Harnessing temperament to elucidate the complexities of serotonin function

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This review highlights the utility of applying concepts of temperament and personality traits in healthy individuals to functional studies of serotonin (5-hydroxytryptamine, 5-HT), in an effort to better elucidate the complex roles of 5-HT, and ultimately advance our understanding of psychopathology. We highlight empirical demonstrations of multifaceted and trait-dependent emotional and behavioural effects of manipulating 5-HT in humans, with emphasis on studies employing the technique of acute dietary tryptophan depletion, and additionally selective serotonin reuptake inhibitors. Relevant evidence from studies of 5-HT in non-human animals is also discussed. We show how the effects of central 5-HT manipulations affect behaviour depending not only upon situational context but also on pre-existing temperament and personality traits such as empathy, psychopathy, neuroticism, impulsivity, and intolerance of uncertainty. These effects can be related to the concept of the baseline (or rate-) dependency of neurochemical effects on behavioural control. We speculate about the neurochemical substrates for some of these trait-dependent effects, as well as their clinical significance.

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Useful concepts for research on neurochemical biomarkers of traits and psychopathology

This Theme Issue on the neurobiology of temperament, personality and psychopathology discusses biomarkers for bio-behavioural taxonomies including the classification of psychiatric disorders [1]. Serotonin (5-HT; 5-hydroxytryptamine) is a plausible biomarker for such taxonomies, having been linked to many psychiatric symptoms [2]. Here, we focus on how serotonin interacts with pre-existing (‘baseline’) tendencies or temperament traits to modulate affective and behavioural control. It is not perhaps surprising that the range of potential interactions with individual differences in temperament is huge, given that serotonin has been said to be ‘involved in everything but responsible for nothing’ [3]. We will thus address how serotonin interacts with impulsivity, empathy, psychopathy, neuroticism, and intolerance of uncertainty to determine behaviour, which may be further shaped by environmental context. Here we speculate that harnessing individual differences in temperament traits or in personality in studies of serotonin function can reveal new dimensions of the role of this neurotransmitter. We consider temperament and personality as overlapping to a great extent although personality has been suggested to depend on social tendencies and cultural

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learning, whereas temperament may be linked more expressly to biological factors and behavioural measures (e.g. ‘reinforcement sensitivity’) [4].

The conclusions to be offered will be speculative but in line with the brief of this Theme issue on the psychobiology of individual differences — broadly defined to include psychopathology as well as temperament/personality. We hypothesise that identifying genetic and neurochemical biomarkers of psychopathology can be facilitated if a tractable, well-supported neurochemical model of temperament is identified and conjoined with self-reported gradations of temperament in healthy individuals [5**,6**]. Historically, the dimensionality of complex human behaviour has been difficult to reduce; thus, here we hypothesise that harnessing temperament and personality traits in empirical studies represents a fruitful avenue towards doing so. The Theme Issue invited a horizon-scanning perspective (‘What’s next?’) given that few concrete and reliable findings have emerged in this research field to date. Indeed, speculative accounts are arguably useful when many attempts to uncover reliable biomarkers in individual differences have proven unsuccessful.

Manipulating human serotonin function via the acute tryptophan depletion (ATD) technique is one of the most common methods for studying serotonin function in humans [7], and was employed in multiple studies presented here. ATD involves removing serotonin’s biosynthetic precursor, the essential amino acid tryptophan, from the diet temporarily while administering other large neutral amino acids (see Ref. [8**]). Various psychiatric symptoms have been elicited by performing ATD on different patient groups, in tests of the hypothesis that serotonin is clinically relevant to these conditions. These findings are reviewed elsewhere (e.g. Refs. [9**,10]), however, briefly: ATD tended to induce relapse in individuals in remission from major depressive disorder (MDD) who used serotonergic medications [11]. Individuals with panic disorder, for instance, showed enhanced panic responses following ATD [12]; in individuals with obsessive-compulsive disorder (OCD), ATD increased distress and lowered mood during symptom provocation [13]. ATD reversed the benefit of SSRIs in social anxiety disorder [14]. ATD has also been studied in cocaine users, bulimia nervosa, autism spectrum, bipolar, and alcohol use disorders, and irritable bowel syndrome (IBS), among others (see Refs. [9**,10]).

Whilst ATD is a short-term intervention, and it is important to study longer term effects of serotonergic interventions, short-term responses to serotonergic challenges can predict longer term responses to SSRIs [15] and there are instances where an acute effect has been shown to be comparable to repeated dosing [16]. Studies with ATD can be supplemented by studies utilising drugs affecting 5-HT; we will also consider effects of the selective serotonin reuptake inhibitors (SSRIs) given acutely or chronically. One of the difficulties associated with human studies is to be sure of the direction of effect on 5-HT after ATD or SSRi treatment (see Ref. [17]); this can be alleviated to some extent by parallel studies of other 5-HT manipulations in experimental animals [18].

Empirical studies of 5-HT manipulations in relation to temperament

Empathy and psychopathy

One indication of the importance of temperamental trait factors was suggested by studies examining effects of ATD and acute SSRI treatment on moral decision-making in the well-known ‘trolley problem’ and ‘ultimatum game’ [19,20**]. These not only showed opposite effects of ATD and acute SSRI treatments but also tested the hypothesis that prosocial effects of the SSRI on moral judgement would be stronger in individuals higher in trait empathy [20**]. In line with this hypothesis, participants high in trait empathy (as measured by the Interpersonal Reactivity Index) showed stronger prosocial effects on moral judgement and behaviour after acute SSRI than those with low trait empathy [20**]. These results suggested that serotonin modulates empathic responses to avoid harming others — by boosting an already present presumed neural signal. The drug boosted responding only in the emotionally highly salient personal scenarios, showing the importance of precise context. It should be noted, however, that acute SSRI administration can paradoxically decrease serotonin concentration in projection areas via 5-HT1A autoreceptors [21], and so the precise neurochemical mechanism of these effects is incompletely understood.

The importance of contextual factors also came to light when considering effects of serotonin manipulations on conditioned responses to emotional faces (signaling ‘innate’ or ‘proximal’ threats) versus other ‘learned threats’ or cues predictive of ‘distal threats.’ Several studies have highlighted a key role of contextual factors in shaping the response to 5-HT; divergent effects of serotonin have been observed depending on the context, or threat level, conveyed by discrete cues [22–24,25**,26], consistent with influential views on serotonin function [27**].

Pavlovian conditioned responses, moreover, can also be shaped by trait factors, such as the transdiagnostic construct intolerance of uncertainty. Intolerance of uncertainty refers to a trait aversion to uncertain situations, with relevance to generalized anxiety disorder, social phobia, panic disorder, agoraphobia, OCD, depression [28,29], and symptoms of post-traumatic stress disorder (PTSD); [30]. It is perhaps unsurprising that individuals with PTSD show heightened return of autonomic responses, indexed by the skin conductance response, when re-
encountering a triggering stimulus [31]. ATD, instead, had an anxiolytic effect on the return of autonomic responses for learned distal threats, which may be even more pronounced in individuals highly intolerant of uncertainty [25**]. Meanwhile, it should be noted that intolerance of uncertainty differs from trait anxiety [32–35]. Indeed, variations in trait anxiety have also been studied in relation to serotonin function, at the level of neurobiology and genetics, leading to findings of varying amygdala activity pertaining to threats [36].

Whilst Pavlovian conditioning paradigms are a common method for studying emotion, another, less commonly discussed role of 5-HT was identified in a study of social emotions and empathy. Motivated by the aforementioned observation on empathy and serotonin interacting to modulate moral decision-making, we extended these results to social emotion. The question addressed was: Do traits (e.g. empathy) interact with serotonin to produce differing social emotions?

Our recent study [8**] employed a novel computerised moral judgement (MJ) task from the EMOTICOM neuropsychological testing battery [37**]. The MJ task involved a series of cartoon scenarios of social and unjust harm — which was sometimes intentional, sometimes unintentional; the participant was sometimes the victim, sometimes the agent. Ratings of guilt, shame, and annoyance, under ATD or placebo, were the primary dependent measures, in response to the scenarios.

Guilt and shame were distinguished by the difference between ‘If only I hadn’t’ as opposed to ‘If only I weren’t’, respectively [8**,38]. Whilst guilt is part of the diagnostic criteria for depression, proneness to shame most consistently relates to a range of psychopathology [8**,39**]. The DSM5 ‘guilt’ criterion may therefore be referring to shame-laden guilt [8**,39**]. Empathy was a factor modulating feelings of guilt in particular under ATD [8**]. Individuals who were clinically depressed also showed association with enhanced guilt and shame on the same MJ task, translated into Danish [40**] (see Ref. [41**], for a study on trait paranoia using this MJ task).

In our study, individuals high in trait empathy self-reported more guilt following diminished availability of serotonin’s biosynthetic precursor [8**], engendered by the ATD procedure, to deplete serotonin transiently [11,42]. The effect on guilt was driven by situations of inflicting (being the agent of) harm, unintentionally [8**]. Shame was elevated in the highly empathic, as well, but may have reached ceiling before the introduction of ATD in high empath [8**]. Irrespective of traits, we used principal components analysis (PCA) to reduce many dependent variables into a smaller number of components. Of these, a component reflecting guilt and shame, when the victim of harm, was elevated after ATD. Also elevated by ATD regardless of trait factors was another principal component, interpreted as inward frustration, or annoyance with oneself for having harmed another [8**].

Moreover, individuals high in trait psychopathy — who classically have preserved theory of mind [43] — showed increased annoyance after ATD, in particular, following unjust harm [8**]. This result concords with the extensive literature on the ultimatum game: increased retaliatory behaviour to injustice has been documented after ventromedial prefrontal cortex (vmPFC) damage, in incarcerated individuals with psychopathy [44], and indeed, in healthy humans after ATD [19]. Whilst psychopathy can involve either goal-directed or impulsive aggression [45,46**], our findings, using the Levenson Self-Report Psychopathy Scale (LSRP; [47]), may be most relevant to goal-directed aggression [8**]. Serotonin-mediated impulsive aggression [48**], meanwhile, can be worsened by alcohol misuse [46**], unleashing a latent (or prepotent) tendency towards irritability (annoyance) or violence.

In summary, our study identified two (classically opposing) traits — empathy and psychopathy — and demonstrated that differing social emotions were amplified by ATD as a function of these traits. Whereas previous work showed an amplification effect of serotonin depletion on social behaviour in relation to individual differences in empathy, we have additionally shown that individual differences in psychopathy versus empathy interact with serotonin depletion to influence the quality as well as the magnitude of social emotion. Hence, serotonin depletion tends to exaggerate the effects of prior dispositions on social behaviour.

**Neuroticism**

Neuroticism is another temperament trait, quite closely related to Trait Anxiety [49,56**], that we hypothesise would interact with serotonin function to modulate emotion, including guilt and shame. Indeed, neurotic individuals were differentially affected by SSRIs, assessed by neural responses to emotional faces [50]. Neuroticism can be defined as an emotional disposition for expecting surprising negative outcomes, complemented with perceived low social support.

It is widely regarded as a risk factor for depression [51], and has additionally been studied longitudinally, neurochemically, and with neuroimaging [50,52–55]. Neuroticism is more apparent in situations of novelty or uncertainty, in which the increased frequency of uncertain outcomes amplifies negative expectations. Neuroticism has been related to neurochemical interactions involving the serotonin, noradrenaline, and opioid systems [56**,57**,58]. By taking an analogous approach to our empathy findings [8**] we recently found that neuroticism (as measured with the STQ questionnaire [59])
and serotonin indeed interacted to modulate guilt and shame, and this effect differed as function of whether the participant was the agent or victim of an unjust harm as depicted in cartoon scenarios of the MJ task (Kanen JW, Trofimova IN, and Robbins TW unpublished observations).

**Impulsivity and impulsive aggression**

As a neurochemical biomarker of psychiatric disorders, serotonin is commonly discussed in the context of depression, but it is also an important factor in trait impulsivity in relation to both executive control over behaviour and its interaction with emotional processing, as occurs in impulsive aggression and ‘negative urgency’. Impulsivity is thus not a unitary construct [60], and serotonin affects different types of impulsivity differently [18,61–63]. In humans, impulsivity may be measured by self-report questionnaires, such as notably the Barratt Impulsiveness Scale (BIS-11) [64], the UPPS-P Impulsive Behavior Scale (IBS) [65], the Eysenck Personality Questionnaire (EPQ) [66] and the Temperament and Character Inventory (TCI) [67]. There is little doubt that serotonin is implicated in certain forms of impulsivity, especially impulsive aggression, based on extensive genetic, neurochemical (including position emission tomography) and pharmacological evidence in humans, including clinical populations, and animals [68,69]. For example, this evidence has focused especially on polymorphisms and transgenic manipulations of the 5-HT1B and 2B receptors [70], as well as the serotonin transporter (SERT), and 5-HT metabolite studies, the general hypothesis being that low 5-HT function is associated with increased aggression. Note that for the measurement of action inhibition, the evidence is less clear. For example, there is little to support a role of 5-HT as measured by the stop signal reaction time task; here, ATD had no effect even when polymorphisms of the SERT were taken into account [62]. On the other hand, when action restraint (or ‘waiting impulsivity’) in the context of reward anticipation was measured, 5-HT depletion in rats and humans (with ATD) had major effects [18,71]. The fact that trait impulsive aggression may depend on low serotonin activity would suggest that 5-HT manipulations in humans such as ATD and SSRIs would have specific effects on such behaviour. Indeed, SSRIs have been employed to treat impulsive aggression successfully in a few studies [69], although more evidence is required.

The distinct effects of ATD and SSRIs on different forms of emotional response, which appear to depend on different baseline levels of 5-HT function as well as on pre-existing traits, are reminiscent of so-called ‘rate-dependent’ effects of stimulant drugs, primarily affecting the catecholaminergic (dopamine and noradrenaline) systems on behaviour [72]. Thus, for example, in agreement with this baseline-dependent principle, drugs such as methylphenidate or cocaine may increase low baseline rates of impulsive responding in rats or decrease initially high rates in trait impulsive animals [73,74]. However, it is now evident that it applies to individual differences in humans in cognitive function as well as behaviour [75]. Furthermore, trait impulsivity (as measured with the BIS-11) in humans affects how dopaminergic drugs influence working memory (ameliorating poor working memory in the case of high trait impulsivity and impairing it in the case of low impulsive individuals). For both rats [76] and humans [77,78], these baseline differences in impulsivity can be related to striatal dopamine (DA) D2 receptor availability. Such findings have obvious clinical implications for understanding the ‘paradoxical’ therapeutic effects of stimulant drugs in attention deficit/hyperactivity disorder (ADHD).

There is a possible interaction of the anti-ADHD effects of stimulants with serotonergic mechanisms as shown via studies in experimental animals. Winstanley et al. [79], for instance, found that the ability of amphetamine to reduce the temporal discounting of reward in rats with baseline high impulsive choice was selectively reduced by forebrain 5-HT depletion. This DA-5-HT interaction was supported by other pharmacological manipulations which included the antagonism of inhibitory 5-HT1A receptors which enhanced the anti-impulsivity effect of amphetamine [80].

**Putative mechanisms of trait-dependent effects of serotonin manipulations**

As well as putative 5-HT-DA interactions being relevant to traits, there is suggestive evidence of 5-HT-hormonal interactions that may account, for example, for the dependence on empathic trait. Interactions between serotonin and the so-called ‘social hormones’ oxytocin (OXT) and vasopressin (VSP), for example, are also plausibly involved in feelings of guilt and shame [81,82]. As we pointed out previously in the ‘Functional Ensemble of Temperament’ (FET) neurochemical model [57*,57**, 58], OXT-VSP regulate social orientational rather than energetic aspects of behaviour, that is, empathy and prosocial perception (in cooperation with estrogen). This is in line with the ‘social salience hypothesis of oxytocin’ [83], underlying the tendency for OXT administration to increase pro-social perception [84–90]. Social anxiety, prominent in neuroticism, has also been linked to OXT [88]. OXT and VSP can have opposite actions in the central amygdala (cAM): OXT decreases hypothalamo-pituitary-adrenal (HPA) axis arousal via gamma aminobutyric acid (GABA) neurons in the cAM and suppresses VSP-responsive neurons [81,89,91].

There are rich 5-HT projections from the dorsal and median raphe nuclei to hypothalamic nuclei, where OXT and VSP are synthesised [92]. 5-HT neurons have OXT receptors, which, if activated, increases 5-HT release from median raphe neurons [93], and OXT can
affect 5-HT$_{1A}$ receptor binding potential [94]. Social interaction can involve coordinated activity of oxytocin and serotonin in the nucleus accumbens [95] and OXT and 5-HT interact in the amygdala when processing threats [89]. In contrast with the mutually supportive interaction between OXT-5-HT, serotonin reportedly inhibits VSP, and so ATD would ease this inhibition, and may contribute to aggression [96].

What’s next? Useful approaches for future research on the role of temperament as a biomarker

First, it is important to note that future endeavors should strive for much larger sample sizes to achieve the necessary statistical power for analysing trait-neurotransmitter interactions [97], although the general level of consensus in some of these preliminary investigations is perhaps encouraging. Collaboration across laboratories, as well as replication of findings may aid in this goal. The pragmatic reality is that it is logistically difficult to execute a neurochemical challenge study – of any size – in humans, and so such collaborative approaches are much needed. Another limitation to be addressed is whether acute manipulations of 5-HT as mainly investigated here will be of significance for long term trait-dependent neurotransmitter effects, especially in a clinical context. The example of the ATD challenge in remitted patients with major depressive disorder producing relapse in mood suggests that they will be.

In this brief review, we have highlighted the complex action of 5-HT in regulation of affective and behavioural control, and provided specific examples in relation to empathy, psychopathy, impulsivity, neuroticism, and intolerance of uncertainty. We also presented an experimental example of involvement of 5-HT in regulation of social emotions (such as guilt and shame), as a rarely discussed functionality of 5-HT. We pointed to research showing that in regulation of these emotions, 5-HT does not work alone mechanistically. Instead, it probably interacts with a number of hormones and probably with different functional neural circuits, given the ramifying influence of the raphe 5-HT projections to many different terminal domains having different behavioural and cognitive functions. Our experimental example also illustrated contextuality of emotions and behaviour seen in differential responses when people were agents or victims of harm.

The impact of impulsivity, empathy, psychopathy, neuroticism, and intolerance of uncertainty, as temperament traits, on responses to experimental tasks demonstrates the importance of screening for temperament in neurochemical experiments, in order to resolve and explain variability of results. Moreover, analysis of temperament may be used in real life to promote mental health by healthcare professionals spanning general practitioners, social workers, clinical psychologists, and psychiatrists. For example, when facing novel challenges in significant life transitions, especially when the new environmental state is more uncertain or volatile, individuals high in trait intolerance of uncertainty [98] or neuroticism may be at particular risk for pathological anxiety [25**,31]. We believe that harnessing temperament, to fractionate serotonin’s role in ‘everything, yet nothing in particular’, has the potential to inform vulnerability, guide treatment, and contribute to re-classification frameworks for mental disorders such as the Research Domain Criteria (RDoC [99]).

Conflict of interest statement

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Data availability

Data will be made available on request.

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