Review

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Cognitive-emotional interactions

Serotoninergic regulation of emotional and behavioural control processes

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5-Hydroxytryptamine (5-HT, serotonin) has long been implicated in a wide variety of emotional, cognitive and behavioural control processes. However, its precise contribution is still not well understood. Depletion of 5-HT enhances behavioural and brain responsiveness to punishment or other aversive signals, while disinhibiting previously rewarded but now punished behaviours. Findings suggest that 5-HT modulates the impact of punishment-related signals on learning and emotion (aversion), but also promotes response inhibition. Exaggerated aversive processing and deficient response inhibition could underlie distinct symptoms of a range of affective disorders, namely stress- or threat-vulnerability and compulsive behaviour, respectively. We review evidence from studies with human volunteers and experimental animals that begins to elucidate the neurobiological systems underlying these different effects.

The paradox of 5-HT

Of the central monoamine neurotransmitters, 5-hydroxytryptamine (5-HT, or serotonin) presents perhaps the greatest challenge in terms of deducing its main role; even when considering its modulatory effect on behaviour and cognition it is difficult to discern one single principle underlying its actions. This is not surprising given the diversity of its neuroanatomical ramifications from the midbrain dorsal and median raphé nuclei (DRN and MRN) to virtually all regions of the brain (Figure 1), and the fact that its actions are mediated by at least 17 distinct receptors. Yet there is no doubting the importance of 5-HT, not only in terms of modulating sensory input and motor output, but also in terms of its central role in cognition and emotion and implication in affective disorders such as anxiety and depression. Given the impact that functional studies of dopamine have had on recent models of reinforcement learning and cognitive control, many researchers have turned their attention to functional investigations of 5-HT in humans, although the variety of methods we have for manipulating 5-HT function in humans is much more restricted than that for experimental animals (Box 1).

Some of the impetus for advancing our understanding of 5-HT has come from the need to explain a major clinical paradox; namely, on the one hand, the anxiety-reducing effects of the benzodiazepines, which reduce 5-HT transmission [1], and on the other hand, the ameliorative effects of the long-term use of selective serotonin reuptake inhibitors (SSRIs), which increase 5-HT transmission (Box 1), in depression and panic disorder [2,3]. This paradox is pertinent given that anxiety is often comorbid with depression, and that both disorders are associated with increased aversive processing and enhanced stress sensitivity.

5-HT is also implicated in impulse control disorders; 5-HT levels are reduced in patients with mania, aggression resulting from alcoholism and in depressed patients committing suicide [4–7]. These findings are consistent with hypotheses, derived from studies with animals, that 5-HT mediates behavioural inhibition [8]. Reduction of anxiety can be construed as the removal of behavioural suppression (i.e. behavioural disinhibition). This provides a potential link between the anxiety-reducing effects of the benzodiazepines and the impulse control failures seen following reductions in 5-HT transmission. Debate continues as to whether the behavioural disinhibition associated with low levels of 5-HT is best explained in motivational or motor terms; that is, whether it reflects removal of anxiety or response facilitation *per se*. Either of

Glossary

Anxiolytic: Reducing anxiety, or an agent that reduces anxiety.
Discrete cue fear conditioning: The process by which a neutral stimulus (e.g. a tone) becomes associated with an aversive stimulus (e.g. a footshock) thus acquiring the capacity to elicit a defensive response (e.g. freezing).
Pavlovian conditioned inhibition: The suppression of appetitive responding (for reward) on the presentation of a conditioned stimulus (e.g. light) that predicts an aversive signal (e.g. shock).
Phasic neurotransmission: A form of neurotransmission triggered by behaviourally relevant signals and burst firing of, for example, dopamine neurons, which release greatly elevated levels of dopamine into the synaptic cleft, leading to stimulation of postsynaptic dopamine receptors [72].
Polymorphism: The existence of interindividual differences in a gene sequence present at >1% in a population.
Tonic neurotransmission: The regulation of constant low levels of extracellular neurotransmitter. For example, tonic dopamine release is thought to depend on slow, irregular spike activity of dopamine neurons that results in the release of low levels of dopamine [72].

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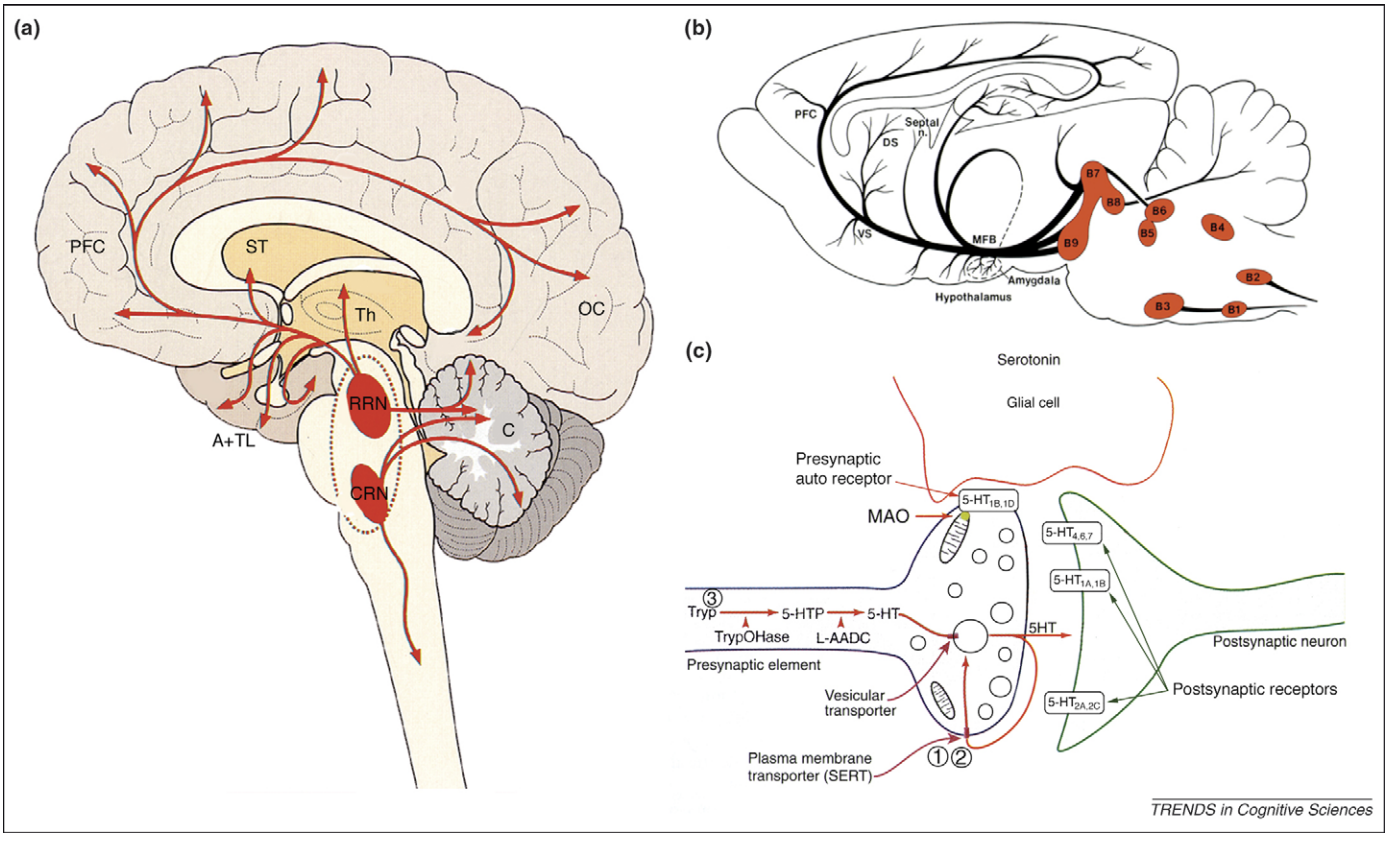

Figure 1. Neurobiology of the central 5-HT systems. **(a)** Neuroanatomical projections in human brain. Depicted here are the projections (shown as red arrows) from the caudal raphé nuclei (CRN) and one of the rostal raphé nuclei (RRN), i.e. the dorsal raphé nucleus. There are also projections from the median raphé nucleus (another one of the RRN), for example to the hippocampus (not shown). C, cerebellum; Th, thalamus; A, amygdala; TL, temporal lobe; ST, striatum; PFC, prefrontal cortex; OC, occipital cortex. **(b)** Neuroanatomical projections (shown as bold branching lines) in rat brain. B7–B9, rostral group of neurons in upper midbrain with ascending projections into forebrain. B1–3 caudal group in lower brainstem with descending projections into medulla and spinal cord. B4–6 are an intermediate group, which may project into both ascending and descending groups. B7= dorsal raphé nucleus, B8= medial raphé nucleus (see page 280 of ref [70]). MFB, medial forebrain bundle; DS, dorsal striatum; VS, ventral striatum; PFC, prefrontal cortex; Septal n, septal nucleus. **(c)** Schematic 5-HT neuron. Tryp, tryptophan; TrpOHase, tryptophan hydroxylase; 5-HTP, 5-hydroxytryptophan; L-AADC, L-amino acid decarboxylase; SERT, serotonin transporter; MAO, monoamine oxidase; 5-HT_{1A}, 5-HT_{1B}, 5$HT_{2A,C}$, etc., pre- and postsynaptic 5-HT receptors. (See Ref. [70] for further details.)

these explanations could involve a mutually inhibitory relationship with neuromodulatory dopaminergic mechanisms, for example, in the amygdala, ventral striatum (nucleus accumbens) or the dorsal striatum (caudate putamen), that underlie appetitive behaviour, the effects of reward or reinforcement and motor control. However, behavioural disinhibition cannot readily account for the role of 5-HT in depressed mood. In depression, it seems

Box 1. Methods for manipulating the 5-HT system

A selective neurotoxin for 5-HT

The most common means of impairing 5-HT function in experimental animals is by use of the selective neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), which is taken up by 5-HT and noradrenergic neurons (see '1' in Figure 1c) and at appropriate doses selectively destroys those neurons. The selectivity of the agent can be enhanced by pharmacological protection of the noradrenaline-containing neurons and by stereotaxic placement into discrete brain regions. The intraventricular administration of 5,7-DHT to the rat can produce an almost complete (90%) and permanent depletion of 5-HT in forebrain regions (e.g. Ref. [52]).

Acute versus chronic effects of SSRIs (see '2' in Figure 1c)

The acute effects of single doses of SSRIs such as Prozac (fluoxetine) and citalopram differ from the effects of chronic (repeated) administration, a fact long recognized in the clinic, where depression only responds to chronic medication. There is evidence that the increase in 5-HT produced by acute administration of SSRIs not only stimulates postsynaptic 5-HT receptors, but also produces a net reduction of activity in the 5-HT system by flooding the somato-dendritic inhibitory 5-HT_{1A} autoreceptors (Figure 1). As these become desensitized during long-term treatment, however, the net effect is for the 5-HT system to be activated, although this could result in a downregulation of certain postsynaptic receptors such as the 5-HT_{2A} and 5-HT_{2C} subtypes [73,74]. These contrasting actions of acute and chronic administration have to be borne in mind when interpreting the effects of these drugs. Rarely have investigators capitalized on the different effects in studies of cognitive or affective functions in healthy volunteers (but see Refs [27,75] and text).

Acute tryptophan depletion (ATD) procedure

Mild 5-HT depletion in humans (or experimental animals) can be achieved transiently through the acute dietary tryptophan depletion (ATD) procedure. Tryptophan is the amino acid precursor of 5-HT (see '3' in Figure 1c). ATD thus produces a rapid decrease in the synthesis and release of brain 5-HT [76–78]. Tryptophan is depleted by ingestion of an amino acid mixture that does not contain this essential amino acid but does include other large neutral amino acids (LNAA) [76]. The amino acid load increases protein synthesis in the liver and increases competition for transport across the blood–brain barrier, with both factors decreasing tryptophan availability in the brain. The tryptophan depletion technique has been employed successfully to support the 5-HT hypothesis of depression and is now a routine procedure in human psychopharmacological studies. A less frequently used procedure is tryptophan loading, which hypothetically boosts 5-HT function.

that the deficient 5-HT activity leads to a bias in processing away from positive and towards negative stimuli, so that the latter have a greater impact on behaviour and cognition [9], with long-term SSRI treatment counteracting this bias.

Deakin and Graeff [1] attempted to resolve the paradox by hypothesizing that anxiety, panic and depression arise from modulation of distinct neural systems (e.g. the DRN projection to the amygdala, the brainstem and the MRN projection to hippocampus, respectively) and implicate different receptors. Here, we recast this controversy in a more contemporary analysis that focuses on similarly paradoxical effects of 5-HT involvement in aversive processing and inhibitory control. Based on this analysis we hypothesize that, at the subcortical level, serotoninergic activity might provide a motivational process opposed to that mediated by dopamine activity. However, direct serotoninergic modulation of the orbitofrontal cortex (OFC) might serve a different function, namely to facilitate descending inhibitory control of subcortical mechanisms that regulate emotional processing and behavioural output.

5-HT: threat, punishment and aversive learning

Enhanced sensitivity to threat-related stimuli and punishment is a cardinal feature of several mood and anxiety disorders that implicate central 5-HT systems [10–14]. Consistent with this observation are findings that 5-HT modulates the responsiveness of the amygdala and connected medial frontal regions to threat-related stimuli in humans and animals; Table 1 summarizes the effects reviewed below [15–19].

5-HT modulation of aversive responses in humans

In humans, the amygdala response to fearful faces and other aversive stimuli depends on allelic variation in the promoter region of the 5-HT transporter (5-HTT) gene [20] (Box 2). Individuals carrying one or two copies of the short allele of the 5-HTT-linked polymorphic region (5-HTTLPR), which is associated with reduced 5-HT transporter expression, are termed 's-carriers'; they display

Box 2. The use of genetic polymorphisms to study 5-HT function

There is a growing catalogue of genetic polymorphisms (see Glossary) in the human population that modulate the functioning of particular neurotransmitters. Thus individual genetic variation might lead to hypothesized changes in regulation of the 5-HT system, which can be exploited to make inferences about how the system functions to produce behaviour and cognition. Such polymorphisms occur in experimental animals, or can be artificially introduced by transgenesis, and this provides a way of testing the neurochemical effect of the polymorphism at the functional level. By logical triangulation, therefore, the relationship to such a change can be related to cognitive or behavioural variation in human samples, which at equilibrium usually have predictable proportions of these genotypes reflecting those in the population as a whole. A prominent example is a polymorphism (5-HTTLPR) linked to the 5-HT transporter and involving a variable repeat sequence in the promoter region of the gene that encodes short (s) and long (l) allelic variants. The 5-HTTLPR regulates the efficacy of the 5-HT transporter (5HTT), and the s and l alleles are associated with its reduced and increased expression, respectively, as evidenced by analyses of postmortem tissue [20]. Although one might expect that reduced expression of the 5-HTT would lead to exaggerated 5-HT transmission, in fact, the s allele has been associated with reduced 5-HT function, possibly as a result of lifelong differences in 5-HTT gene transcription leading to long-term neurochemical adaptations [23]. The hypothesis that effects of the 5-HTT polymorphisms reflect developmental changes rather than direct effects in adulthood was also suggested by a lack of difference in 5-HTT binding in humans *in vivo* [79]. The 5-HTT polymorphism has been exploited most notably in a study showing that in combination with life events, s-carriers exhibit a greater incidence of depression [22]. Other genetic polymorphisms of interest include those affecting the expression of tryptophan hydroxylase (the synthetic enzyme for 5-HT) and the 5-HT_{2A} receptor.

Table 1. Reviewed effects of serotoninergic manipulations on aversive processing

References	Manipulation	Negative bias	Hypothesized effect on (tonic) 5-HT levels
Human volunteers			
Reviewed in [20]	5-HTTLPR genotype: s-allele	Up: increased amygdala BOLD response to fearful faces	Down
[19,24]	ATD	Up: increased amygdala BOLD response to fearful faces	Down
[26]	Repeated citalopram	Down: reduced fear recognition and reduced amygdala BOLD response to fearful faces	Up
[31]	ATD	Up: enhanced punishment prediction learning	Down
[32]	ATD	Up: increased Stroop interference from negative words	Down
[9]	ATD	Up: enhanced interference from sad distractors	Down
[33]	ATD	Up: reduced distraction by happy relative to sad words and enhanced 'limbic' BOLD response to sad words	Down
[36]	ATD	Up: reduced discrimination between choices associated with distinct reward magnitudes	Down
[34,35]	ATD	Up: reduced speeding with increasing probability of reward and punishment	Down
[37]	Single dose of citalopram	Up: enhanced tendency to switch following punishment during reversal learning	Down
[38]	ATD	Up: enhanced BOLD response in dorsomedial PFC to punishment during reversal learning	Down
Experimental animals			
Reviewed in [39]	Stimulation of 5-HT neurons in the DRN	Down: inhibited active escape from brainstem stimulation	Up
[40]	Iontophoresis of 5-HT on amygdala neurons	Down: inhibited glutamate-induced excitation of amygdala neurons	Up
[42]	Single dose of citalopram	Up: enhanced discrete fear conditioning	Down
[42]	Repeated citalopram administration	Down: impaired discrete fear conditioning	Up

greater levels of trait anxiety [21] and are at greater risk for depression following stress (i.e. stress vulnerability) [22]. These same s-carriers exhibit greater amygdala activation in response to fearful faces than individuals homozygous for the long allele. One assumption is that the short allele could be associated with reduced 5-HT function [23] (Box 2) and, accordingly, these observations can be reconciled with the hypothesis that low levels of 5-HT enhance the brain response to threat-related stimuli.

Consistent with this interpretation is the demonstration that acute depletion of the 5-HT precursor tryptophan (acute tryptophan depletion, ATD; Box 1) in young healthy male participants enhanced the amygdala response to threat-related stimuli (fearful faces), particularly in vulnerable, threat-sensitive individuals [19,24]. This effect concurs with the effect of long-term SSRI treatment (thought to enhance 5-HT transmission; Box 1) in healthy volunteers, which reduced the ability to recognize fearful expressions (but see Ref. [25]) and decreased the amygdala response to fearful, but not happy faces [26]. The effect of repeated, long-term SSRI treatment contrasted with that of a single SSRI dose, which enhanced the detection of fearful facial expressions in healthy volunteers [27,28]. This latter effect could reflect the hypothesized paradoxical reduction in 5-HT activity after a single dose of SSRI treatment (Box 1).

Fearful faces might act as predictive cues (conditioned stimuli) signalling the presence of threat-related (unconditioned) stimuli in the environment [29,30]. Direct evidence for a specific effect of 5-HT on punishment prediction was obtained in a recent ATD study in which an observational learning task was employed that enabled the separate investigation of reward prediction and punishment prediction [31] (Figure 2a). Subjects were presented with one stimulus associated with reward (a smiley face, a pleasant tone and a +£100 sign) and another stimulus associated with punishment (a sad face, an unpleasant tone and a –£100 sign). On each trial, one of the two stimuli was highlighted,

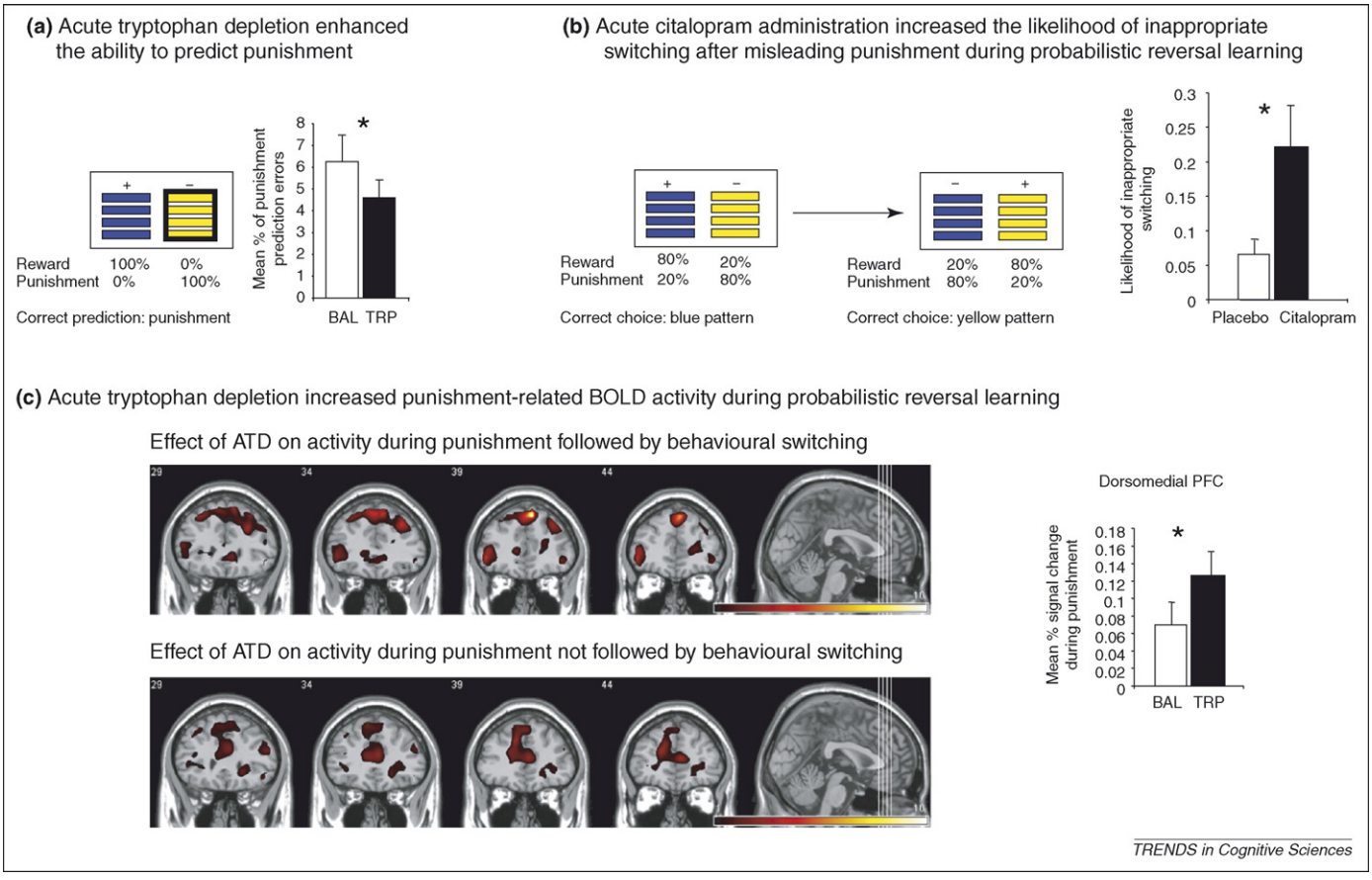

Figure 2. Effects of 5-HT manipulation on punishment-related processing in humans. **(a)** ATD enhanced the ability to predict punishment [31]. In this study, subjects were presented with two abstract visual patterns, one of which was associated with reward, the other with punishment (these contingencies reversed multiple times to maximize learning demands). On each trial, one of the two patterns (here, the yellow pattern) was highlighted with a black box, after which subjects predicted either reward or punishment (by pressing one of two buttons). The outcome was presented after the subject made his or her prediction (here, punishment) and depended on the highlighted stimulus, not on the response of the subject. Subjects made significantly fewer punishment prediction errors after the tryptophan-depleting (TRP) drink than after the tryptophan-balancing (BAL) drink. **(b)** Acute administration of the SSRI citalopram (which probably reduces 5-HT transmission) impaired probabilistic reversal learning by increasing the likelihood of inappropriate switching following misleading punishment [37]. In this study, subjects had to learn to choose the usually rewarded pattern and to avoid the usually punished pattern. After an initial acquisition stage, the contingencies reversed. Subjects on citalopram were significantly more sensitive to the probabilistic punishment than were subjects on placebo and made more inappropriate switches. **(c)** A pharmacological functional magnetic resonance imaging study showed that ATD potentiated the BOLD response to punishment during probabilistic reversal learning [38]. Shown are the ATD effects on activity during punishment events that led to behavioural switching relative to baseline correct responses (top panel) and the ATD effects on activity during punishment events that did not lead to behavioural switching relative to baseline correct responses (bottom panel). Displayed are all activations with *t*-test values >1 (see colour bars), superimposed on four coronal slices through the anterior frontal lobe (as shown on the sagittal slice) of the Montreal Neurological Institute (MNI) individual template brain (right = right hemisphere). Shown in the panel on the right is the effect of ATD on percent signal change during punishment (collapsed across switch and nonswitch events) extracted from a region of interest in the dorsomedial PFC (coordinates *x*, *y*, *z* = 8, 32, 52), defined based on reversal-related activity obtained in a previous study [71]. *, P<0.05.

after which subjects had to predict, based on trial-and-error learning, whether the chosen stimulus was associated with reward or punishment. ATD facilitated the prediction of punishment, but did not affect reward prediction.

The negative emotional bias following reductions in central 5-HT might be expressed in other ways. For example, ATD in young healthy volunteers increased interference from negative words on colour naming in the Stroop test [32] and slowed response latencies to happy words relative to sad words in an affective go–nogo task, probably reflecting enhanced interference from distracting sad words [9]. The latter finding concurred with a recent functional magnetic resonance imaging (fMRI) study, which revealed that an attentional bias towards happy relative to sad distractors was abolished by ATD, which potentiated the neural response to emotional, in particular sad, words in several subcortical areas [33]. Furthermore, reductions in 5-HT can impair cognitive performance and decision-making by enhancing the impact of punishment relative to reward. For example, we found that ATD abolished feedback-induced speeding of responding on a challenging choice reaction-time task, particularly in certain vulnerable (high-impulsive and 5-HTTLPR s-carrying) individuals [34,35]. In these studies, the probability of feedback was signalled to subjects on each trial by a colour cue. This feedback consisted of reward and punishment (in terms of bonus points) for correct and incorrect responses, respectively. Under baseline, subjects speeded their reaction times with increasing anticipated feedback probability, as a result of enhanced motivation to obtain bonus points. This feedback-induced speeding was abolished after intake of the tryptophan-depleting drink. It should be noted that this lack of speeding could have resulted either from reduced impact of anticipated reward for correct responses [36] or from enhanced impact of anticipated punishment for incorrect responses (Box 2).

Manipulation of central 5-HT also affects probabilistic reversal learning through its negative biasing effect (Figure 2b). In this task, subjects are presented with two abstract visual patterns, and they have to discover by trial and error which of the two is correct. The correct pattern is rewarded on 80% of trials, but punished on 20% of trials. Thus the task requires the maintenance of discriminative responding in the face of (probabilistic) punishment and the behavioural adaptation following contingency reversals. Not only does ATD impair performance of this task [9], but so does a single dose of citalopram (hypothesized to reduce 5-HT transmission through action at presynaptic receptors, Box 1). Specifically, Chamberlain *et al.* [37] demonstrated that a single dose of citalopram increased the likelihood of inappropriate switching following probabilistic punishment, suggesting an enhanced impact of misleading negative feedback (Figure 2b). The same probabilistic learning paradigm was employed to assess the neural effects underlying the consequences of acute 5-HT reduction (here by ATD) on this task in a pharmacological fMRI study with young healthy male volunteers [38] (Figure 2c). In keeping with the effects of acute citalopram, ATD significantly increased the task-related blood oxygenation level development (BOLD) response in the dorsomedial prefrontal cortex (PFC) during negative feedback that was followed by behavioural switching (Figure 2c). It is unlikely that this effect in the dorsomedial PFC reflects a modulation of behavioural inhibition because it was also seen during negative feedback events that did not lead to switching. The study suggests that ATD alters performance of probabilistic learning paradigms by abnormally enhancing the impact of punishment and concurs with the above-described evidence for a role of 5-HT in controlling the impact of aversive signals.

5-HT modulation of aversive processing in experimental animals

In keeping with the negative bias observed following 5-HT reductions in humans is the classic observation that 5-HT inhibits (unconditioned) aversion generated by stimulation of brainstem structures in experimental animals [39]. Furthermore, electrophysiological work with animals has shown that amygdala neurons that are excited by electrical stimulation of glutamate-releasing inputs from the cortex are inhibited by concurrent iontophoresis of 5-HT, probably by the activation of cells releasing GABA through excitatory 5-HT receptors in the amygdala [40,41] (Figure 1). Deficient 5-HT function might result in enhanced processing of harmful stimuli because of diminished inhibitory modulation of excitatory sensory afferents, thereby enabling innocuous sensory signals to be processed by the amygdala as emotionally salient [40].

In addition, manipulation of 5-HT levels in rats modulates the acquisition of discrete cue fear conditioning, which is thought to implicate the amygdala [42–45]. Discrete cue fear conditioning was enhanced by administration of a single dose of citalopram [42]. This is consistent with the anxiety-enhancing effects of acute SSRI treatment (which is hypothesized to reduce 5-HT transmission; Box 1). By contrast, long-term administration of citalopram (enhancing 5-HT transmission) impaired discrete fear conditioning consistent with its anxiolytic effects [42] (see Refs [44–46] for a more complex story on contextual fear conditioning that also implicates the hippocampus). Although it is convenient to interpret these results in terms of effects on aversive processing, it should be noted that, in the case of fear conditioning, there is the unavoidable confound of behavioural inhibition as indexed by changes in the release of freezing [8].

Summary

We reviewed a series of experiments demonstrating enhanced aversive processing after reductions of 5-HT levels and attenuated aversive processing after increases in 5-HT (Table 1). The changes in aversive processing concur with observations that reductions in 5-HT potentiate neural activity in the amygdala, which is innervated by the DRN and is often associated with fear processing. Thus serotoninergic modulation of the amygdala might affect a motivational process opposed to that mediated by dopamine activity. For example, 5-HT might mediate a form of punishment prediction error (see Box 3). This punishment prediction error might in turn be transmitted to dorsomedial frontal cortical regions, which have been implicated in error processing [47], and where neural activity is also enhanced after reductions in 5-HT.

Box 3. Motivational opponency between 5-HT and dopamine

Serotoninergic activity has long been considered to be the crucial substrate of an aversive motivational system [1]. The aversive system might serve as a motivational opponent to the appetitive system, which has been associated with dopamine activity. A specific role for 5-HT in threat or punishment prediction rather than reward prediction was proposed by Daw *et al.* [80], who extended previous hypotheses that fast phasic responses of dopamine cells carry a temporal difference prediction error of future reward [81,82]. In this model, 5-HT was proposed to act as a motivational opponent to dopamine in prediction learning, so that learning to predict future punishment depends on a transfer, with learning, of a high-amplitude phasic 5-HT response from an aversive stimulus to a conditioned stimulus that predicts it. At first sight, our observation that ATD enhances the impact and anticipation of punishment [31] seems to contradict this theoretical model in addition to classic arguments that 5-HT release provides a punishment learning system [1,80]. However, our observation would be remarkably consistent with the proposal that 5-HT mediates a punishment prediction error [80], if the modest reductions in background levels of tonic 5-HT enhanced the dynamic range of phasic 5-HT activity (Figure I). It is possible that ATD shifted the system from a tonic to a phasic mode of neurotransmission, effectively increasing the signal-to-noise ratio. Such effects would certainly mirror similar interactions between phasic and tonic neurotransmission modes that have been proposed for dopamine and noradrenaline, where tonic levels regulate phasic responses to behaviourally relevant stimuli [72,83,84]. Thus this hypothesis might reconcile observations that reductions in (tonic) 5-HT with ATD enhance the impact of punishment with classic and more recent theorizing that 5-HT release provides a punishment learning system [1,80]. It remains to be determined how the relationship between putative tonic and phasic 5-HT might be affected by other manipulations, such as administration of 5,7-DHT and SSRI.

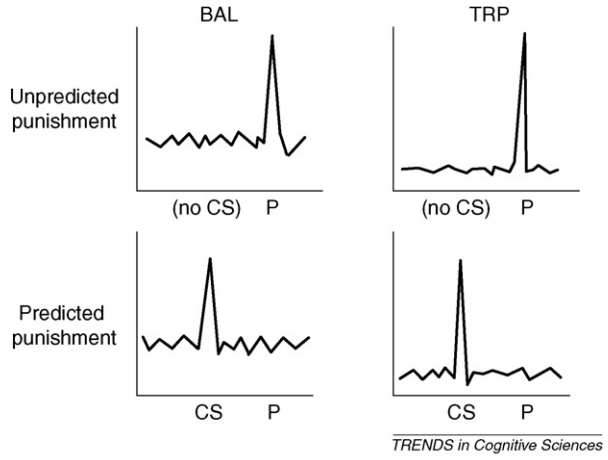

Figure I. Schematic representation of the hypothetical effect of the reduction in background 5-HT levels after ATD on phasic 5-HT activity, during unpredicted and predicted punishment. The phasic bursts illustrated are hypothesized by analogy with dopamine only; evidence for such firing of 5-HT neurons is not yet available. CS, conditioned stimulus predicting punishment, P. TRP, tryptophan-depleting drink; BAL, tryptophan-balancing drink. This illustration was made based on a presentation-style used previously by Schultz [82] to show data from dopamine neurons that code reward prediction errors.

Inhibitory response control

The hypothesis that 5-HT has a major role in behavioural inhibition has a long history, which has run somewhat parallel and counter to the hypothesis that 5-HT modulates biases towards aversive processing. There are many different forms of inhibition [48] occurring at both cortical [49] and subcortical levels [50] that could be affected by 5-HT, including, for example, Pavlovian conditioned inhibition (see Glossary). Reductions in 5-HT function increase appetitive responding for reward in conditioned inhibition paradigms [51] and several other situations in which it is appropriate to suppress responding, including tests of so-called 'impulsivity' [8,52,53]. In such cases, the inverse relationship between 5-HT function and aversive processing has been invoked; namely that 5-HT depletion reduces the effects of anxiety-related aversive stimuli that signal reward omission or postponement.

Purely motivational accounts of these findings, in terms of reduced anxiety, have difficulty explaining the opposing effects of 5-HT manipulation in certain appetitive paradigms that depend on similar motivational factors but differ as a function of the need for passive or active response contingencies. For example, we assessed the effects of depleting forebrain 5-HT on the acquisition and performance of a conditional visual discrimination task, by intracerebroventricular infusion of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) in rats (Box 1). In one case, the task required the acquisition of a stimulus–response rule or habit (i.e. if stimulus flashes FAST, then go left; if stimulus flashes SLOW, then go right) and the selection of one of two active responses on each trial (go–go). In the other case, the task required the discrimination between an active and a passive response (i.e. if stimulus flashes FAST, then 'go'; if stimulus flashes SLOW, then 'nogo'). The effects of 5-HT depletion were diametrically opposed; discrimination between two active responses was improved [54], whereas discrimination between an active and a passive response was impaired [55]. The improvement on the go–go task (which depends on the integrity of the striatum [56]) resembled that seen in rats with anterior cingulate cortex (ACC) lesions [57], the results being interpreted as reflecting the removal of interference from competitive stimulus–reward or response–reward associations on the formation and expression of stimulus–response associations mediated by the striatum. Thus, 5-HT depletion could have shifted the balance away from ACC-mediated (goal-directed) control by stimulus–reward or response–reward associations towards (habitual) control by striatum-mediated stimulus–response associations. Intriguingly, the impairment on the go–nogo task was caused by a selective inability to acquire the 'nogo' response rule [55]. In fact, 'go' responding was facilitated as in the previous study [54]. The contrasting effects of 5-HT depletion in these two cases cannot be readily explained by changes in aversive processing; clearly, additional factors must be involved.

Further strong evidence for behavioural disinhibitory consequences of 5-HT depletion comes from a recent series of studies on reversal learning with non-human primates (marmosets), showing that depletion of 5-HT by injection of 5,7-DHT selectively into the PFC (specifically in the orbitofrontal cortex, OFC) impairs reversal performance by inducing perseveration, that is, an inability to cease responding to the previously rewarded stimulus (Figure 3a) [49,58]. The deficit was present only when

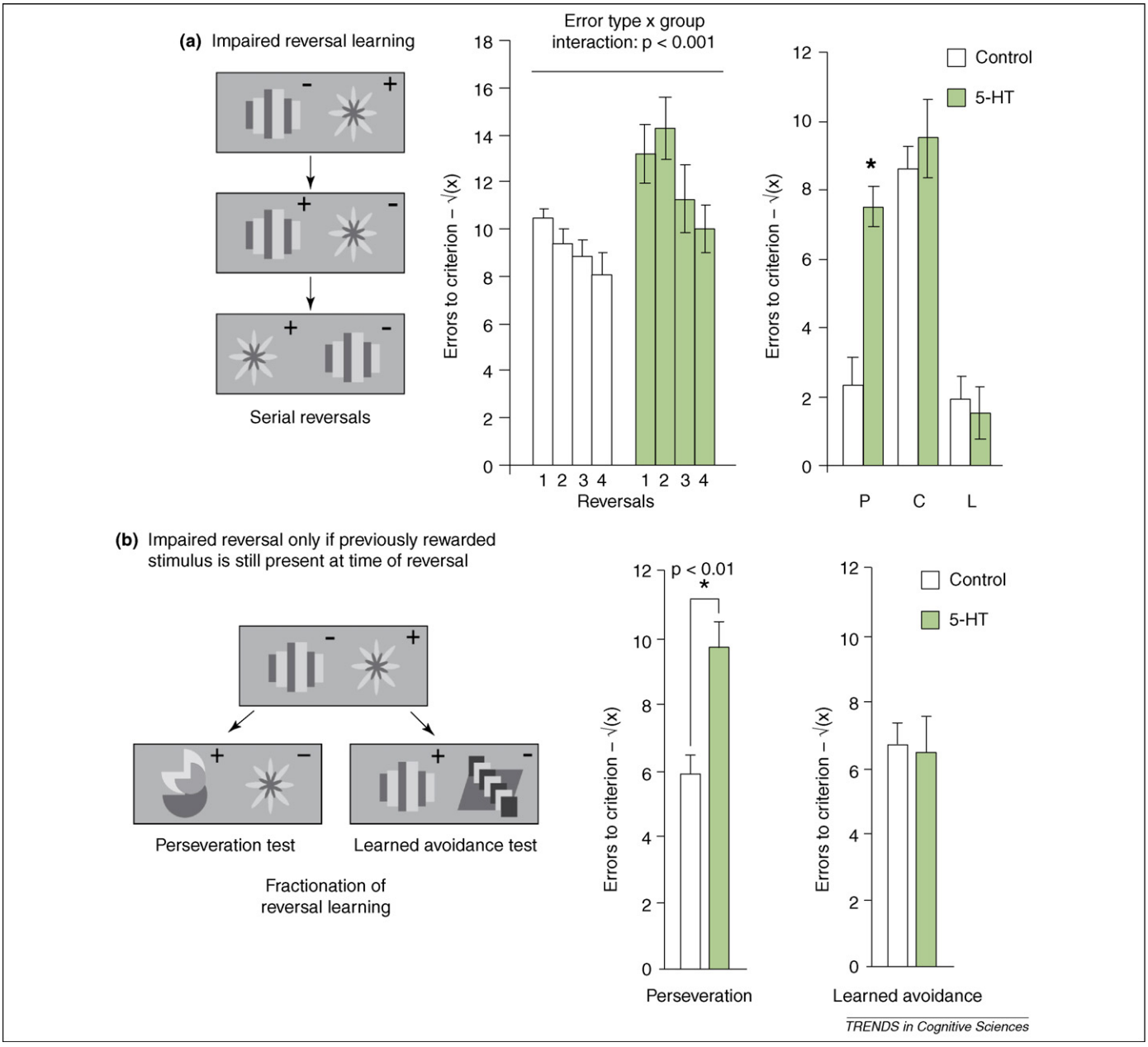

Figure 3. Effects of 5,7-DHT-induced depletions of 5-HT from OFC on visual discrimination reversal learning in marmosets. **(a)** Animals with 5,7-DHT lesions of the OFC made more errors than controls before reaching criterion across a series of reversals, the errors being primarily perseverative in nature. In this study, all animals, post-surgery, were required to regain criterion (90% correct in a session of 30 trials) on a discrimination they had learnt before surgery. They then acquired a novel discrimination before performing a series of four reversals in which the reward contingencies were repeatedly reversed between the two exemplars, as illustrated in the schematic. Unlike their impaired performance on the reversals, their performance on the retention of a discrimination and on the acquisition of a novel discrimination was intact (not shown). **(b)** The deficit in reversal learning was dependent upon the presence of the previously rewarded stimulus (perseveration test) at the time of the reversal. By contrast, reversal performance was intact if the previously rewarded stimulus was replaced by a novel stimulus (learned avoidance test), also shown in (b). The + and − signs indicate whether the stimuli were associated with reward or not. Control groups all received sham-operated control procedures. P, C and L refer to the perseverative, chance and learning stages, respectively, within a reversal. For details of how these stages were defined see Ref. [58].

the previously rewarded stimulus was still available for selection after a reversal (Figure 3b) [58]. When that previously rewarded stimulus was replaced with a novel stimulus, then selection of the previously unrewarded stimulus was unaffected. Thus, the depletion left unaffected the ability to initiate responding to the previously unrewarded stimulus, indicating that the reversal impairment was not a result of exaggerated 'aversion' to this previously unrewarded stimulus. The reversal learning deficit in marmosets probably reflects a failure to inhibit prepotent responding in response to an unexpected reward omission.

These results parallel findings that reductions of central 5-HT and genetic variation impair performance of go–nogo tasks in humans [59–62]. However, the behavioural disinhibition is not generalized because studies using the related stop-signal reaction time paradigm have demonstrated that 5-HT does not modulate the ability to cancel already activated responses [63] (but see Ref. [64]). Hence the release of behavioural output seen following 5-HT depletion could reflect an increased tendency to initiate or select responses rather than an inability to stop already initiated responding.

To summarize, reductions in 5-HT function impair behavioural inhibition in several situations, including Pavlovian conditioned inhibition and reversal learning tasks. Selective 5,7-DHT lesion studies with marmosets have revealed that the OFC has a particularly important role in the perseverative deficit in reversal learning paradigms. Thus serotoninergic modulation of the OFC might alter inhibitory control mechanisms, which will influence processing in strongly connected subcortical structures that mediate emotional regulation and behavioural output such as the amygdala and the striatum.

Concluding remarks

These findings highlight the paradox outlined in our opening paragraphs, namely that a release of punished responding following reduced serotoninergic transmission is in apparent direct contrast to the enhanced responsiveness to and prediction of aversive stimuli reviewed above.

How to resolve this paradox? One might argue that the experimental analysis is incomplete and the comparisons might not pay sufficient attention to the different methods that are used; for example, ATD produces a mild and only transient reduction in 5-HT in humans, which contrasts with the profound and long-lasting effects of 5-HT depletion in experimental animals by 5,7-DHT. These methods might also have different consequences for the presumed dynamic balance between tonic neurotransmission and phasic neurotransmission (Boxes 3 and 4). Furthermore, the apparent discrepancy between the perseverative reversal deficits in marmosets (Figure 3) [49,58] and the punishment deficit during reversal learning in humans (Figure 2) [37,38] could reflect the differential emphasis of the animal and human paradigms on inhibitory control and aversive processing, respectively. Specifically, the discrimination reversal paradigm administered to marmosets did not load heavily on aversive processing, because, unlike humans, the marmosets were not explicitly punished for incorrect responses. On the other hand, it could have loaded more heavily on inhibitory control mechanisms than the human paradigm, because the correct responses of the animals were followed by prolonged (5-second) reinforcement.

However, we speculate that fluctuations in 5-HT affect diverse neural systems in the control of emotion and behaviour, probably through different receptors [65,66], plausibly accounting for the apparently diverse findings. Thus, at the subcortical level, serotoninergic activity might provide a motivational process opposed to that mediated by dopamine activity, for example in the form of enhanced punishment prediction errors, which might be transmitted to cortical control regions (e.g. the medial PFC). By contrast, direct serotoninergic modulation of OFC function might serve to bias descending inhibitory control mechanisms that regulate subcortical mechanisms underlying, for example, the expression of emotional processing in the amygdala and behavioural output in the striatum. This accounts not only for the bias to aversive processing but also for the bias to (habitual) control by stimulus–response associations as distinct from (goal-directed) control by response–reward associations following 5-HT depletion. Furthermore, there is also evidence that descending control from the medial PFC in the rat regulates 5-HT activity in the DRN during stress [67], which has been related to stress resilience in depression. Our proposal extends the hypothesis from Deakin and Graeff [1] that distinct 5-HT projections from the DRN and the MRN (i.e. to the amygdala and the hippocampus) facilitate anxiety and resilience to depression, respectively, and incorporates the importance of cortical–subcortical interactions. Our hypothesis parallels findings that dopaminergic manipulations have contrasting cognitive effects as a function of distinct underlying cortical and subcortical neural systems [68,69] and can account for the observation that enhanced aversive processing, disinhibited behaviour and stress-vulnerability often co-occur in affective disorders.

Box 4. Questions for future research

- Future research will need to address the question whether 5-HT subserves a common behavioural function that will nevertheless be distorted to some extent by differential processing ongoing in innervated target areas, or whether its different effects simply reflect modulated output from distinct processing mechanisms that occur within different terminal areas.
- The likely availability of new serotoninergic agents with specific receptor actions that can also be safely administered to human subjects will greatly accelerate progress in dissecting the various roles of the distinct 5-HT receptor subtypes in different emotional and cognitive paradigms. For example, already in the rat it is clear that 5-HT_{2A} and 5-HT_{2C} receptor antagonists have contrasting effects on measures of impulsivity [65].
- It will also be advantageous to use the developments in functional brain imaging using either event-related fMRI paradigms (e.g. Figure 2c) or positron emission tomography with specific 5-HT ligands to test how 5-HT modulates the dynamic balance between cortical and subcortical regions.
- Moreover, it will be desirable to characterize effects of 5-HT, for example, on punishment prediction error, using human (intracranial) electrophysiological measures of cortical and subcortical function.
- In awake behaving animals, the challenge will be to identify postulated phasic and tonic modes of responding in the ascending 5-HT systems, using voltammetry or other biosensors, to provide information of value for neurocomputational theory.
- Finally, further conceptual and empirical development is required to provide an integrated account of the role of 5-HT in socio-emotional decision-making and cognition.

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