed anatomy.

Marr's algorithmic/representational level, which is tied to psychological concerns, specifies in detail the procedures for realizing computations and also the way that critical information is represented. Crudely speaking, neuromodulators appear to represent

information about homeostatically relevant states or state changes. This representation may be direct, as in the level of hunger or thirst, or abstract, such as an increased expectation of receiving one of a number of different possible rewards or punishments. Neuromodulators thus represent key signals for the implementation of affective control. For instance, dopamine has been suggested as representing errors in predictions of the appetitive worth of future outcomes; this signal may drive synaptic plasticity, presumably to improve the predictions. Neuromodulators may be intimately involved in only part of the implementation because there is ample behavioral evidence supporting the existence of a number of structurally different procedures for determining optimal actions.

Finally, the computational level, which is tied to ethological data and models, concerns the rationale underlying information processing procedures. For affective control, this is the engineering and statistical theory of adaptive optimal decision making, and particularly the field of reinforcement learning (RL) (Sutton & Barto 1998). Dopamine has a special involvement in control associated with appetitive outcomes; serotonin appears to be particularly closely related to aversion (Daw et al. 2002, Deakin & Graeff 1991).

Marr's levels of analysis are tied together by mathematical models. In our case, these should indicate how the implementational properties associated with serotonin realize particular aspects of at least approximately ethologically optimal behaviors evident in the psychological data on learned decision making.

Overview

We fabricate a qualitative computational account in two stages. The next section focuses on the implementational and representational characteristics of serotonin. It uses examples from invertebrate model systems associated with feeding, fighting, and fleeing, for which the computational-level descriptions are either simple or moot. It describes a view of neuromodulators as imbuing structurally fixed motor and central pattern-generating networks with the flexibility of state dependence (Getting 1989, Getting & Dekin 1985, Harris-Warrick & Marder 1991), mediated by a variety of effects on synapses, neurons, and networks. It illustrates opponency between serotonin and other neuromodulators such as octopamine and dopamine and discusses a variety of representational assignments. This section also makes the more speculative claim that, as the structural and functional differentiation and sophistication of motor systems evolved, the role for relatively general neuromodulators such as serotonin apparently changed. On top of the shards of ancient schemes (Jacobs & Fornal 1999) were added more overarching and widespread roles in affective processing and inference. We later interpret this palimpsest as giving rise to the interpretational battle between opposing abstractions about serotonin: the mainly electrophysiological conclusion that serotonin is involved in motor excitation (Jacobs & Fornal 1999) versus the mainly pharmacological conclusion that it is involved in behavioral inhibition (Soubrié 1986). We also emphasize the fact that there is not a single serotonin system with a single function; rather there are multiple serotonin systems, one or two more widespread and others more specific.

The following section, Aversive Representation and Computation, builds on this analysis, providing a computational view of the more global serotonin systems. We suggest that they have a general role in aversion that can be seen as a partial reflection of the better-understood general role for dopamine in appetitive learning and processing. We describe a key difference between the natural statistics of rewards and punishments and suggest that this underlies the apparent contradiction in the findings that serotonin is both positively and negatively associated with aversion. Both these opposing views are supported by diverse and apparently compelling bodies of evidence. We discuss the possibility that the primary representational aspect of serotonin is pro-aversive, and we interpret behavioral inhibition in terms of a preprogrammed response to serotonergically

RL: reinforcement learning

reported predictions of future aversive outcomes that underlies much of the evidence about serotonin's anti-aversive associations.

Finally, in the Discussion section, we highlight some of the many caveats associated with our analysis and the gaps in our review. We also set the stage for an impending new era of experiments.

IMPLEMENTATION AND REPRESENTATION

It is fruitful to think of neuromodulators as implementational palliations of the constraints of anatomy. The networks of neurons that actually control motor behavior, sensorimotor transformations, and general neural information processing are structurally rather static. This presents an obvious implementational problem if different sorts of motor control involving the same effectors, or different transformations, are necessary in different circumstances. For instance, different challenges to homeostasis, or sorts of threat or opportunity in an environment, might all require different resolutions. Neurohormones, neuropeptides, and neuromodulators appear to offer a solution. They represent information about states or circumstances such as hunger, thirst, and threats and are distributed flexibly, via specific synapses [possibly gated by local glutamatergic interactions; Marrocco et al. (1987)] but also by extrasynaptic, paracrine, and volume transmission (Bunin & Wightman 1999, Zoli et al. 1999). They have the potential to alter dynamic properties of network components in a coordinated manner, fashioning a flexible pleo- or polymorphic (Getting 1989, Getting & Dekin 1985, Harris-Warrick & Marder 1991) portfolio of adaptive networks out of one, fixed, network.

In this section, we first provide a theoretical overview of the resulting implementational issues surrounding neuromodulators in general, and serotonin in particular. We discuss how different kinds of flexibility are made possible by serotonin's action at different spatial and temporal scales, within, and importantly also across, networks and consider the representational properties serotonin thus acquires. We then illustrate these issues through a set of examples: escape swimming and feeding in *Pleurobranchaea*, control of dominant and subordinate postures in lobsters, and the gill withdrawal reflex in *Aplysia californica*. Finally, we set the stage for the forthcoming computational analysis of serotonin's rather more general roles in aversive affective control in mammals.

Theory

Neuromodulators operating at a range of spatial and temporal scales realize pleomorphism both within and between networks. Within networks, they can directly excite or inhibit neurons, manipulate their excitability, and influence the properties of selected synapses, all via rich collections of receptors (Cooper et al. 2002, Hoyer et al. 1994). By altering the properties of networks' building blocks, neuromodulators can alter their dynamics and integrative properties. Neuromodulatory neurons can themselves be integral parts of the networks, directly influenced by recurrent interactions (thus straddling the boundary between classical neurotransmission and neuromodulation). They can also operate from afar via axonal connections or volume transmission. These may be combined, allowing for a general, unified signal, with different, locally specific effects on network subcomponents. Further flexibility comes via potentially exponential interaction patterns among different neuromodulators (Marder & Thirumalai 2002). Thus, in implementational terms, neuromodulators allow for the multiplexing of functions within individual networks.

At a larger functional scale, neuromodulators can alter the balance between different networks. This can be done by broadly distributing signals to some or all networks, which may, for instance, set the gains at which they operate. It can also be done by influencing the interaction of the networks in a more targeted manner, for instance boosting components that are responsible for mutual inhibition.

Neuromodulators operate at a variety of temporal scales. First, their own tonic and

phasic release may be under separate control [a possibility that has been particularly discussed for dopamine and norepinephrine (Aston-Jones & Cohen 2005, Goto et al. 2007)]. Indeed, neuromodulators are subject to complex direct and indirect positive and negative feedback interactions with themselves and each other. By tightly regulating long-run concentrations, these interactions may have the effect of emphasizing phasic signaling. Second, fluctuations in their concentrations at their targets are influenced by the nature and dynamics of active transport mechanisms, which can be spatially inhomogeneous; and different receptors can also have different temporal characteristics. Finally, the effects of the neuromodulators can be exerted very speedily, via quick-acting receptors, but can also be very prolonged, particularly through influences over long-term synaptic plasticity.

This diversity of actions complicates the representational issues for neuromodulators in terms of the semantics of the internal and external states and state changes that they report. A single implementational mechanism (such as changing the gain of a particular set of neurons) can have quite different functional roles. It may nevertheless be possible to identify particular dynamical behaviors with single neuromodulators and thus to view the latter as indices of network functions or behavioral selectors. Such identifications may be most fitting for networks close to motor outputs, providing for a form of state-based, chemical coding of behavior (Bicker & Menzel 1989). When modulation is isolated within particular networks, the choice of the neuromodulator involved may seem to be relatively arbitrary.

Vertebrates and mammals additionally have a range of general purpose control systems such as the striatum and neocortex, which lie hierarchically above the specific, e.g., spinal, sensorimotor control circuits. Information about some aspects of state, such as impending rewards and punishments, is important for a whole wealth of behaviorally relevant computations; widely distributed neuromodulators such as serotonin, which become centralized in vertebrate neural architectures, are in an ideal position to relay information of this sort. We might even speculate that the widespread nature of their report may lead to pressure for the semantics of the information being broadcast to be simplified. Generalized effects could coexist with locally specific modulation of particular subnetworks, although the semantics of the local and global signals could remain quite different and even mutually opposed.

Examples

These broad principles play out in almost every animal studied. Implementational issues have been a particular target of research in invertebrate preparations including the nematode *Caenorhabditis elegans* (Horvitz et al. 1982, Zhang et al. 2005), molluscs and leeches (Getting 1989, Gillette 2006), the sea hare *Aplysia* (Hawkins 1984), crustaceans (Flamm & Harris-Warrick 1986a,b; Kravitz 2000), and cockroaches (Walz et al. 2006), giving rise to a wealth of well-reviewed examples. **Figure 1** shows two cases taken from feeding and escape in the mollusc *Pleurobranchaea* (Jing & Gillette 2000) and postural aggression in the lobster (Kravitz 2000); we use these, along with learned defense in *Aplysia* (Hawkins 1984, Roberts & Glanzman 2003), to illustrate some of the key theoretical points.

Figure 1*a* shows an abstract cartoon of the role of serotonin neurons in *Pleurobranchaea* in three key motor networks: those associated with escape swimming, avoidance turns, and feeding. Escape swims are strong and swift reactions to an aversive encounter with a potentially predatory conspecific. They compete with mere avoidance turns to less aversive stimuli. Serotonin neurons [As1–4 in the escape network and the metacerebral giant (MCG) neurons in the feeding network] play a key role in energizing and organizing the relevant behaviors. The As neurons project to an interneuron pair (called A4), which is responsible for avoidance turns, and thereby influence the instantiation and direction of such turns. During escape swimming, which is induced by stronger noxious stimuli, they fire faster and are entrained

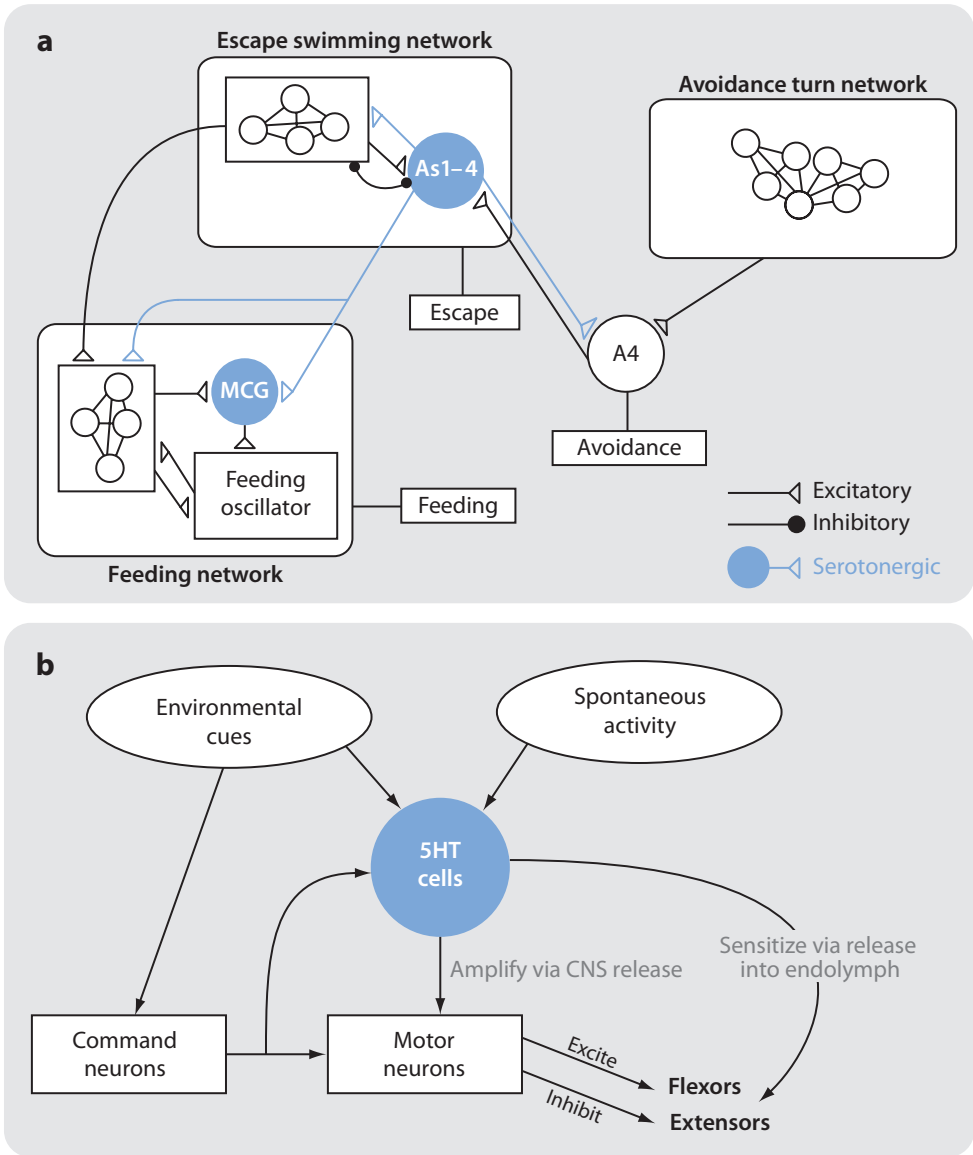

Figure 1

Invertebrate model neuromodulatory systems. (*a*) The outline structure of three motor networks in the mollusc *Pleurobranchaea* associated with avoidance turns, escape swimming, and feeding. The key serotonergic neurons are the As1–4 neurons in the escape network and the MCG neurons in the feeding network; the former appear to exert certain hierarchical influences over the latter. Figure adapted from Jing & Gillette 1999, 2000, 2003). (*b*) Cartoon of the involvement of serotonin in the control of posture in a lobster (adapted from Kravitz 2000). Serotonin boosts motor circuits, but the particular association between serotonin and the dominant posture arises as a result of selective afferents from one group of command neurons together with an apparently weak bias in its output effects.

to the swimming rhythm. They may thus suppress avoidance turning by preventing appropriate patterns of activity in the A4 neurons (Getting 1989; Jing & Gillette 1999, 2003).

However, the As1–4 neurons also act as hierarchic central organizers associated with arousal, mediated in this context by their excitatory influence on the (also serotonergic) MCG neurons. In the absence of threat, serotonin plays a direct part in boosting the excitability and activity of the motor networks associated with feeding; even the serotonin content of the MCG neurons (and therefore presumably release) is higher in hungry animals, and the neurons themselves are less active in animals whose guts are full (stretch being the apparent distal measure of satiation). These neurons are thus collectively in a position to influence a threshold that governs the animal's choice between orienting toward and avoiding potential foods. Exogenously applied serotonin also lowers feeding thresholds and stimulates patterns of activity in the isolated nervous system that can be described as appetitively oriented fictive swimming (Gillette 2006).

This example illustrates some of the general points above. First, at an implementational level, serotonin's action involves effects within single networks, but it also modulates the relationships among somewhat separate networks. Interactions between these networks make serotonin's pattern of influence complex. Second, although serotonin can exert quite a general facilitatory influence (even exogenous application has an effect on feeding thresholds), it also has much more specific roles in particular networks. Third, it does not act in a straightforward way by mediating a single behavior. Rather, it facilitates behavioral selection indirectly by influencing neurons involved in mutual inhibition between escaping and feeding. Indeed, the connection from the As1–4 neurons that facilitate escape swimming is excitatory rather than inhibitory on the MCG neurons, despite the system-level competition between escaping and feeding. This latter effect may promote an overall adaptive response by boosting and suppressing multiple behaviors in a coordinated manner. A further instance of this is apparent in serotonin's involvement in feeding in nematodes (Chase & Koelle 2007). When the animal reaches a bacterial lawn, serotonin (here, apparently signaling food rather than hunger) changes the balance between behaviors, facilitating some (notably pharyngeal pumping and egg laying) but simultaneously inhibiting others (locomotion). Fourth, we note the varied representational associations of serotonin in these systems, including aversion.

Figure 1*b* shows a schematic of a part of the circuitry in the lobster that controls posture (Kravitz 2000). Lobsters can be dominant or subordinate, adopting corresponding postures that are controlled by the postural flexor or extensor muscles, respectively. Collections of identified serotonin cells in thoracic and abdominal ganglia are involved in postural control, along with command neurons and motor neurons. Investigators initially found that injecting serotonin itself into the hemolymph of the animals causes the animals to adopt the dominant posture, whereas injecting octopamine, another neuroactive amine, causes the animals to appear subordinate [indeed exactly the same opponency applies to postural control in other crustaceans (Bevengut & Clarac 1982, Helluy & Holmes 1990)]. However, as the circuit in the figure implies, this is not a straightforward product of behavioral selection through serotonin because activating the neurons themselves [albeit not in a completely natural pattern (Ma et al. 1992)] does not seem to lead to the dominant posture. Rather, firing these neurons in concert with extension or flexion commands facilitates either, boosting the effect of command neuronal activity on the motor neurons and acting at the neuromuscular junction. Specificity in the system comes from the excitation or inhibition of the serotonin cells by flexion and extension commands, together with a rather partial bias toward boosting the flexion command connections over the extension connections (Ma et al. 1992). The excitation of the serotonin neurons may depend on further inputs because high induced firing rates of the command neurons lead only to a

very modest increase in the firing rate of the serotonin cells, from their background spontaneous activity of ~0.5–1 Hz to only 3–5 Hz.

This example also teaches some important general lessons. First, serotonin acts indirectly, as a gain-setter (Kravitz 2000, Ma et al. 1992) rather than as a selector, merely orchestrating behavior (Bicker & Menzel 1989, Sombati & Hoyle 1984). Ma et al. (1992) discuss a bevy of possible reasons for the difference between bath application of serotonin and stimulation of the neurons; however, the previous example is an important reminder of the limitations of global serotonin manipulations. Second, this example indicates how serotonin may act over multiple timescales: The tonic activity of the serotonin neurons implies that there will be a basal level or tone of serotonin setting the state of both the nervous system and the muscles; phasic activation or suppression might allow for additional fast modulation riding on top of the effects of the tonic background. Third, postural control provides an example of opponent neuromodulator interaction, which is an extremely prominent feature of neuromodulatory systems. However, the specific role of octopamine in mammals may be assumed by other neuromodulators such as dopamine (Daw et al. 2002). Dopamine does still play an important role in appetitive affect in molluscs (Brembs et al. 2002), though in insects both dopamine and octopamine can be involved in aversive processing (Zhou et al. 2008). A final comment for this example is that serotonin neurons may corelease other substances such as the neuropeptide proctolin (Siwicki et al. 1987); cotransmission is again a very common motif (Trudeau & Gutiérrez 2007), which makes interpretation more complex.

Our final example is serotonin's action at the rather different spatial scale of a synaptic terminal. Serotonin is a critical regulator of *Aplysia's* gill and siphon withdrawal reflex, which shifts the animal from a state associated with feeding or the potential for feeding to one associated with defense (see Hawkins 1984). Following a shock, serotonin is released onto the synapses connecting sensory neurons to motor neurons associated with the withdrawal. It then exerts a variety of presynaptic effects mediated by various intracellular signaling messengers that ultimately boost the strengths of the synapses concerned (Byrne & Kandel 1996, Hawkins 1984), sensitizing the reflex. Serotonin is also involved in longer-term, associative plasticity in this system, through which otherwise too weak sensory stimuli can, through the course of learning, elicit the reflex. Serotonin's involvement in learning may have presynaptic components, which expand on those involved in sensitization (Hawkins 1984), as well as a postsynaptic component (Roberts & Glanzman 2003).

This example shows two successively longer timescales of serotonin's action, in addition to the relatively immediate effects shown in the other cases, modulating networks directly as well as adapting the setting and function of the networks in response to environmental changes. It also implies that serotonin neurons can directly represent affectively important external stimuli such as shocks; the third section of this review is devoted to an in-depth analysis of serotonin's role in this type of aversive processing and learning in rodents and primates.

The different simultaneous roles of serotonin in instantaneous neuromodulation and the influence over plasticity are not always obviously consistent. For example, we mentioned above that serotonin in the nematode *C. elegans* facilitates behaviors suitable for the presence of food (Chase & Koelle 2007). Serotonin also influences plasticity in a manner that is appropriate to these representational semantics. For instance, it can substitute for the presence of actual nutrients in suppressing a form of learning in which odors associated with the absence of food come to be avoided (Nuttley et al. 2002). However, serotonin may be positively involved in aversive rather than appetitive learning in other cases. Certain bacteria can be dangerous to *C. elegans*; exposure to one of these bacteria causes an excess increase in serotonin in a class of chemosensory neurons; animals then change their olfactory preferences, avoiding those bacteria in favor of familiar, safe foods

(Zhang et al. 2005, although it seems the causal link between this learning and serotonin has yet to be proven).

From Slugs to *Sapiens*

Most of these general implementational messages apply to serotonergic and other neuromodulation in vertebrates and mammals as well, including gain-setting, opponency, indirect actions, tonic and phasic modes, and different timescales of effects up to and including synaptic plasticity.

However, there are various elaborations and differences too. Rather than being dispersed throughout the motor networks they modulate, the soma of the serotonin neurons in mammals are concentrated in or around the raphe nuclei in the medial midbrain (Dahlström & Fuxe 1964, Jacobs & Azmitia 1992). The motor circuits also become somewhat functionally and anatomically specialized. There are two groups of raphe nuclei: a caudal group (called B_1-B_4; Dahlström & Fuxe 1964), located in the medulla, containing the neurons that project to the spinal cord; and a rostral group with ascending projections (Cooper et al. 2002, Dahlström & Fuxe 1964). The rostral group includes the dorsal (DRN; or B_6; B_7) and median (MRN; or B_8) raphe, which have distinct pharmacological sensitivity (Judge & Gartside 2006) and patterns of connections, and even different sorts of synaptic terminals [thinner axons from the DRN, axons with large spherical varicosities from the MRN (Kosofsky & Molliver 1987)]. For instance, the MRN is the primary source of serotonin in the dorsal hippocampus and the caudal shell of the nucleus accumbens; the DRN is responsible for serotonin in the amygdala and in much of the rest of the accumbens (including the core) (Azmitia & Segal 1978, Brown & Molliver 2000, McQuade & Sharp 1997).

The largest body of electrophysiological data on the activity of raphe neurons in awake behaving mammals (in this case, cats) suggests a positive correlation between spiking of a subset of particularly caudal neurons and arousal and tonic and repetitive motor activity (Jacobs et al. 2002, Jacobs & Fornal 1993, 1997, 1999). Indeed, serotonin is involved in the control of archetypal rhythmic movements such as respiration (Richter et al. 2003) and whisking (Hattox et al. 2003). However, for cells in both caudal and rostral groups, analyses also reveal substantial, though incompletely understood, substructures in these nuclei (Lowry 2002, Peyron et al. 1997), and more recent electrophysiological recordings of (presumably both serotonergic and nonserotonergic) neurons in selected nuclei in macaque monkeys during controlled actions show a huge range of different behavioral correlates for activity patterns (Nakamura et al. 2008). Furthermore, recent single-neuron juxtacellular labeling studies in rats have shown that characterizing serotonergic neurons from extracellular electrophysiological recording alone is likely to be difficult or impossible (Allers & Sharp 2003, Hajós et al. 2007, Schweimer et al. 2008).

One elaboration over invertebrate serotonergic neuromodulation is an apparent increase in the complexity of receptor types and mechanisms. Different receptors can act in opposition to each other (notably, the 5-HT_2 receptors against the 5-HT_1 receptors); furthermore, their different affinities for serotonin may allow the serotonin signal to be multiplexed into tonic and phasic modes, with high-affinity receptors detecting low concentrations across large distances and low-affinity receptors detecting high concentrations across small distances. Specificity may also come from heterogeneous expression of both the receptors and the reuptake mechanism across serotonin target regions [with reuptake even being different in axons from the MRN versus the DRN (Brown & Molliver 2000, Kosofsky & Molliver 1987, Rattray et al. 1999) and being dependent on extra contextual factors such as corticosterone levels (Gasser et al. 2006)]. In addition, the receptors are subject to posttranslational modification in specific target zones. Of note are further complexities of interneuromodulator interaction, for instance when serotonin both boosts the release of dopamine (acting at

DRN: dorsal raphe nucleus

MRN: median raphe nucleus

5-HT: 5-hydroxytryptamine (serotonin)

5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and certain other receptors) and suppresses it (acting at 5-HT_{2C} receptors). (Alex and Pehek 2007).

In some cases, receptor-based effects replace intrinsic cellular mechanisms. For example, in lobsters, the serotonin cells exhibit a prominent pause in their spontaneous firing after being strongly activated (Heinrich et al. 1999). The same is true in vertebrate serotonin neurons (Aghajanian & Vandermaelen 1982) and other neuromodulatory neurons too; however, in the former, the pause is an intrinsic property of the cells, whereas in the latter, it normally depends on 5-HT_{1A} autoreceptors that are presynaptic on the serotonergic cells. A different (5-HT_{1B}) autoreceptor mediates suppression of the serotonin release by synapses of these cells. All together, these different receptors presumably impart great flexibility to the system as a whole; they can certainly be separately regulated pharmacologically.

An additional difference between vertebrate and invertebrate organisms is that there seems to be a change in the sign of certain neuromodulatory effects: For instance, serotonin has been associated with appetite suppression in mammals rather than the appetite promotion seen in leeches and molluscs (Halford et al. 2005). Also, albeit with the many complexities discussed below, it reduces reactive aggression in mammals rather than increasing it, as in lobsters and other invertebrates (Edwards & Kravitz 1997, Weiger 1997).

However, perhaps the most striking change in vertebrates and mammals is the addition of what may be described as relatively general-purpose processing structures, such as the striatum and neocortex, acting in parallel with, or on top of, more specific sensorimotor circuits. This change could be associated with a differentiation between general and specific modulation. General roles would be played by neuromodulators such as serotonin, dopamine, norepinephrine, and acetylcholine, with relatively widespread axonal and volume transmission schemes to diverse targets. These same neuromodulators could still play specific roles in particular motor-control circuits but could share this role or cede it to special-purpose, perhaps peptide-based, neuromodulators. Just such a scheme has been suggested for feeding (Gillette 2006). Particular neurons in the hypothalamus are sensitive to different sorts of specific nutrient requirements, and peptides such as orexins and neuropeptide Y also play key specific roles (Arora & Anubhuti 2006); this leaves for serotonin a yet more general role (notably in suppressing appetite) in regulating these regulators. Such schemes also provide an obvious rationale for corelease of a neuromodulator and one or more neuropeptides to instantiate the general as well as the specific consequences of states or events.

The widespread reports of general state information associated with such things as affective values could influence processing and plasticity in a way that generalizes across certain details of particular cases. Substantial evidence supports just such an arrangement for the neuromodulator norepinephrine (Aston-Jones & Cohen 2005), whereby it reports state information associated with unexpected events in the environment that are of potential relevance to almost all ongoing computations (Aston-Jones & Cohen 2005, Dayan & Yu 2006, Doya 2002). Of the other neuromodulators, such a general role is best established for dopamine [as a reporter of the prediction error for future rewards (Montague et al. 2004)]. Although Yu & Dayan (2002, 2005) have postulated a common role for aspects of acetylcholine (ACh) in processing a form of uncertainty, consistent with its general effect on cortical and hippocampal processing and plasticity (Everitt & Robbins 1997, Hasselmo 1995, Holland 1997, Sarter et al. 2005), ACh has a complex and differentiated architecture, including separate systems in regions such as the striatum (Apicella 2002, Kawaguchi 1997, Pisani et al. 2001). Serotonin appears to be more like ACh than dopamine: Along with the general nature that we consider below, there is a mix of functional specificity associated with the different groups of serotonergic raphe nuclei (Cooper et al. 2002) and subspecificity within these groups (Lowry 2002) and their efferents.

In sum, we have discussed a wealth of implementational properties of neuromodulators, many, though not all, of which are common to invertebrates and mammals. However, we argue that the computational interpretation of serotonin, in terms of the information it conveys and the effect it has on computational processing, may have a significantly more abstract and general form in mammals. This arises because of the existence of general-purpose information-processing structures, and because the substantial increase in the overall complexity of the systems involved in control lifts the burden formerly shouldered by serotonin of implementing a range of particular solutions for particular challenges to the organism. Residual specificity, for instance in the groups of serotonin neurons projecting to the spinal cord, could allow islands of individual effects, such as the facilitation of particular motor circuits, to exist amid an ocean of general effects, of which behavioral suppression and inhibition appear most important. In functional terms, the focus moves from the implementational properties of serotonin, in its representation and conveyance of a broad range of different signals, to the computational properties of a serotonin signal with more unitary semantics.

AVERSIVE REPRESENTATION AND COMPUTATION

At a most global level, serotonin is richly involved in the behavioral neuroscience of punishments and threats. This suggests that we should seek a computational account associated with aversive affective processing. However, in their masterly reviews, Deakin & Graeff (1991), based mainly on the animal literature (and with illuminating critiques such as Panksepp 1991), and Cools et al. (2008), based on the human literature, point out a key paradox: Aversive events or predictions can seemingly covary either positively or negatively with levels of serotonin and activity at its various receptors. We first describe the thesis and antithesis of this paradox, along with one suggested synthesis based on serotonin's involvement in behavioral inhibition (Soubrié 1986). We then describe the rather better understood case of dopamine and, based on this discussion, attempt to provide a refined computational view.

Negative covariance between serotonin and aversion is demonstrated by serotonin's analgesic properties (**Figure 2*a*,*b***) (Behbehani & Fields 1979, Millan 2002, Oliveras et al. 1975, Tenen 1968, Zhao et al. 2007); indeed, selective serotonin reuptake inhibitors (SSRIs) taken chronically (which boost serotonin) have an important role in the clinical management of chronic and neuropathic pain (Sawynok et al. 2001, Sommer 2004). Serotonin also suppresses panic-related escape reactions to immediately present aversive stimuli [such as shocks and water immersion (Cryan et al. 2005, Dekeyne et al. 2000, Maier & Watkins 2005)], possibly by involving the dorsal peri-aqueductal gray matter (dPAG), a region that plays a critical role in organizing such species-specific defensive responses (Bandler & Shipley 1994, Blanchard & Blanchard 1988, Bolles 1970, Keay & Bandler 2001, McNaughton & Corr 2004, Nashold 1974). Along the same lines, low levels of serotonin metabolites correlate with reactive, nonadaptive aggression in mammals (Miczek et al. 2007), including humans (de Almeida et al. 2005, Linnoila et al. 1983, Moffitt et al. 1998, Raleigh & McGuire 1991). Temporary dietary tryptophan depletion (ATD) in humans, which is thought to reduce serotonin levels acutely by limiting its synthesis precursor, increases aggressive responding upon provocation (Marsh et al. 2002, Moeller et al. 1996), and boosts aversive processing as measured in many experiments (reviewed in Cools et al. 2008), such as the enhanced recognition, impact, and processing of aversive stimuli (Cools et al. 2005, Evers et al. 2005, Harmer 2008, Roiser et al. 2007). Finally, in depression, serotonin appears to covary positively with appetitive processing: Chronic SSRIs constitute a major therapy, and ATD can powerfully reinduce disease symptoms (Delgado 2000, Nutt 2006, Smith et al. 1997).

The opposite is also evident, however: Serotonin can correlate positively with aversion

SSRI: selective serotonin reuptake inhibitor

PAG: periaqueductal gray

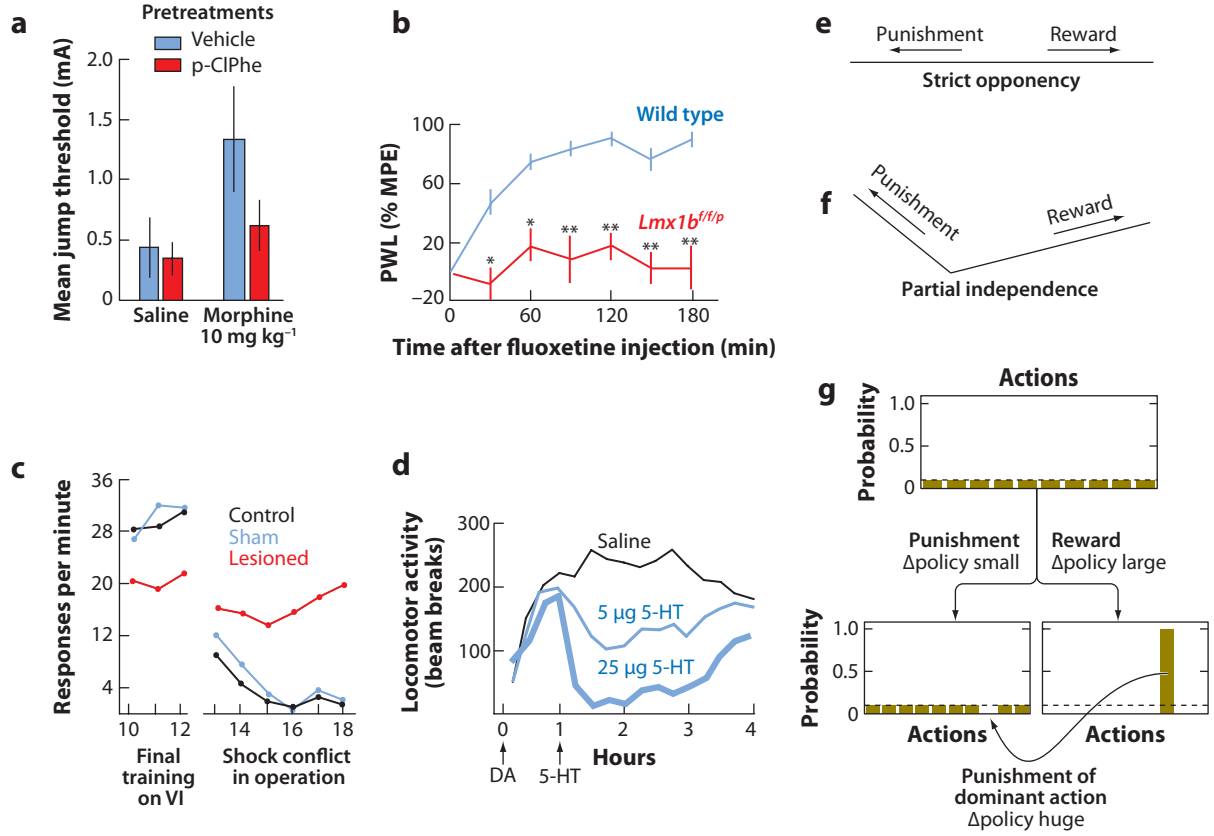

Figure 2

Serotonin's effects on affective behaviors. Panels *a* and *b* show examples of serotonin's negative covariance with aversion. *a*: Oral pretreatment with *p*-clorophenylalanine (p-ClPhe, which decreases serotonin levels) suppresses the analgesic effect of morphine. Bars show the current at which animals jumped when shocks were applied to the grid floor. Adapted from Tenen (1968). *b*: The analgesic effect of the SSRI fluoxetine is abolished in *Lmx1b*$^{f/f/p}$ mice genetically engineered to lack serotonin. The lines show the paw withdrawal latency (PWL) from a thermal stimulus as a fraction of each animal's maximum possible effect (MPE). Adapted from Zhao et al. (2007). *c*: The suppressive effect of aversive contingencies on appetitive behavior is nullified by central serotonin depletion. Animals are trained on a variable interval (VI) schedule to press a lever for reward. From session 13 on, each reward delivery is also accompanied by a conflicting delivery of a shock; only the animals in which serotonin neurons were lesioned pharmacologically with 5,7-dihydroxytrypatmine (5,7-DHT) fail to lower their response rate. Adapted from Tye et al. (1977). *d*: Serotonin-dopamine opponency. The locomotor activity following dopamine injection (20 µg; no stereotypies observed) into the nucleus accumbens is antagonized by injecting serotonin in a dose-dependent manner. Adapted from Carter & Pycock (1978). *e*: The critical question is whether punishments are indeed negative rewards and thus lie together with rewards on a single axis, in which case the most desirable action to be chosen merely by summing up the rewards and punishments and choosing the action with the maximal such sum. *f*: If the strict opponent relationship is not respected, rewards and punishments can be seen as spanning a higher dimension, and actions can no longer be selected according to a simple linear ordering. *g*: Information associated with punishments and rewards. Given a moderately large behavioral repertoire (here 10 actions), suppressing one of many actions leads to a small change in overall policy (*left*). However, if reward can pick out one of the actions, then the policy change is larger. Punishments here have large effects mainly when they prevent actions in situations in which the behavioral repertoire is (effectively) small, for instance when one action is strongly promoted by the appetitive system.

and negatively with rewards. Serotonin has hyperalgesic effects (Millan 2002, Millan et al. 1996) in addition to its involvement in analgesia. Microdialysis and *c-fos* imaging indicate that serotonin neurons and/or release are activated in conditions involving exposure to inescapable shocks (Bland et al. 2003; Grahn et al. 1999; Takase et al. 2004, 2005) or mild forced swimming (Kirby et al. 1997, Mogil et al. 1996). Furthermore, intraventricular infusions of serotonin increase animals' sensitivity to punishment (Wise et al. 1972). Meanwhile, depleting animals of serotonin reduces the behavioral suppression associated with expectations of aversive events, be it in tasks in which aversive expectations are innate, such as fear of open fields or heights (Bechtholt et al. 2007, Dulawa & Hen 2005, Gordon & Hen 2004, Graeff et al. 1996, Gray 1991, Griebel 1995, Griebel et al. 1994, Lowry et al. 2005, Rex et al. 1998), or in tasks in which aversive expectations are acquired, such as punished suppression (**Figure 2*c***) (Cervo et al. 2000, Dekeyne et al. 2000, Geller & Seifter 1960, Graeff 2002, Graeff & Schoenfeld 1970, Kennett et al. 1997, Lucki 1998, Stevens et al. 1969, Tye et al. 1977). Finally, serotonin also opposes dopamine directly, for example via the suppressive effect of $5HT_{2c}$ receptors on the activity of dopaminergic neurons (Higgins & Fletcher 2003), and boosting or suppressing serotonin counters or enhances the behavioral effects of tonic dopamine manipulations. For instance, the hyperlocomotion elicited by dopamine is dramatically antagonized by serotonin (**Figure 2*d***) (Carter & Pycock 1978).

An important caveat is that in a large number of experiments serotonin seems to correlate negatively with activity: When faced with immediately present punishments, it suppresses escape behaviors (e.g., the paw withdrawal response to a painful stimulus); when faced with aversive expectations, it suppresses exploration, feeding, and appetitive instrumental behaviors. These cases all involve suppressing actions, though differently motivated ones. Thus an important, alternative notion is that serotonin's main effect is behavioral suppression or inhibition (Brodie & Shore 1957, Depue & Spoont 1986, Soubrié 1986), perhaps using its ability to suppress theta rhythmicity in the hippocampus (Gray & McNaughton 2003). However, inhibition is certainly not completely general (Chamberlain et al. 2006, Clark et al. 2005) and must also be interpreted within the context of serotonin's overall positive association with activity, as discussed in the previous section (Jacobs & Fornal 1999).

Deakin & Graeff (1991) and Cools et al. (2008) suggest that anatomical and receptor specificities could resolve the essential paradox with separate serotonin projections to (*a*) the PAG, suppressing panic; (*b*) the amygdala, enhancing anxiety; and (*c*) the hippocampus, associated with depression. Furthermore, Cools et al. (2008) link inhibition and aversion by suggesting that (*d*) the serotonin projection to the orbitofrontal cortex could be involved in suppressing structures such as the amygdala. This mechanism could mediate the boosted aversive processing of such stimuli as fearful faces that is apparent under serotonin depletion. This resolution provides an important implementational account of serotonin's involvement in aversive processing. In this section, we suggest a computational and algorithmic rationale for it within the rather complex (e.g., Balleine 2005, Daw et al. 2005, Dickinson & Balleine 2002, Everitt & Robbins 2005, Killcross & Coutureau 2003) overall architecture of affective control. This architecture has been subjected to detailed computational modeling in the framework of reinforcement learning (Bertsekas 2007, Puterman 2005, Sutton & Barto 1998) and has provided a foundation for understanding dopamine's role in appetitive conditioning (Barto 1995; Daw et al. 2005; Friston et al. 1994; Montague et al. 1995, 1996).

To preview the argument, we consider a general role for serotonin as a signal associated with predictions and prediction errors for future aversive outcomes. Behavioral inhibition becomes a preprogrammed response to such predictions. We suggest that serotonin is an imperfect reflection of dopamine because the opponency between reward and punishment is

fundamentally asymmetric; rewards, at least in species such as rats and primates, are typically rare and caused by actions of the self, and punishments are typically common and originate in environmental contingencies.

Dopamine and Appetitive Control

Briefly, at a computational level, appetitive instrumental learning concerns the acquisition of policies for acting that maximize the total reinforcements collected over a period extending into the distant future. One component computation of this is predicting the long-term rewards that will accrue starting at a particular state (called a state value) and/or associated with executing a particular action (called a state-action value). States with higher values and actions with bigger state-action values are better. Here, the notion of state incorporates many things, including experimentally presented stimuli and internal variables, and it changes over time as the sequence of natural or experimental events evolves.

A psychologically and algorithmically important fault line lies between two different classes of learning procedure: instrumental or operant conditioning, in which the actions a subject takes in particular states are related to or influence its rewards and punishments; and Pavlovian conditioning, in which subjects receive the reinforcers independent of their actions and can merely predict them on the basis of their states. Subjects generate responses to Pavlovian predictors, such as approaching and engaging with stimuli predicting food, without having to learn that approach is appropriate (Brown & Jenkins 1968) and will emit such responses even when they are deleterious, resulting in lower rewards than could be obtained by an optimal instrumental controller (Breland & Breland 1961, Dayan et al. 2006, Williams & Williams 1969). The mapping of prediction to Pavlovian response appears to be evolutionarily preprogrammed (Hirsch & Bolles 1980) and static and inflexible, but it is generally highly adaptive (Dickinson 1980, Mackintosh 1983). Computationally, we might think of Pavlovian responses in terms of prior knowledge about likely environmental contingencies.

Algorithmically, one way of learning state and state-action values [though for sure not the only way; see Balleine (2005), Daw et al. (2005)] is via prediction errors. A key observation in RL is that predictions from successive states of long-run rewards should be mutually consistent (in the same way that each step subjects take in a known maze should bring them one step closer to the exit). Inconsistencies (also taking account of any reinforcements that are actually obtained) are prediction errors that can be used to improve predictions. It appears that the phasic activities of many dopamine neurons offer a direct representation of such a prediction error associated with unexpected rewards (Barto 1995, Montague et al. 1996, Schultz et al. 1997, Wickens 1990). Implementational data also suggest that the dopaminergic projection to the nucleus accumbens has a particular involvement in the learning of appetitive state values; and although the neural rules governing the selection of preparatory Pavlovian responses, such as approach, and consummatory Pavlovian responses, such as the way a particular food is handled, are not completely clear, this projection appears to exert an important influence (Reynolds & Berridge 2001, 2002). The dopamine projection to parts of the dorsal striatum is implicated in learning state-action values (Joel et al. 2002, Morris et al. 2006, O'Doherty et al. 2004, Roesch et al. 2007, Suri & Schultz 1999), and thus instrumental conditioning. Dopamine also plays a role in appetitive conditioning in invertebrates (Brembs 2003, Brembs et al. 2002, Nargeot et al. 1999), although the evidence that this involves an analogous prediction error is as yet strongly suggestive only in bees (Hammer 1993).

The full computational requirement for appetitive control includes choosing not only which action to perform, but also when to perform it. This decision presents a final implementational role for dopamine because increasing its tonic (and perhaps also phasic) levels,

for instance via amphetamines, boosts the vigor of appetitive responding (Berridge 2004, McClure et al. 2003, Murschall & Hauber 2006, Panksepp 1998, Salamone & Correa 2002, Satoh et al. 2003, Taylor & Robbins 1984). Niv et al. (2007) accounted for this effect of dopamine using a framework in which subjects are seen as seeking to optimize the average rate of rewards per unit time. They suggested that this average rate is reported by tonic levels of dopamine and acts as an opportunity cost for actions. In situations for which average reward rates are high, much reward is lost by procrastination, so acting more quickly and vigorously is better. Niv et al. (2007) also suggested that such an opportunity cost might underlie a dopaminergically influenced (Murschall & Hauber 2006) effect known as general Pavlovian-instrumental transfer (PIT) (Balleine 2005, Estes 1943, Lovibond 1983), in which Pavlovian state values associated with one reward can enhance the vigor of instrumental actions aimed at eliciting a different one, perhaps by boosting the estimated average rate of rewards.

In sum, RL provides a [not universally accepted; see Berridge (2007)] multilevel understanding of the phasic and tonic aspects of dopamine's role in appetitive instrumental conditioning and the learning of state values through Pavlovian conditioning. This understanding is normative in the sense that it has a sound computational foundation in statistics and optimal control theory. Pavlovian responses can be seen as arising from priors about the environment; they are instrumentally inappropriate only in unusual circumstances. Other Pavlovian effects, such as PIT, may arise via approximations. We next consider how this understanding helps us provide a computational account of serotonin's role in affective control.

Serotonin and Aversive Control

One horn of the paradox above holds that serotonin covaries positively with aversion and is thereby functionally opposed to at least the part of dopamine that covaries positively with reward. Indeed, we mentioned in the previous section that opponency is a common motif for neuromodulators and that direct behavioral and cellular evidence supports opponency between serotonin and dopamine (Carter & Pycock 1978, Higgins & Fletcher 2003, Kapur & Remington 1996, Redgrave 1978). These data suggest that serotonin might be viewed as an opponent to dopamine in affective control and raise three algorithmic and implementational questions: Does serotonin provide a prediction error that can be used to learn aversive state values and aversive state-action values? Is serotonin involved in modulating or mounting Pavlovian responses? Does serotonin influence the vigor of responding? We see below that the answers to these questions illuminate serotonin's involvement in inhibition and its negative covariance with aversion.

We should stress at the outset that, despite the evidence from dialysis and *c-fos* imaging described above and the existence of fast, stimulus-bound, phasic responses of putative serotonin neurons (Heym et al. 1982), only extremely little (Walletschek & Raab 1982) physiological evidence currently demonstrates that the activity of serotonin neurons reports anything like an aversive prediction error (Jacobs & Fornal 1993, 1999).

Serotonin and aversive predictions and prediction errors. From a computational viewpoint, it is essential to have single state-action values that combine and integrate future benefits and costs to determine optimal sequences of actions. **Figure 2*e*** illustrates that in RL, costs are typically subtracted from benefits, creating a single scalar value by treating punishments as negative rewards (or vice versa). In certain behavioral settings, rewards and punishments certainly do appear to behave in this manner (Crespi 1942, Dickinson & Balleine 2002, Dickinson & Dearing 1979, Ganesan & Pearce 1988, Gray 1991): for instance, the unexpected absence of punishment has some of the properties of an unexpected reward, and the

PIT: Pavlovian-instrumental transfer

frustration of not receiving an expected reward partially resembles a punishment. However, such a single continuum involving both rewards and punishments might be implemented or approximated neurobiologically in different ways, and thus a critical general representational and implementational issue is how this actually works, and why two neuromodulators rather than just one might be involved in this representation.

One possibility is that positive and negative aspects of the continuum are represented separately, maybe akin to ON and OFF retinal ganglion cells. In fact, dipoles (Grossberg 1984) or opponent pairs of systems (Solomon & Corbit 1974) are common solutions to the problem of representing both positive and negative quantities instead of having high baseline activities representing neutral or zero values. The direct opponency of serotonin with dopamine (e.g., Cameron & Williams 1995, Fletcher et al. 2002, Fletcher et al. 1999, Fletcher & Korth 1999, Luciana et al. 1998) is consistent with this view, and perseveration in reversal learning tasks after serotonin depletions (Clarke et al. 2007, Dias et al. 1996) could be interpreted as evidence that serotonin is involved in representing a negative prediction error learning signal. However, data on the effects of serotonin on the acquisition of aversive Pavlovian values themselves are contradictory at present (Burghardt et al. 2004, 2007; Hashimoto et al. 1996; Inoue et al. 1996). Furthermore, there is uncertainty about the architecture of opponency, i.e., the separation between appetitive and aversive evaluation systems (Paton et al. 2006) and/or prediction errors (Daw et al. 2002). Indeed, despite their low background firing rate, phasic decreases below the baseline of dopamine neuron activity may indicate the absence of expected rewards (Bayer & Glimcher 2005), with the effect of controlling aversive or negative prediction learning (Frank et al. 2004). Finally, the reliance on two systems to report on what is essentially a single entity introduces a degree of representational freedom with possibly complex consequences (**Figure 2*f***) for prediction learning and action selection.

Serotonin and aversively motivated actions. Even if serotonin is involved in aversive aspects of state values, the case of aversive state-action values and instrumental conditioning is complicated by an asymmetry in the natural statistics of rewards and punishments. Animals with large behavioral repertoires and sparse rewards face the problem of working out what to do rather than what not to do (see **Figure 2*g***). Rewards are more informative about the former, punishments about the latter. Furthermore, animals arguably gain rewards on the basis of their own active choices but are in less control of the punishments in an environment. Thus, we might speculate that increasing the probability of an action that leads to reward may be more critical than decreasing the probability of an action that leads to punishment, at least unless the action is already highly probable (see **Figure 2*g***). Aversive events are certainly not less relevant in general; they can have much more extreme consequences than appetitive ones. However, the asymmetry does suggest a particular role for punishments in inhibiting prepotent actions (and not vice versa; consistent, for instance, with the lack of evidence of direct opponency of dopamine on serotonin release).

Thus, learning instrumental actions to avoid punishment (i.e., active avoidance) might depend on both appetitive action learning and on aversive state learning (Klopf et al. 1993, Moutoussis et al. 2008, Mowrer 1947, Schmajuk & Zanutto 1997). Actions could be positively reinforced for moving the actor from a state with negative expectations to one that is neutral. Although serotonin may be involved in the acquisition or representation of the aversive state value, the prediction error arising when moving to a safe state would putatively be coded by dopamine, allowing it to inspire action learning. Data from conditioned avoidance learning under dopamine antagonists offer some support for this view (Beninger et al. 1980, Moutoussis et al. 2008).

Serotonin and Pavlovian responses. The asymmetry between rewards and punishments thus shifts the emphasis toward the complex

structure of preprogrammed aversive responses (Blanchard & Blanchard 1988, Bolles 1970, Keay & Bandler 2001). Indeed, aversive Pavlovian learning, linking stimuli to such responses, is very fast and powerful, whereas aversive instrumental learning [at least of actions that are not the species-specific responses to particular aversive stimuli; see Brembs & Heisenberg (2000)] is slower and harder to achieve (Bolles 1970). If serotonin does indeed have a role in predicting future aversive outcomes, what interpretation does this give for its Pavlovian effects (Deakin & Graeff 1991; Graeff 2002, 2004; McNaughton & Corr 2004)?

At least two sets of answers have been given to this question, together offering a central coupling between aversive predictions and behavioral inhibition of prepotent responses (Soubrié 1986). First, Deakin (1983), Deakin & Graeff (1991), and Graeff (2004) argue that part of the sophistication of the Pavlovian mechanisms associated with punishment and threat is suppressing primitive panic-associated reflexes in favor of particular, more adaptive responses enabled by the predictions. They argue that this suppression is mediated by a serotonergic projection into the PAG, one structure responsible for mounting these responses in the first place.

The asymmetry between rewards and punishments provides a second link to behavioral inhibition. Given predictions of (increasing) future rewards, it is a reasonable heuristic for the animal to continue performing the actions in which it is presently engaged (Montague et al. 1995). Given predictions of future punishment, no such heuristic can favor any particular action; at best, it might require the subject to stop doing whichever action is ongoing and causing trouble. If, as suggested by Cools et al. (2008), this sort of inhibition is normally responsible for preventing engagement with potentially aversive stimuli, then suppressing serotonin could have an apparently proaversive consequence in the enhanced processing of fear-inducing or negatively valenced stimuli. Dayan & Huys (2008) made a similar argument supporting the effects of serotonin under normal circumstances of creating overoptimistic evaluations of states, and thus the reinduction of depression symptoms that are induced by tryptophan depletion (Delgado 2000, Nutt 2006, Smith et al. 1997).

Serotonin and sloth. The final facet of aversive signaling considered in this review is the relationship to vigor, where the opponency between dopamine and serotonin is perhaps seen at its clearest. Serotonin antagonizes a wide variety of energizing effects of drugs that elevate tonic dopamine (although a complicating factor is that serotonin's own release and reuptake are affected by some of them): It antagonizes the effects of dopamine on consummatory appetitive behaviors, such as intracranial self-stimulation to the medial forebrain bundle (Redgrave 1978), feeding (Fletcher 1991, Simansky 1996), sexual behavior (Balon 2006, Fadda 2000), motor activation (Carter & Pycock 1978; see **Figure 2*d***), conditioned reinforcement (Fletcher 1996, Fletcher et al. 1999), and more general aspects of drug reward (Higgins & Fletcher 2003). These results are consistent with appetitive/aversive opponency according to the argument above that tonic dopamine carries an estimate of long-run reward rates that enforces vigorous actions by implying an opportunity cost for the time lost in behaving slowly (Niv et al. 2007). Opportunity costs would also be large if actions could postpone punishments, i.e., if animals have control over their punishments. It has been argued that this mechanism may underlie some of dopamine's positive covariance with punishment (Bland et al. 2003, Cabib & Puglisi-Allegra 1996, Horvitz 2000, Weiss 1968), and indeed serotonin activity appears to be suppressed (via the medial prefrontal cortex) when punishments are under subjects' control (Amat et al. 2005).

The aversive aspect of PIT provides another view of behavioral inhibition. Expectations of appetitive events (instigated by Pavlovian conditioned stimuli) can enhance the vigor of ongoing instrumental behavior, putatively via a dopaminergically represented prediction of higher long-term rewards, which suggests that expectations of higher long-run punishment

rates could lead to less vigorous and more slothful actions [see Dickinson & Pearce (1977) and Herrnstein & Sidman (1958) for an in-depth discussion of aversive PIT]. Normatively, this would be true if wasting time can postpone the arrival of the aversive outcomes. However, most punishments are not caused by the subject, and in tasks involving unavoidable or uncontrollable shocks, acting slowly cannot help. Maybe, as suggested for the case of appetitive Pavlovian influences over instrumental responding, it is just an approximation to couple sloth with predicted aversion. It could certainly have the beneficial effect of preserving energy for a possibly brighter future.

That serotonin might decrease the opportunity cost for time could underlie its antiimpulsive effects, as observed in discounting tasks in which subjects choose between an early, small reward and a delayed, large reward (Doya 2002; Mobini et al. 2000a,b; Thiébot et al. 1992; Wogar et al. 1993). Suppressing serotonin would increase the costs of waiting and thus cause subjects to make more impulsive choices. Note, however, that Tanaka et al. (2007) and Schweighofer et al. (2008) have made the alternative suggestion that serotonin determines the discount factor (interest rate) that allows distant rewards and punishments to be weighted against proximal ones, and they used fMRI data to link this hypothesis to changes in the topographic structure of the representation of predictions and prediction errors across the striatum (Tanaka et al. 2004).

To summarize, we argue that the primary interpretation for serotonin signaling may come from its positive covariance with aversive predictions or prediction errors. Asymmetries between reward and punishment imply that Pavlovian mechanisms are more powerful in the latter than in the former and provide a reason for the alacrity of Pavlovian, compared with instrumental, aversive learning. They are also associated with serotonin's important involvement in behavioral inhibition, opposing dominant appetitive and aversive behaviors. The Pavlovian refusal to engage with actually or potentially aversive stimuli and states leads to anomalies of values and actions that generate the apparent negative covariance between serotonin and aversion, which we also describe.

DISCUSSION

We have adopted a computational perspective on the function of serotonin, although we have not constructed anything like a complete computational theory. We started with a description of the properties of neuromodulators as mediators of the effects of (largely bodily) state on behavior on the basis of rather well-characterized invertebrate model systems. We then discussed the possibility that the increasing sophistication of behavioral circuits could provide an opportunity for the major neuromodulators such as dopamine and serotonin to offer widespread reports of information that is of general importance for substantial swathes of cortical and subcortical processing and plasticity. Finally, we considered serotonin's involvement in the prediction of aversive outcomes and thus, through the effects of such predictions on Pavlovian behavioral inhibition, accounted for a set of results in which serotonin is negatively rather than positively associated with aversion.

Although the notion of opponency between appetitive and aversive systems, with serotonin playing the starring role in the latter, is much older in both experimental (Brodie & Shore 1957, Solomon & Corbit 1974) and computational (Grossberg 1984) communities, our perspective is most directly an evolution of the ideas of Deakin (1983), and Deakin & Graeff (1991) and the theoretical work of Daw et al. (2002) that was based on these earlier ideas. The main elaboration comes from a refined analysis of the interaction between Pavlovian and instrumental conditioning (Dayan et al. 2006, Dayan & Huys 2008, Mackintosh 1983), and thereby a richer view of the immediate effect of predictions of future aversive outcomes on actions, and by addressing the apparent paradox for opponency that lowered serotonin can lead to apparently enhanced processing of stimuli with negative affective value.

These notions are fragmentary and are based on a very incomplete exegesis of many of serotonin's effects. In particular, we resolved the paradox associated with serotonin being either a behavioral excitor (Jacobs & Fornal 1999) or an inhibitor (Depue & Spoont 1986, Soubrié 1986) by fiat, arguing that excitation of particular motor circuits could coexist with a general inhibitory function, given appropriate anatomical specificity. However, this argument is really a placeholder for what should be a more extensive investigation reconciling these views. Indeed, we have repeatedly stressed that there is not a single serotonin system or function for this neuromodulator, but rather a collection of more general and more particular systems and functions.

Furthermore, we have ignored many important issues associated with the wealth of different types of serotonin receptors (Cooper et al. 2002; Hoyer et al. 1994, 2002). These presumably give rise to exquisite tuning of serotonin function; however, given only limited pharmacological tools, many of which are insufficiently specific for serotonin over other neuromodulators, let alone for one subclass of serotonin receptor over another, it is very difficult to understand exactly how. Worse yet, these receptors interact with serotonin release and the release and effect of other neuromodulators according to a feedforward and feedback control scheme that operates over a huge range of timescales, and of which we have only somewhat vague ideas. As often remarked, the extreme difference between the pharmacologic and therapeutic delays in the action of SSRIs in psychiatric diseases [up to 12 weeks in obsessive-compulsive disorder (Mansari & Blier 2006)] implies a critical challenge in building adequate dynamic accounts. We have also not considered the substantial issues around the differences [or even interactions (Lechin et al. 2006)] between the median and dorsal raphe nuclei, with their different projection patterns, pharmacologic sensitivities, and even axonal structures.

Next, because of page limitations, we have not addressed serotonin's prominent role in social interactions and psychiatry. Serotonin has a rich and complex influence over social behavior. For instance, it suppresses reactive aggression and promotes affiliative actions, both of which have been linked to social status in primates (Howell et al. 2007, Raleigh et al. 1991), and influences choice in neuroeconomic games that probe inequity processing and the formation of cooperation (Crockett et al. 2008, Wood et al. 2006). Mechanisms involving serotonin appear fundamental in a large fraction of psychiatric diseases, and serotonergic drugs are considered first-line treatment for many mood disorders. Indeed, RL models of the sort we have discussed are set to provide a framework to understand psychiatric failures in affective decision making (Huys 2007, Moutoussis et al. 2008, Rangel et al. 2008, Smith et al. 2007, Williams & Dayan 2005).

Finally, we note that there are multiple controllers that interact in ways that are only incompletely understood (Balleine 2005, Daw et al. 2005). For appetitive outcomes, dopamine's role in one of these, the habitual (or cached or model-free) controller, is clearer than for the goal-directed (or model-based) controller, and indeed special features of dopamine's projection to prefrontal regions (Lacroix et al. 2000, Lammel et al. 2008, Williams & Goldman-Rakic 1995) may be most closely involved in the latter. The understanding for serotonin is even more primitive.

One of the main reasons for the difficulties in understanding serotonin is that it has been very hard to measure or manipulate with high spatial, temporal, or functional precision. The main existing methods for manipulation (Cools et al. 2008) include pharmacologic treatments aimed at particular receptor types (many of which lack adequate specificity); neurotoxins such as 5,7-dihydroxytryptamine (5,7-DHT), which can kill serotonin (and, unless care is taken, noradrenergic) neurons; acute tryptophan depletion, which may disrupt the normal balance between tonic and phasic signaling (Cools et al. 2007); and inhibitors of the serotonin transporter (SSRIs), which prevent serotonin from being removed from the synaptic

cleft and beyond, allowing it to act for longer time periods. Various of these methods suffer from auto- and cross-regulation of the neuromodulators (Panksepp & Huber 2002), so SSRIs, for instance, can cause reductions as well as increases in serotonin concentrations because boosted serotonin levels at the 5-HT_{1A} autoreceptor can dramatically reduce the activity of the serotonin neurons themselves (Artigas 1993, Blier & de Montigny 1999) in a way that might differ in different neural populations (Beyer & Cremers 2008). Furthermore, in the face of blocked serotonin transport, dopamine synapses become loaded with, and release, serotonin as well as dopamine because the dopamine transporter has a (weak) affinity for serotonin and co-releases both neuromodulators (Zhou et al. 2005).

Fortunately, a range of new methodologies for investigating serotonin is under active development. We describe just a few examples (Schweimer et al. 2008; Z.F. Mainen, personal communication; R.M.Wightman, personal communication). First is the possibility of measuring serotonin concentrations (or relative concentrations) in target structures using the sort of fast-scan cyclic voltammetry that has produced important data on phasic dopamine concentrations (Phillips et al. 2003, Robinson et al. 2003). As mentioned above, obtaining this measurement is difficult because the cyclic voltammogram for serotonin is easy to confuse with that for dopamine, and the absolute concentration of dopamine in key target structures such as the striatum is typically much higher. However, because the spatial distributions of dopamine and serotonin projections differ, it might be possible to observe the activity of at least some of the multitudinous parts of the serotonin system.

Second, the use of juxtacellular labeling methods in the raphe nuclei of anaesthetized rats subject to mild aversive inputs should provide a clearer picture of both the external correlates of serotonin neuron activity and the spike-shape criteria that investigators have historically adopted to discriminate serotonergic from nonserotonergic cells in extracellular recordings (Schweimer et al. 2008). This same method greatly improved our understanding of the activity of dopamine neurons (Ungless et al. 2004) by showing that the key population of provably dopaminergic neurons was all inhibited by punishments. Unfortunately, the method does not currently allow for investigation in awake, behaving animals, which rather, though not completely (Pang et al. 1996, Rosenkranz & Grace 2002), hinders the use of behaviorally meaningful paradigms.

Third, the development of opto-genetic methods such as channelrhodopsin and halorhodopsin for exciting and inhibiting genetically defined populations of neurons using laser light of particular colors (e.g., Gradinaru et al. 2007) will offer a powerful set of new tools. For instance, it could be possible (Z. F. Mainen, personal communication) for channelrhodopsin to be expressed exclusively in serotonergic cells in mice by placing transcription of the sequence expressing the channel under the control of a promoter that is exclusive to serotonin cells. Light could be shone onto the raphe nuclei (perhaps using an optic fiber) to activate those cells in a pattern of the experimenter's choice and thus could be used to test theories that suggest conjoint behavioral and neurophysiological effects of phasic (and/or tonic) serotonin release. By correlating electrophysiological activity to photostimulation, this same technique could also be used to support the serotonergic basis of activity recorded by extracellular electrodes. This confirmation would then underpin the findings of subsequent behavioral neurophysiological studies. The burgeoning collection of genetically encoded markers for different sets of neurons (Jensen et al. 2008) may then provide insight into subclasses of serotonin neurons that have hitherto been seen using anatomical and cellular imaging (Lowry 2002, Peyron et al. 1997).

The methods for measuring the activity or output of serotonin neurons may all benefit from the increasing sophistication of behavioral and behavioral neuroscience paradigms. These can, for instance, provide sharper

characterizations of factors that we argued are central to the understanding of serotonin, such as separate model-based and model-free contributions to control, and to the interaction of Pavlovian and instrumental conditioning.

Fourth, genetics and molecular biology allow increasingly specific subparts of serotonergic systems to be modulated over long, and increasingly also short, timescales. Molecular techniques have already been extremely valuable in refining our understanding of the contributions of different receptor types (Gordon & Hen 2004, Julius 1998, Lira et al. 2003, Rocha et al. 1998) and the specificity of these contributions within different brain areas (Weisstaub et al. 2006). Serotonin also plays a critical role in normal and abnormal development (Azmitia 2001, Buznikov et al. 2001), and researchers are developing tools to tease apart this aspect of its contributions (Ansorge et al. 2004).

Finally, advances and refinements in techniques of functional and pharmacological neuroimaging are helping investigators to generalize critical findings to humans and to tackle uniquely human disorders and behaviors. Most imaging techniques, and particularly fMRI, suffer from an inability to link their measurements to serotonin concentrations or release. Nevertheless, there is a wealth of work aimed at improving brain stem imaging (D'Ardenne et al. 2008), developing more specific ligands for positron emission tomography (Hinz et al. 2007), using more powerful behavioral tasks (Mobbs et al. 2007, O'Doherty et al. 2004), and combining imaging with pharmacology (e.g., Pessiglione et al. 2006) and genetic information (Hariri et al. 2002, Meyer-Lindenberg & Zink 2007, Pezawas et al. 2005).

In sum, the importance and ubiquity of serotonin in the brain have for far too long vastly outweighed our ability to interpret it. We hope that computationally more precise characterizations of the structure of affective control and neuromodulatory influence over it will help herald a whole new comprehension of many aspects of serotonin.

DISCLOSURE STATEMENT

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