

Serotonin in Affective Control

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Abstract

Serotonin is a neuromodulator that is extensively involved 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, in endowing specific structurally fixed networks with plasticity at multiple spatial and temporal scales to aspects of homeostatic state. 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 to do with 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 an essential asymmetry between the natural statistics of rewards and punishments.

1 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 plus a great capacity for adaptivity. Divining levels of serotonin activity *in vivo* at timescales shorter than a few minutes is currently difficult, since 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 and Cohen, 2005; Barto, 1995; Cohen and Blum, 2002; Dayan and Yu, 2006; Doya, 2002; Montague et al., 1996; Yu and 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 and Graeff, 1991; Hoyer et al., 1994; Jacobs and Fornal, 1999; Lucki, 1998; Soubri , 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. Further, there are as yet many unknowns, so we can only paint a rather impressionistic picture in places.

We adopt Marr (1982)'s 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. This 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 dynamical characteristics of 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, 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. By this means, neuromodulators represent key signals for the algorithms of affective control, for instance errors in predictions of the appetitive worth of future

outcomes that drive synaptic plasticity, presumably to improve the predictions. One important algorithmic theme, reflected in ample behavioral evidence, is the existence of a number of structurally different procedures for determining optimal actions, only some of which involve neuromodulators directly.

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 and Barto, 1998). Dopamine has a special involvement in control in the face of appetitive outcomes; serotonin appears to be particularly closely related to aversion (Daw et al., 2002; Deakin and Graeff, 1991).

Marr's levels of analysis are tied together by mathematical models. In our case, these aim at indicating 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. Section 2 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 and Deakin, 1985; Harris-Warrick and 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. Section 2 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 and Fornal, 1999) were added more over-arching 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 and 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; others more specific.

Section 3 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. 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 interpret behavioral inhibition in terms of a pre-programmed response to serotonergically-reported predictions of future aversive outcomes that underlies much of the evidence about serotonin's anti-aversive associations.

Section 4 highlights some of the many caveats associated with our analysis, and the gaps in the review. It also sets the stage for an impending new era of experiments.

2 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 extrasynaptic, paracrine and volume transmission (Bunin and Wightman, 1999; Zoli et al., 1999). They have the potential to alter dynamic properties of network components in a coordinated fashion, fashioning a flexible pleo- or poly-morphic (Getting, 1989; Getting and Dekin, 1985; Harris-Warrick and Marder, 1991) portfolio of adaptive networks out of one, fixed, one.

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 computational analysis in section 3 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 amongst different neuromodulators (Marder and 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 and 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 signalling. Further, 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. This may be most common for networks close to motor outputs, providing for a form of state-based, chemical coding of behavior (Bicker and 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, are 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, with the semantics of the local and global signals being quite different, and even mutually opposed.

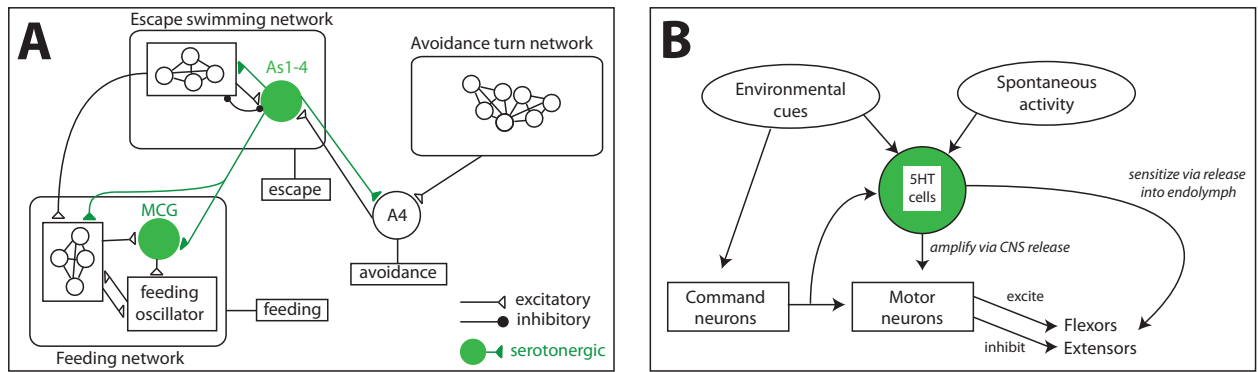


Figure 1: Invertebrate model neuromodulatory systems. A) The outline structure of three motor networks in the mollusc *pleurobranchaea* associated with avoidance turns, escape swimming and feeding. The key serotonergic neurons are the As1-4 neurons in the escape network and the MCG neurons in the feeding network; the former appear to exert some hierarchical influence over the latter. Figure adapted from (Jing and Gillette, 1999, 2000, 2003). B) Cartoon of the involvement of serotonin in the control of posture in a lobster, 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.

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 *C. elegans* (Horvitz et al., 1982; Zhang et al., 2005), molluscs and leeches (Getting, 1989; Gillette, 2006), the sea hare *aplysia* (Hawkins, 1984), crustaceans (Flamm and Harris-Warrick, 1986a,b; Kravitz, 2000), cockroaches (Walz et al., 2006) and well beyond, giving rise to a wealth of well-reviewed examples. Figure 1 shows two cases taken from feeding and escape in the mollusc *pleurobranchaea* (Jing and Gillette, 2000) and postural aggression in the lobster (Kravitz, 2000); we use these, along with learned defense in *aplysia* (Hawkins, 1984; Roberts and Glanzman, 2003), to illustrate some of the key theoretical points.

Figure 1A 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. Escapes are strong and swift reactions to an aversive encounter with a potentially predatory conspecific, and are in competition with mere avoidance turns to less aversive stimuli. Serotonin neurons (As1-4 in the escape network; and the metacerebral giant neurons, MCG, 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 to the swimming rhythm. They may thus suppress avoidance turning, by preventing appropriate patterns of activity in the A4 neurons (Getting, 1989; Jing and Gillette, 1999, 2003).

However the As1-4 neurons also act as 'hierarchical central organisers' 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, with even the serotonin content of the MCG neurons (and therefore presumably release) being higher in hungry animals, and the neurons themselves being 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 choice of the animal between orienting towards, 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 also the modulation of the relationship between somewhat separate networks. Interactions between these make serotonin's pattern of influence complex. Second, although serotonin can exert quite a general facilitatory influence, with even exogenous application having 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. Another example of this is that serotonin is also involved in feeding in nematodes (Chase and Koelle, 2007), having an important effect when the animal reaches a bacterial 'lawn' (here, apparently signalling food rather than hunger). Its net effect is to facilitate some behaviors (notably pharyngeal pumping and egg laying), but simultaneously to inhibit others (locomotion). Fourth, we note the varied representational associations of serotonin in these systems, including aversion.

Figure 1B 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. An initial finding was 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, Bevington and Clarac, 1982; Helluy and Holmes, 1990). However, as the circuit in the figure implies, this is not a straightforward product of behavioral selection through serotonin, since 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 shows facilitation of *either*, boosting the effect of the activity of the command neurons on the motor neurons, and also 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 towards boosting the flexion command connections over the extension connections (Ma et al., 1992). The excitation of the serotonin neurons may be indirect, since high induced firing rates of the command neurons leads only to a very modest increase in the firing rate of the serotonin cells, from

their background spontaneous activity of around 0.5-1Hz to only 3-5Hz.

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 and Menzel, 1989; Sombati and 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; but, with the previous example, this 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 a faster modulation riding on top of this. 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 taken over by other neuromodulators such as dopamine (Daw et al., 2002). Interestingly, 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 co-release other substances such as the neuropeptide proctolin, (Siwicki et al., 1987); co-transmission is again a very common motif (Trudeau and Gutiérrez, 2007) which adds obvious complexity to interpretation.

Our final example is the action of serotonin 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 signalling messengers that ultimately boost the strengths of the synapses concerned (Byrne and Kandel, 1996; Hawkins, 1984), sensitizing the reflex. Serotonin is also involved in longer-term, associative, plasticity associated with this system, in which otherwise too weak sensory stimuli come, over the course of learning, to be able to elicit the reflex. This involvement of serotonin in learning may have pre-synaptic components, which elaborate those involved in sensitization (Hawkins, 1984) and also a post-synaptic component (Roberts and Glanzman, 2003).

This example shows two successively longer timescales of the action of serotonin on top of 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 changes in the environment. It also implies that serotonin neurons can directly represent affectively important external stimuli such as shocks; as mentioned, section 3 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 and 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 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 the causal link between this learning and serotonin has seemingly 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 and Fuxe, 1964; Jacobs and Azmitia, 1992). The motor circuits also become somewhat functionally and anatomically specialized. There are two groups of raphe nuclei, a caudal group (called B₁-B₄ Dahlström and 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 and Fuxe, 1964). The rostral group includes the median (MRN, or B₈) and dorsal (DRN; or B₆;B₇) raphe, which have distinct pharmacological sensitivity (Judge and 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 and Molliver, 1987). For instance, serotonin in the dorsal hippocampus and the caudal shell of the nucleus accumbens primarily arises from the MRN; serotonin in the amygdala and much of the rest of the accumbens (including the core) from the DRN (Azmitia and Segal, 1978; Brown and Molliver, 2000; McQuade and 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 and Fornal, 1993, 1997, 1999; Jacobs et al., 2002). 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 non-serotonergic) 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). Further, recent single-neuron juxtacellular labelling studies in rats have shown that characterizing serotonergic neurons from extracellular electrophysiological recording alone is likely to be highly error-prone (Allers and 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-HT₂ receptors against the 5-HT₁ receptors); further, their different affinities for serotonin may allow for multiplexing of the serotonin signal into tonic and phasic modes, with high affinity receptors detecting low concentrations across large distances, and low affinity

ones 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 (the latter even being different in axons from the MRN versus the DRN, Brown and Molliver 2000; Kosofsky and Molliver 1987; Rattray et al. 1999, or having contextual dependence based on extra factors such as corticosterone levels, Gasser et al. 2006). In addition, the receptors are subject to post-translational modification in specific target zones. Note further the complexities of inter-neuromodulator interaction, for instance with serotonin acting at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and certain other receptors *boosting* the release of dopamine, and serotonin acting at 5-HT_{2C} *suppressing* it (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 and Vandermaelen, 1982) and other neuromodulatory neurons too; however, in the former, it is an intrinsic property of the cells whereas in the latter, it normally depends on the 5-HT_{1A} autoreceptors that are presynaptic on the serotonergic cells. A different (5-HT_{1B}) autoreceptor mediates suppression of the release of serotonin by synapses of these cells. Altogether, 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 is seemingly a change in the 'sign' of certain neuromodulatory effects, for instance with serotonin being associated with the *suppression* of appetite in mammals rather than the *promotion* of it seen in leeches and molluscs (Halford et al., 2005) and, albeit with many complexities discussed in section 3, reducing reactive aggression in mammals rather than increasing it, as in lobsters and other invertebrates (Edwards and 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. Conversely, specific roles could still be played by these neuromodulators in particular motor-control circuits, but also by more specific, for instance peptide-based, neuromodulation. 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 and 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 co-release of a neuromodulator and one or more neuropeptides, to effect 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. There is substantial evidence for just such an arrangement for the neuromodulator norepinephrine (Aston-Jones and Cohen, 2005), in which it reports state information associated with unexpected events in the environment of potential relevance to almost all ongoing

computations (Aston-Jones and Cohen, 2005; Dayan and 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 a common role in processing a form of uncertainty has been postulated for acetylcholine (ACh; Yu and Dayan, 2002, 2005), consistent with its general effect on cortical and hippocampal processing and plasticity (Everitt and Robbins, 1997; Hasselmo, 1995; Holland, 1997; Sarter et al., 2005), ACh actually has a much more complicated 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, with a mix of functional specificity associated with the different groups of raphe nuclei (Cooper et al., 2002), sub-specificity within the groups (Lowry, 2002) and their efferents, but all along with the putative generality that we consider in section 3.

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 argued 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, given the existence of general-purpose information processing structures, and with the burden of particularity being lifted by increased overall complexity. 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 amidst 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 which has more unitary semantics.

3 Aversive Representation and Computation

At a more 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 and Graeff (1991), based mainly on the animal literature (and with illuminating critiques such as Panksepp, 1991), and Cools et al. (2008), 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 it, attempt to provide a refined computational view.

Negative covariance between serotonin and aversion is seen in the fact that serotonin has analgesic properties (Figure 2A,B; Behbehani and Fields, 1979; Millan, 2002; Oliveras et al., 1975; Tenen, 1968; Zhao et al., 2007), so that selective serotonin reuptake inhibitors (SSRIs) taken chronically (which boost serotonin) have an important role in the clinical management of pain (Sawynok et al., 2001; Sommer, 2004). Serotonin also suppresses panic-related escape reactions to immediately present aversive stimuli (such as shocks, water immersion etc.; Cryan et al. 2005; Dekeyne

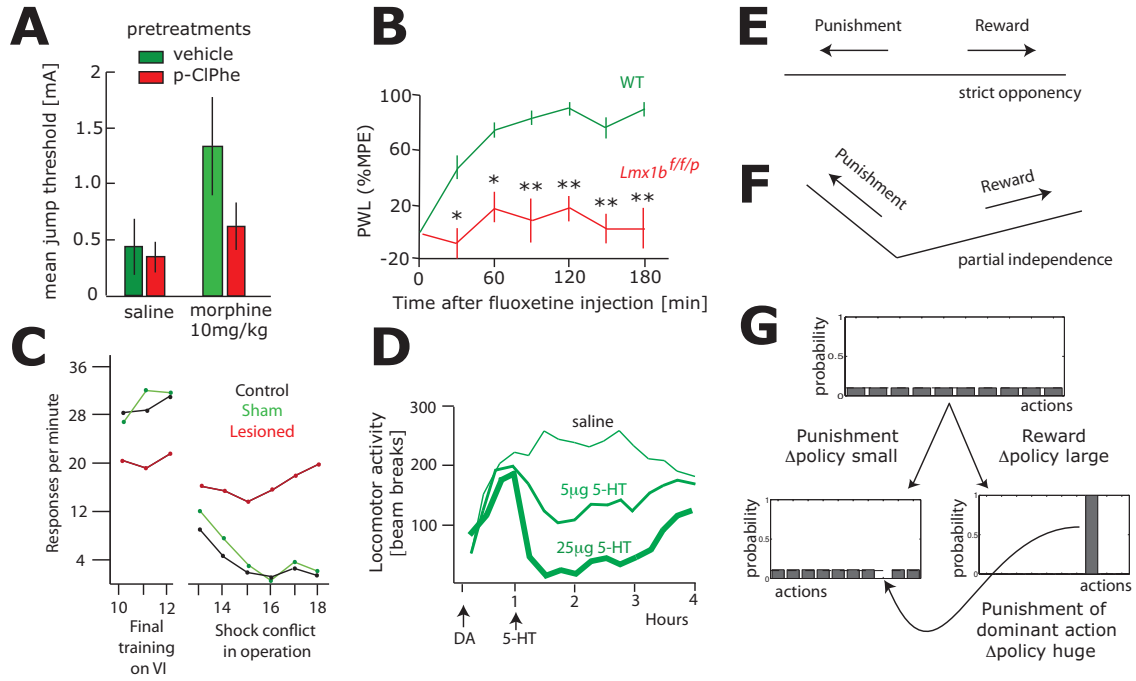


Figure 2: Serotonin's effects on affective behaviors. Panels A and B show examples of serotonin's negative covariance with aversion. **A**: Oral pre-treatment with *p*-chlorophenylalanine (p-CIPhe; which decreases levels of serotonin) abolishes the analgesic effect of morphine. Bars show the current 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 abolished 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 additionally accompanied by a conflicting delivery of a shock; only the animals in which serotonin neurons were lesioned pharmacologically with 5,7-dihydroxytryptamine (5,7-DHT) fail to lower their response rate. Adapted from Tye et al. (1977). **D**: Serotonin-dopamine opponency. The locomotor activity following DA injection (20µg; no stereotypies observed) into the nucleus accumbens is antagonised by injection of serotonin in a dose-dependent manner. Adapted from Carter and Pycoc (1978). **E**: The critical question is whether punishments are indeed negative rewards and thus lie on a line. This allows 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 order. **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 mainly have large effects when they prevent actions in situations where the behavioral repertoire is (effectively) small, for instance when one action is strongly promoted by the appetitive system.

et al. 2000; Maier and Watkins 2005), possibly via its actions on the dorsal peri-aqueductal gray matter (dPAG), a region that plays a critical role in organising such species-specific defensive responses (Bandler and Shipley, 1994; Blanchard and Blanchard, 1988; Bolles, 1970; Keay and Bandler, 2001; McNaughton and Corr, 2004; Nashold, 1974). Equally, low levels of serotonin metabolites correlate with reactive, non-adaptive aggression in mammals (Miczek et al., 2007), including humans (de Almeida et al., 2005; Linnoila et al., 1983; Moffitt et al., 1998; Raleigh and McGuire, 1991). Temporary dietary tryptophan depletion (ATD) in humans, which is thought to reduce levels of serotonin 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 a whole wealth of 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 are a major therapy, and ATD can powerfully re-induce symptoms of the disease (Delgado, 2000; Nutt, 2006; Smith et al., 1997).

On the other hand, the opposite is also evident: serotonin can correlate positively with aversion 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). Further, 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 where aversive expectations are innate, such as fear of open fields or heights (Bechtholt et al., 2007; Dulawa and Hen, 2005; Gordon and Hen, 2004; Graeff et al., 1996; Gray, 1991; 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 2C; Cervo et al., 2000; Dekeyne et al., 2000; Geller and Seifter, 1960; Graeff, 2002; Graeff and Schoenfeld, 1970; Kennett et al., 1997; Lucki, 1998; Stevens et al., 1969; Tye et al., 1977). Finally, serotonin also opposes dopamine directly via 5HT_{2c} receptors on dopaminergic neurons (Higgins and 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 antagonised by serotonin (Figure 2D; Carter and Pycock, 1978).

An important caveat is that in a large number of experiments, serotonin seems to correlate negatively with activity: in the face of immediately present punishments, it suppresses escape behaviors (e.g. the paw withdrawal response to a painful stimulus); in the face of aversive expectations, it suppresses exploration, feeding and appetitive instrumental behaviors. These cases all involve suppressing actions, though differently motivated ones. Thus, an alternative notion is that serotonin's main effect is behavioral suppression or inhibition (Brodie and Shore, 1957; Depue and Spoont, 1986; Soubrié, 1986), perhaps via its ability to suppress theta rhythmicity in the hippocampus (Gray and McNaughton, 2003). However, inhibition is certainly not completely general (Chamberlain et al., 2006; Clark et al., 2005), and also has to be interpreted within the context of serotonin's overall positive association with activity, as discussed in section 2 (Jacobs and Fornal, 1999).

Deakin and Graeff (1991) and Cools et al. (2008) suggest that anatomical and receptor specificities

could resolve the essential paradox, with separate serotonin projections to the (i) PAG suppressing panic; (ii) amygdala enhancing anxiety; and (iii) hippocampus being involved in depression. Further, Cools et al. (2008) link inhibition and aversion by suggesting the serotonin projection to the (iv) orbitofrontal cortex could be involved in suppressing structures such as the amygdala. This could mediate the boosted aversive processing of such stimuli as fearful faces that is associated with serotonin depletion. This resolution provides an important implementational account of the involvement of serotonin in aversive processing. In this section, we suggest a computational and algorithmic rationale for it within the rather complex (*eg* Balleine, 2005; Daw et al., 2005; Dickinson and Balleine, 2002; Everitt and Robbins, 2005; Killcross and Coutureau, 2003) overall architecture of affective control. This architecture has been subject to detailed computational modeling in the framework of reinforcement learning (Bertsekas, 2007; Puterman, 2005; Sutton and 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 pre-programmed response to such predictions. We suggest that serotonin is an imperfect reflection of dopamine, because the opponency between reward and punishment is fundamentally asymmetric, with, at least in species such as rats and primates, rewards being typically rare and caused by actions of the self, and punishments being typically common and originating 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 changes over time and 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 Pavlovian conditioning, in which subjects receive the rewards independent of their actions, and can merely predict them based on the state. Importantly, subjects generate responses to Pavlovian predictors, such as approaching and engaging with stimuli predicting food, without having to learn that approach is appropriate (Brown and Jenkins, 1968), and will emit such responses even when they are instrumentally deleterious, resulting in lower rewards than otherwise obtainable (Breland and Breland, 1961; Dayan et al., 2006; Williams and Williams, 1969). The mapping of prediction to Pavlovian response appears to be evolutionarily pre-programmed (Hirsch and Bolles, 1980), static and inflexible, but 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 emphatically not the only one; 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 and 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 and Schultz, 1999), and thereby instrumental conditioning. Dopamine also plays a role in appetitive conditioning in invertebrates (Brembs, 2003; Brembs et al., 2002; Nargeot et al., 1999), although there is not yet even the suggestive evidence there is for octopamine in bees (Hammer, 1993) that this involves an analogous prediction error.

The full computational requirement for appetitive control includes choosing not only which action to perform, but also when to perform it. This provides a final implementational role for dopamine, since 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 and Hauber, 2006; Panksepp, 1998; Salamone and Correa, 2002; Satoh et al., 2003; Taylor and Robbins, 1984). Niv et al. (2007) accounted for this 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 this might underlie a dopaminergically-influenced (Murschall and 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 getting a different one, perhaps by boosting the estimated average rate of rewards.

In sum, RL provides a (not universally accepted, Berridge, 2007) multi-level understanding of the phasic and tonic aspects of dopamine's role in *appetitive* instrumental conditioning and the learning of state values in 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 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 the role of serotonin.

Serotonin and aversive control

One side 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 section 2 that opponency is a common motif for neuromodulators, and there is direct behavioral and cellular evidence for opponency between serotonin and dopamine (Carter and Pycock, 1978; Higgins and Fletcher, 2003; Kapur and Remington, 1996; Redgrave, 1978). This suggests that serotonin might be viewed as an opponent to dopamine in affective control, and raises three algorithmic and implementational questions: does serotonin provide a prediction error which can be used to learn a) aversive state values and b) aversive state-action values? Is serotonin involved in modulating or mounting Pavlovian responses? Does serotonin influence the vigor of responding? We will see 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), there is currently extremely little (Walletschek and Raab, 1982) physiological evidence showing that the activity of serotonin neurons reports anything like an aversive prediction error (Jacobs and 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 in order to work out what it is optimal to do. Figure 2E illustrates that RL typically subtracts costs 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 and Balleine, 2002; Dickinson and Dearing, 1979; Ganesan and Pearce, 1988; Gray, 1991), for instance with the unexpected absence of punishment having some of the properties of an unexpected reward, and the frustration of not getting an expected reward being aversive. However, there are different ways that such a single continuum involving both rewards and punishments might neurobiologically be implemented or approximated, and thus a critical general representational and implementational issue is the extent to which it is, and why two neuromodulators might be involved in representing it, rather than just one.

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 and 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 on dopamine (e.g., Cameron and Williams, 1995; Fletcher et al., 2002; Fletcher and Korth, 1999; Fletcher et al., 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 at present contradictory (Burghardt et al., 2007, 2004; Hashimoto et al., 1996; Inoue et al., 1996). Further, 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 baseline of the activity of dopamine neurons have been suggested as reporting on the absence of expected rewards (Bayer and 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 2F) 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. Crudely, animals with large behavioral repertoires and sparse rewards face the problem of working out what to do, and not what not to do (see Figure 2G). Rewards are more informative about the former; punishments about the latter. Further, animals arguably gain rewards based on 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 2G). 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 inhibition of 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 and Zanutto, 1997). Actions could be positively reinforced for moving the actor from a state with negative expectations to one that is neutral. While serotonin may be involved in the acquisition or representation of the aversive state value, the prediction error consequent on 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 offers some support for this view (Beninger et al., 1980).

Serotonin and Pavlovian responses: This consequence of the asymmetry between rewards and punishments shifts the emphasis towards the complex structure of pre-programmed aversive responses (Blanchard and Blanchard, 1988; Bolles, 1970; Keay and Bandler, 2001). Indeed, aversive Pavlovian learning, linking stimuli to such responses is very fast and powerful, while aversive instrumental learning (at least of actions that are not the species-specific responses to particular aversive stimuli; see Brembs and 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 and Graeff, 1991; Graeff, 2002, 2004; McNaughton and Corr, 2004)?

There are at least two sets of suggestions associated with this, together offering a central coupling between aversive predictions and behavioral inhibition of prepotent responses (Soubrié, 1986). First, Deakin (1983); Deakin and Graeff (1991); 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. This is very closely related

to the inhibition of predominant responses suggested above.

The asymmetry between rewards and punishments provides a second link to behavioral inhibition. Given predictions of (increasing) future rewards, it is a reasonable heuristic to continue doing whatever action is ongoing (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 whatever action is ongoing and is leading to 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 pro-aversive consequence in the enhanced processing of fear-inducing or negatively-valenced stimuli. Dayan and Huys (2008) made a similar argument for the effects of serotonin under normal circumstances of creating over-optimistic evaluations of states, and thus the reinduction of symptoms of depression that is induced by tryptophan depletion (Delgado, 2000; Nutt, 2006; Smith et al., 1997).

Serotonin and sloth: The final facet of aversive signaling we consider is the relationship to vigor, where the opponency between dopamine and serotonin is perhaps seen at its clearest. Serotonin abolishes a wide variety of energizing effects of drugs that elevate tonic dopamine (although a complicating factor is that serotonin's own release and reuptake is affected by some of them): it antagonises 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) and sexual behavior (Balon, 2006; Fadda, 2000); on motor activation (Carter and Pycock, 1978, see figure 2D;); on conditioned reinforcement (Fletcher, 1996; Fletcher et al., 1999); and on drug reward more generally (Higgins and Fletcher, 2003). This is consistent with appetitive/aversive opponency, under 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 may underlie some of dopamine's positive covariance with punishment (Bland et al., 2003; Cabib and 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 Pavlovian-instrumental transfer (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. This suggests that expectations of higher long-run punishment rates could lead to less vigorous and more slothful actions (see Dickinson and Pearce 1977; Herrnstein and 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 to 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 anti-impulsive effects as observed in discounting tasks in which subjects choose between an early, small, 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 Schweighofer et al. (2008); Tanaka et al. (2007) have made the alternative suggestion that serotonin determines the discount factor (interest rate) which allows distant rewards and punishments to be weighted against proximal ones, and linked this using fMRI data to changes in the topographic structure of the representation of predictions and prediction errors across the striatum (Tanaka et al., 2004).

To summarize, we have argued that the primary interpretation for serotonin signalling 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 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 that we also described.

4 Discussion

We adopted a computational perspective on the function of serotonin, though 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, based on 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 import for substantial swathes of cortical and subcortical processing and plasticity. Finally, in the light of this, we considered serotonin's involvement in the prediction of aversive outcomes, and, via the effects of such predictions on Pavlovian behavioral inhibition, accounting 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 and Shore, 1957; Solomon and Corbit, 1974) and computational (Grossberg, 1984) communities, our perspective is most directly an evolution of the ideas of Deakin (1983); Deakin and Graeff (1991), via the theoretical work of Daw et al. (2002). The main elaboration comes from a refined analysis of the interaction between Pavlovian and instrumental conditioning (Dayan and Huys, 2008; Dayan et al., 2006; Mackintosh, 1983), and thereby a richer view of the immediate effect of predictions of future aversive outcomes on actions, and a means of addressing the apparent paradox for opponency that *lowered* serotonin can lead to apparently *enhanced* processing of stimuli with negative affective value.

These notions are only partial, and are based on a very incomplete exegesis of many of the effects of serotonin. In particular, we resolved the paradox associated with serotonin's being either a behavioral excitator (Jacobs and Fornal, 1999) or inhibitor (Depue and Spont, 1986; Soubrié, 1986)

by fiat, arguing that excitation of particular motor circuits could co-exist with a general inhibitory function, given appropriate anatomical specificity. However, this is really a place-holder for what could 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.

Further, we have ignored many important issues associated with the wealth of different types of serotonin receptor (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 sub-class of serotonin receptor over another, it is very hard to understand exactly how. Worse, these receptors interact with serotonin release and the release and effect of other neuromodulators according to a feedforward and feedback control scheme which operates over a huge range of timescales, and of which we have only somewhat vague ideas. As often remarked, the extreme difference between the pharmacological and therapeutic delays in the action of selective serotonin reuptake inhibitors (SSRIs) in psychiatric diseases (up to twelve weeks in obsessive-compulsive disorder, Mansari and Blier, 2006) implies a critical challenge in building adequate dynamical 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, pharmacological sensitivities, and even axonal structures.

Next, for reasons of space, we have not been able to address 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 first-line treatment in many mood disorders. Indeed, reinforcement learning 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 and Dayan, 2005).

Finally, we noted that there are multiple controllers which interact in ways that are only incompletely understood (Balleine, 2005; Daw et al., 2005). For appetitive outcomes, the role of dopamine 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 there may be special features of the dopamine projection to prefrontal regions (Lacroix et al., 2000; Lammel et al., 2008; Williams and Goldman-Rakic, 1995) that are 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 pharmacological 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 signalling (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. Various of these suffer from problems of auto- and cross-regulation of the neuromodulators (Panksepp and 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 and de Montigny, 1999), in a way that might differ in different neural populations (Beyer and Cremers, 2008). Further, in the face of blocked serotonin transport, dopamine synapses become loaded with, and release, serotonin as well as dopamine, since the dopamine transporter has a (weak) affinity for serotonin, and co-release both neuromodulators (Zhou et al., 2005).

Fortunately, a range of new methodologies for investigating serotonin is under active development. We will just describe a few examples (Wightman, personal communication, Schweimer et al., 2008, Mainen, personal communication). One 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, this is hard, 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, since the spatial distributions of dopamine and serotonin projections differ, it might be possible to get a window onto the activity of at least some of the multitudinous parts of the serotonin system.

Second, the use of juxtacellular labelling 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 also the spike-shape criteria that have historically been adopted to discriminate serotonergic from non-serotonergic 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 were 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 and 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 (Mainen, personal communication) to have channelrhodopsin 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 this could be used to test theories suggesting 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 provide certainty about the serotonergic basis of activity recorded by extracellular electrodes. This 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 have argued are central to the understanding of serotonin, such as separate model-based and model-free contributions to control, and the interaction of Pavlovian and instrumental conditioning.

Fourth, genetic and molecular biology allow for modulation of increasingly specific subparts of serotonergic systems over long, and increasingly also short, timescales. They have already been extremely valuable in refining our understanding of the contributions of different receptor types (Gordon and 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 tools are being developed 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 critical findings to be generalized to humans, and also permitting investigation of 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 improving brainstem 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 and 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 the influences over it of neuromodulators, will help herald a whole new comprehension of many aspects of serotonin.

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