The effect of raising and lowering tryptophan levels on human mood and social behaviour

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Acute tryptophan depletion (ATD) studies indicate that low serotonin can lower mood and also increase aggression, although results vary somewhat between studies with similar participants. Lowering of mood after ATD is related to the susceptibility of the study participants to clinical depression, and some participants show no effect on mood. This indicates that low serotonin can contribute to lowered mood, but cannot—by itself—cause lowered mood, unless other unknown systems interact with serotonin to lower mood. Studies using tryptophan supplementation demonstrate that increased serotonin can decrease quarrelsomeness and increase agreeableness in everyday life. Social interactions that are more agreeable and less quarrelsome are associated with better mood. Thus, serotonin may have direct effects on mood, but may also be able to influence mood through changes in social behaviour. The increased agreeableness and decreased quarrelsomeness resulting from increases in serotonin will help foster congenial relations with others and should help to increase social support. As social support and social isolation have an important relationship with both physical and mental health, more research is needed on the implications of the ability of serotonin to modulate social behaviour for the regulation of mood, and for future physical and mental health.

1. Introduction

The demonstration, shortly after the discovery of antidepressants, that levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) are low in the cerebrospinal fluid (CSF) of depressed patients [1] was one of the factors that resulted in the hypothesis that depression might be associated with a deficit in serotonin function, and that antidepressants act by increasing serotonin function [2]. However, subsequent studies found that the difference between CSF 5-HIAA in depressed patients and controls was small, with a large overlap between groups, and that low CSF 5-HIAA was associated with suicide, and in particular violent suicide rather than depression [3]. Suicide tends to be associated with aggression, and a large body of animal research suggests that lowering serotonin causes aggression. Furthermore, low CSF 5-HIAA is associated with aggression in humans [4]. Also, much of the evidence relating low serotonin to mood or aggression in humans was correlational, with no direct evidence on causation. Therefore, in the early 1980s the extent to which serotonin might have a direct control on mood or aggression or both was not clear. The idea behind the acute tryptophan depletion technique was simplistic—temporarily lower serotonin in human brain by lowering tryptophan levels, and study the effects on mood and aggressive responding in a laboratory setting.

2. The acute tryptophan depletion technique

In humans, as in experimental animals, tryptophan hydroxylase is usually only about half saturated with tryptophan [5], so giving tryptophan can increase the rate of serotonin synthesis up to two-fold, whereas decreasing brain tryptophan will lower serotonin synthesis. Research on rats showed that feeding the
animals a meal containing all the essential amino acids except for tryptophan resulted in a decline in tryptophan levels in blood and brain, and, therefore, in brain serotonin [6]. The meal induces protein synthesis and as tryptophan is incorporated into protein its level in blood and tissues declines [7]. Concú et al. [8] demonstrated that a 18.7 g amino acid mixture containing no tryptophan caused a 42 per cent decline in human plasma tryptophan. Subsequently, Young et al. [9] used a 100 g amino acid mixture and found a much greater lowering of tryptophan levels, which was associated with a modest lowering of mood in males without overt psychopathology. The 100 g mixture lowered human brain serotonin synthesis by more than 85 per cent, according to a method using positron emission tomography and \( {\alpha}^{13}C \)-methyl-L-tryptophan as a tracer [10].

3. The effect of acute tryptophan depletion on mood

Numerous studies have looked at the effect of acute tryptophan depletion (ATD) on mood in healthy participants, in healthy participants with a family history of depression, in patients with depression, in newly recovered patients on antidepressants and in recovered depressed patients off antidepressants. A number of reviews have summarized these studies [11–14]. Results are somewhat variable, but some important patterns emerge. In healthy individuals, there is little or no lowering of mood, although results can be quite variable between studies, with some lowering of mood seen more often in women than in men. I suggest a possible cause for this variability later in this review. In healthy participants with a family history of depression, there is a lowering of mood although mood remains within the normal range of mood. In newly recovered depressed patients on antidepressants that act on the serotonergic system, 50 per cent or more of the patients show a temporary reappearance of the depressed mood they experienced before recovery. In recovered depressed patients off antidepressants, only a small percentage of the patients show a marked lowering of mood. In recovered depressed on noradrenergic antidepressants, there is no lowering of mood.

The results of the ATD studies suggest that lowering serotonin synthesis can lower mood in some circumstances, and that the magnitude of the effect tends to be greater in people with a greater susceptibility for depression. Low serotonin by itself is not enough to cause depressed mood, but of course it would be surprising if it did, given that the number of serotonin neurons in the brain is small. Several possible mechanisms might explain the different response in those who exhibit a lowering of mood after ATD and those who do not. First, in those who do not show a lowering of mood, other neuronal systems that modulate mood may be able to buffer the effects of low serotonin, whereas in those who show lowered mood, there may be suboptimal function of those other systems. Second, the lack of effect on mood in some people may be due to adaptive changes. One suggestion is the downregulation of cortical serotonin receptors that has been shown in healthy volunteers undergoing ATD [15], and possibly this does not occur in those showing a lowering of mood. Third, lowered mood may be associated with decreased release of serotonin, but serotonin release may not be changed by ATD in those who show no lowering of mood.

Decreased synthesis of serotonin over a period of a few hours may not always be enough to deplete serotonin stores sufficiently to lower serotonin release from neurons. Decreased serotonin release presumably implies a decrease in the amount of serotonin stored in each vesicle in the pool of vesicles that is preferentially released on neuronal firing. How this might be influenced by decreased serotonin synthesis is not clear, but it will presumably depend in part on the rate of firing of serotonin neurons, and the extent to which the serotonin that is released is recycled into vesicles. ATD is likely to have a greater effect when there is a greater release of serotonin, which should exhaust stores of serotonin more quickly. In experimental animals, serotonin release increases with increasing arousal [16]. Therefore, a plausible hypothesis is that greater arousal is more likely to lead to a greater effect of ATD on mood. However, arousal has not yet been studied as a factor that might explain some of the variability in response to ATD.

Presumably, if serotonin neurons are firing at a very low rate, any effect of ATD is likely to be small. In experimental animals, serotonin neurons virtually cease activity during rapid-eye-movement (REM) sleep [17]. If the same is true in humans, then people who have a marked lowering of mood after ATD when awake should not show any lowering of mood during dreams, if they undergo ATD before sleep.

A review combing the results from a number of studies investigated variables that might explain why some recovered depressed patients show a marked lowering of mood after ATD, whereas others do not [18]. The reduction in plasma tryptophan levels was 77 ± 15% (mean ± s.d.), and, at this level of depletion, there was no relationship between the degree of plasma tryptophan depletion and the degree of lowering of mood. This suggests that, above a certain threshold in depletion of tryptophan, serotonin synthesis is small enough that its variation is no longer functionally significant in the control of mood. Among the clinical variables, chronicity of depression was the most powerful predictor of relapse in mood, but female gender, exposure to SSRI (selective serotonin reuptake inhibitor) antidepressant and previous serious suicidal thoughts or attempts were also significant predictors. Women may be more susceptible to the effect of ATD, because the procedure lowers serotonin synthesis more in women than in men [10]. The lowering of mood in patients on SSRIs may be related more to the mechanism of action of SSRIs than to the role of serotonin in the aetiology of depression. The other variables are all consistent with the idea that a susceptibility to depression is an important factor in the response to ATD.

4. The effects of acute tryptophan depletion on aggression and irritability

A review published in 2002 included 11 studies looking at the effect of ATD on laboratory measures of aggression or irritable mood [13]. Most of the studies were on men, but two were on women. The majority of studies found increased aggressive responding or irritability, but some did not. An increase in aggression did not seem to be related always to the susceptibility of the participants to aggression. For example, those with intermittent explosive disorder showed no increase in irritability or aggressive outbursts after ATD [19]. An additional four more recent studies all found increased aggression after ATD. This was so for women
performing a laboratory task of aggression during the premenstrual phase [20], and for healthy women whose menstrual cycle was not controlled for, but only in those with higher plasma tryptophan [21]. Males were also tested using laboratory tests of aggression, and ATD increased aggressive responding in children with attention deficit hyperactivity disorder [22], and in healthy controls and patients with intermittent explosive disorder [23].

While the results suggest that ATD can increase aggressive responding under some circumstances, the results are variable. Two factors might explain this. The first is biological. Twelve of the men with high trait aggression, who participated in an ATD study looking at changes on an aggression rating scale [24], also participated in a study investigating 5-HT1A receptor sensitivity using temperature change in response to ipsapirone [25]. Combining the results from the two studies revealed that the six participants who had a marked increase in ratings of aggression after ATD, compared with the six who showed no marked increase in aggression, had a blunted hypothermic response to ipsapirone [26]. This suggests that those who showed increased aggression after ATD have decreased 5-HT1A receptor sensitivity. While differences in the serotonin system may account for some of the differences between studies, the second possible cause is methodological. While there are well-established scales for measuring mood and irritability, aggression is more difficult to study over a short time period in a controlled setting. Two behavioural measures have been used to study aggression after ATD in a laboratory setting: the Taylor aggression task [27] and the point subtraction task [28]. In both tasks the participants are told that they are competing against another person, but in fact they are playing against a computer program. In the Taylor task, participants are told that they are participating in a reaction time task. Each time they win they deliver an electric shock to their ‘partner’, using any of eight buttons that deliver varying shock intensities from mild to just below the painful threshold. When they lose, they receive a shock of varying intensity in each trial. The measure of aggression is the average intensity of shocks delivered to the ‘partner’. In the point subtraction task, players can press one button to obtain points that are later exchanged for cash, or another button that subtracts points from their ‘partner’. The measure of aggression is the number of points subtracted from the ‘partner’, in response to different levels of point subtraction from the participant by the ‘partner’. Both tasks depend on deception, and the extent to which the deception might have been successful is not always assessed. The tasks are also artificial, and response may depend on such factors as the exact instructions given, the way in which they are delivered, the fact that participants may want to be seen acting in a positive manner and so on. All these are factors that may differ between studies and may explain part of the variability between ATD aggression studies.

5. Tryptophan supplementation and social behaviour

Aggression is an extreme but important form of social behaviour, and regulation of aggression is a phylogenetically old function of serotonin. Serotonin plays a role in the regulation of aggression in many invertebrates [29], although the effects are not always consistent between species and may depend on context. For example, serotonin modulates aggression in lobsters, but the exact effect depends on factors such as the relative dominance of the animals involved [30]. However, in many situations, low serotonin promotes aggression, whereas increased serotonin promotes prosocial behaviours. For example, increased serotonin levels are involved in the transformation in locusts from being solitary to collecting together in swarms [31].

A wealth of data support the idea that low serotonin promotes aggression in mammals [32]. The idea that low serotonin may contribute to aggression resulted in two small clinical trials comparing tryptophan supplementation with placebo for the treatment of aggression. In the first, 12 aggressive patients with schizophrenia, whose aggression was not treated adequately with antipsychotics drugs, were given tryptophan and placebo for 4 weeks in a cross-over study [33]. Tryptophan, relative to placebo, decreased incidents on the ward requiring intervention. In the second study on 20 aggressive psychiatric inpatients, tryptophan, relative to placebo, decreased the need for antipsychotics and sedatives [34]. Subsequently a number of trials have shown the efficacy of serotonergic antidepressants in the treatment of aggression [35].

Overt aggression is at one end of an axis that is described, among other names, as affiliative–agonistic. The traditional view of serotonin is that it inhibits response to a number of different stimuli, of which provocation, that might lead to aggression, is just one [36,37]. However, increased serotonin function may also promote affiliative behaviours. As mentioned above, serotonin is involved in the swarming of locusts [31], and in vervet monkeys increasing serotonin through a variety of pharmacological interventions will increase the extent to which an animal will approach, sit next to and groom another animal [38,39]. This raises the question of whether serotonin regulates more normal aspects of human social behaviour, along the affiliative–agonistic axis, in addition to its effect on overt aggression.

Research in social psychology over the past few decades has resulted in the development of a method for studying human social behaviour in everyday life along two independent axes, agreeable–quarrelsome and dominant–submissive [40]. A recent review discusses this method, and how it can be applied studying the biological aspects of behaviour [41]. The method uses a technique referred to as ecological momentary assessment (EMA). Participants fill in a one-page form after each social interaction lasting more than 5 min, throughout the day. The form contains a number of statements concerning the participant’s behaviour during the interaction. There are groups of statements for each of four behaviours, agreeable, quarrelsome, dominant and submissive. Example of behaviours for each of these categories are: ‘I complimented or praised the other person’ (agreeable); ‘I discredited what someone said’ (quarrelsome); ‘I assigned someone to a task’ (dominant); ‘I did not state my own views’ (submissive) [40]. The participant checks off each behaviour on the list that she or he exhibited during the interaction. The setting (home, work, other setting) and the interaction partner (romantic partner, friend, acquaintance, supervisor, supervisee, co-worker, parent, other) are also marked on the form. Obviously, the behaviours vary greatly from one interaction to another. However, with increasing measurements, mean values become increasingly stable up
to about 70 measurements. As most participants fill in about 6 forms per day, 12 days of measurement are usually enough. Mean values obtained this way are stable across time for any individual [42].

To test whether increasing serotonin might alter behaviour along the agreeable–quarrelsome axis, Moskowitz et al. [43] studied 98 healthy men and women in a double-blind, placebo-controlled study. The treatments, 3 g of tryptophan per day and placebo, both given with meals, were given for 12 days each in counterbalanced order, with a 2 day washout period between treatments. Tryptophan caused a significant decrease in quarrelsome behaviours, but only when placebo was given first. This result was seen in both men and women, in different settings and with different types of interaction partners. There was no effect of tryptophan on agreeableness or on mood. At the end of study, the participants were asked to guess which treatment they were taking during which period. The guesses of the women were slightly better than that expected by chance, but the men did no better than chance. Therefore, the effect of tryptophan was not likely due to unblinding. Nor was the decreased quarrelsome due to better mood.

The results of this study raise two main questions. Why was there no effect of tryptophan when it was given first, and why was there no increase in agreeableness with increased serotonin? The original report of the study suggests that the lack of effect of tryptophan when given first could be due to a carryover effect. If the participants were more agreeable to those they frequently conversed with, the more agreeable tone may have been reciprocated, causing a change in tone of the interactions that may have persisted beyond the time tryptophan was given. If this is true, then increasing the washout period should result in a decrease in quarrelsome whatever the order of treatments. The lack of an increase in agreeableness after tryptophan may have been due to a ceiling effect. The participants in the study described above were typical of healthy people, in that they exhibited agreeable behaviours much more frequently than quarrelsome behaviours. Therefore, there may have been little scope for an increase in agreeableness. If the lack of an effect on agreeableness was due to a ceiling effect, tryptophan should increase agreeableness in less agreeable people.

The two ideas put forward in the paragraph above were tested in a study by aan het Rot et al. [44]. Participants were recruited for this second study from those who responded to an advertisement that included statements such as: Do you have problems with irritability? Do you repeatedly lose control of your temper? Do you get easily agitated? Those who answered the advertisement were screened to rule out the presence of current depression or alcoholism, and to score at least one standard deviation above the mean on one scale of irritability, and at least half a standard deviation above the mean on another scale of irritability. The scales were the Buss–Durkee Hostility Inventory [45], and an adapted version of the NEO Five-Factor Inventory that included the entire Angry Hostility subscale of the Revised NEO Personality Inventory [46]. A total of 39 men and women were recruited. The design, as in the previous study, was double-blind placebo-controlled crossover using 3 g tryptophan or placebo. The wash out period was increased from 2 to 6 days, and to ensure that the participants started each arm of the study on the same day of the week, the treatment period was increased from 12 to 15 days.

Tryptophan decreased quarrelsome behaviours with a medium effect size, and this effect was seen irrespective of which treatment was given first. This supports the idea that, in the first study, quarrelsome was not reduced by tryptophan when tryptophan was given first because of the short washout period and a carryover effect from the tryptophan treatment to the placebo treatment. In the study on quarrelsome people, tryptophan increased agreeable behaviours, supporting the idea that the lack of effect on agreeableness in the first study was due to a ceiling effect.

In a more recent study carried out in a laboratory setting, boys with a history of physical aggression, average age 10, were given tryptophan (500 mg; n = 12) or placebo (n = 11) under double-blind conditions [47]. In one of the tests tryptophan, relative to placebo, resulted in a trend (p = 0.07) towards increased prosocial behaviour. The study demonstrated the feasibility of using tryptophan in children, and suggested that in children, as in adults, increasing serotonin may increase prosocial behaviours.

Overall, the results discussed above suggest that altered serotonin in can influence behaviour along the entire spectrum of behaviour from agreeable to quarrelsome to overt aggression.

6. Potential implications of the effect of serotonin on social behaviour

(a) Social behaviour and health

The effect of serotonin on social behaviour has implications for both mental and physical health. Hostility, which is the mental state associated with quarrelsome, is associated with decreased social support and social isolation [48]. Furthermore, research confirms that positive emotions and agreeableness foster congenial relationships with others [49,50]. This in turn will create the conditions for an increase in social support. The implications of social support or lack of social support for human health are great. As stated in a recent review, ‘Social interactions have long-term physiological, psychological, and behavioural consequences. Social isolation is a well recognized, but little understood risk factor and prognostic marker of disease; it can have profoundly detrimental effects on both mental and physical well being, particularly during states of compromised health. In contrast, the health benefits associated with social support (both reduced risk and improved recovery) are evident in a variety of illnesses and injury states’ [51, p. 67]. A meta-analysis of the effects of social relationships and mortality concluded that poor social integration is as big a risk factor for mortality as well-established factors such as smoking [52]. Research has also shown associations between health and behaviour along the agreeable–quarrelsome axis. For example, hostility is a risk factor for many disorders such as coronary heart disease (CHD) [53], whereas agreeableness was a significant protective factor against mortality in a sample of older, frail patients [54]. So far, the amount of evidence suggesting that serotonin is an important factor in the relationship between social behaviour and health is very limited. However, a recent study looked at serotonin-related measures, including measuring the levels of the serotonin metabolite 5-hydroxyindoleacetic acid in CSF, and concluded that their results were ‘consistent with the hypothesis that increased CNS serotonin is associated with a more favourable
psychosocial/metabolic/cardiovascular profile, whereas decreased CNS serotonin function is associated with a less favourable profile' [55, p. 601]. A review concluded that the serotonin system, as indexed by polymorphisms of the serotonin transporter, ‘is an important link between the social environment and health’ [56, p. 107].

The extent to which behaviours mediated by serotonin or social networks act to influence health is not known. Social factors may influence factors such as inflammation and stress responses that can impact on health [51]. Alternately, neurotransmitter systems may have separate effects on social behaviour and aspect of metabolism associated with health. For example, in mice, 5-HT₃C receptors expressed by pro-opiomelanocortin neurons are physiologically relevant regulators of insulin sensitivity and glucose homeostasis in the liver [57]. Whatever the mediating mechanisms, there is great scope for future studies looking at the effects of tryptophan administration on social behaviour and health-related measures in humans. For example, in irritable people, would supplemental tryptophan help them to expand their social network? Would tryptophan be a useful adjunct in couple counselling with quarrelsome couples? Would tryptophan decrease hostility, alter metabolic profiles and decrease CHD in irritable people at risk for CHD? Would it alter metabolic profiles and decrease CHD in people who are not irritable but are at risk for CHD, thereby suggesting that irritability is not a causative factor in CHD? While the long-term risks of tryptophan administration would have to be balanced carefully against potential benefits, in general, side effects and adverse effects of tryptophan are small [58].

(b) Possible role of social behaviour as a factor mediating the effects of acute tryptophan depletion on mood

As discussed above, there is a degree of variability in the effect on mood of ATD that is not explained. Part of this may be due to a lack of control of social behaviour during ATD studies. A decrease in quarrelsome behaviours is associated with improved mood [44], and presumably an increase in quarrelsomeness would contribute to a lowering of mood. Therefore, the lowering of mood after ATD in healthy people may depend on the extent to which they have the opportunity to have quarrelsome social exchanges with others. One method to test this would be to give tryptophan-deficient amino acid mixtures to groups of participants. If a group of people all had a deficient amino acid mixture together, this would increase the opportunity for quarrelsome interactions. Given that the perceptions that others are less agreeable and more quarrelsome is also associated with lowered mood [59], lowering serotonin in a group of individuals could potentiate any lowering of mood (or create a lowering of mood) both because of the individuals’ quarrelsome behaviours and because of their interaction partners’ quarrelsomeness. This hypothesis could be tested easily. Of course, the hypothesis does not imply that all changes of mood are mediated by altered social interaction. The dramatic lowering of mood seen in newly recovered depressed patients on antidepressants that act on the serotonergic system could not be due just to changes in social behaviour. Presumably, while serotonin has separate actions on mood and social behaviour, there is a two-way interaction between mood and social behaviour in the same way that there is a two-way interaction between mood and cognition.

(c) Serotonin’s effect on social behaviour as a possible explanation for serotonin’s effect on more complex behaviours

As discussed above, the regulation of social behaviour is a phylogenetically old function of serotonin. Based on the evidence already reviewed, the role of serotonin in social behaviour is to regulate the tone of interactions along the axis that is often described as agonistic–affiliative in animals, and, in humans, runs from agreeable to quarrelsome to overt aggression. In this way serotonin differs from oxytocin, which seems to be involved in the formation of bonds [60]. The evidence described above suggests that serotonin may alter the tone of the interactions between individuals once some sort of bond has formed. High serotonin resulting in more agreeable behaviours might help strengthen bonds once formed, but there is currently no evidence that serotonin is involved in the initial formation of social bonds. Another interesting difference between serotonin and oxytocin is that, while serotonin exists in species with a very primitive nervous system, oxytocin itself exists only in mammals, although there are related peptides in lower species [61].

Tryptophan can increase agreeable behaviours without the individual being aware of this change, given that the adult participants in the two studies described above could not always guess, better than by chance, when they were on tryptophan and when they were on placebo. This suggests that the drive to be agreeable or quarrelsome that serotonin modulates is not in areas of the brain accessed by consciousness. This conclusion is not surprising given that serotonin modulates social behaviour in species with a very primitive nervous system. Thus, serotonin may be modulating a basic drive to be social. As discussed below, serotonin has also been implicated in more complex aspects of social behaviour and cognition in humans. However, sometimes these more complex changes may be a secondary effect of changes along the agreeable–quarrelsome axis.

The effect of ATD was studied on behaviour in the Prisoner’s Dilemma (PD) game [62], which measures social cooperation based on reciprocal altruism. In the iterated PD game used in this study the participant plays against a series of ‘partners’ (actually a computer program). In the game, both players decide separately whether they want to cooperate or defect. In this study, if both cooperated they received a monetary prize, 20 pence. If one player cooperated and the other defected, the one who defected received 30 pence and the other nothing. If both defected, they received 10 pence. The participants played two games of 20 rounds, with the ‘partner’ always choosing first in each round whether to cooperate or defect. In the first game, the partner chose to cooperate, and in the second game to defect. In subsequent trials, the partner followed a tit-for-tat strategy. ATD, relative to the control amino acid mixture, resulted in a significant reduction in cooperation. A plausible interpretation of this result is that the increased quarrelsomeness resulting from ATD could have been the basic mechanism that resulted in the decrease in cooperation.

A second study involved ATD and a different game using monetary gain, the ultimatum game [63]. Once again, the
participant played with a ‘partner’, and once again the ‘partner’ was really a computer program. However, each trial was with a different partner, and a picture of each partner’s face was shown on a monitor. In the ultimatum game, the partner proposed to split a sum of money with the participant. The partner specified the percentage that would go to the participant, and the percentage the partner would keep. The participant could accept the offer, in which case both were paid according to the proposed split of the money, or reject the offer, in which case neither received anything. ATD resulted in the participants rejecting more unfair offers, defined as those in which the participant was offered only 20 per cent of the money. This was interpreted as serotonin modulating behavioural reactions to unfairness. However, an ATD-induced increase in quarrellousness is a possible primary factor in mediating these results.

The participant stood to gain the most money by accepting all offers, as each trial was with a new ‘partner’, thus preventing retaliation and learning. Again, a plausible explanation for the results is that, after ATD, the participant had a more quarrelsome disposition towards the partners, so that punishing the partner became more of a priority than monetary gain.

A recent review suggests that the link between serotonin and prosocial behaviour has been demonstrated convincingly, but considers that the mechanism is not known, given that ‘constructs such as cooperation, affiliation, and aggression are complex and are likely composed of several smaller elements’ [64, p. 78]. For example, the effect of altered serotonin on cooperation in games such as those described above ‘could be motivated by a desire for fairness, a fear of retaliation, or long-term strategic goals, any of which could be modulated by 5-HT’ [64, p. 78]. However, while this may be true in humans, such complex cognitions are less likely to play a role in non-human primates, and are certainly not mediators of the effects of serotonin on social behaviour in more primitive species. The hypothesis I am proposing is that the effect of ATD on behaviour in games such as those described above is mediated by a non-conscious drive that alters how people react to others along the agreeable–quarrelsome axis. This is certainly not incompatible with such a drive altering different aspects of cognition, and those cognitions being mediating factors in the resulting behaviour. However, it places the phylogenetically old function of serotonin as the primary factor with altered cognitions as possible secondary mediating factors.

(d) Serotonin, mood and cognition

One open question is the extent to which serotonin influences mood directly or though cognitive effects. The first study demonstrating a lowering of mood after ATD measured one aspect of cognitive performance in addition to measuring mood [9]. The participants performed a proofreading task while listening to low, high and dysphoric distractors. After tryptophan depletion, but not after the control amino acid mixture, the participants performed worse with the dysphoric distractor than with the low or high distractor. The suggestion that ATD may result in enhanced attention to dysphoric stimuli has been confirmed in many other studies. These studies were reviewed by Harmer et al. [65] and Harmer [66], who suggest that the lowering of mood after ATD may be secondary to cognitive changes. Harmer [66, p. 1026] also suggests that raising serotonin by giving antidepressants causes ‘positive re-biasing of automatic processing’ and that this may explain how antidepressants work. The idea that the lowering of mood after ATD is secondary to cognitive changes is supported by two studies on recovered depressed patients [67,68]. In both studies, a low-dose tryptophan-depleting amino acid mixture had no effect on mood, but altered cognitive processing of emotional stimuli in the direction seen in depressed patients. However, in my opinion, the direction of causality remains an open question. The lack of change in mood with changes in cognition in the two studies mentioned above may have been due to the greater sensitivity of the cognitive measures to detect change. Furthermore, the interaction between mood and cognition may be in both directions, with altered mood influencing cognitive processing of emotional stimuli and cognitive processing of emotional stimuli influencing emotion.

(e) Serotonin, social behaviour and social cognition

If the effect of serotonin on the cognitive appraisal of emotional stimuli can contribute to serotonin’s role in regulating mood, can alterations in social cognition influence serotonin’s effect on social behaviour? A number of studies have looked at the effect of ATD on the response to faces with different expressions. Results have been rather variable. In healthy participants, ATD impaired recognition of fearful faces only in women [69], but in another study impaired recognition occurred only in carriers of the short allele of the serotonin transporter, irrespective of gender [70]. A different specificity has also been seen in healthy participants, with ATD decreasing recognition of facial expressions depicting anger, disgust and surprise, but not fear and sadness [71]. Furthermore, in two other studies on healthy participants ATD failed to alter recognition of emotion in faces [72,73]. One study found different results in healthy women and those with a history of depression. There was no effect on recognition of fearful faces, but ATD increased recognition of happiness in women who had never been depressed, and decreased it in recovered depressed women [67]. Raising tryptophan with alpha-lactalbumin, a protein with high tryptophan levels, enhanced the recognition of both fearful and happy faces in healthy participants [74]. However, in another study, in which healthy people received tryptophan supplements for two weeks, tryptophan increased the recognition of happy facial expressions but decreased the recognition of disgusted facial expressions in women, without altering the responses of men [75].

Investigations on how altered tryptophan levels influence the recognition of different facial expressions are relatively easy to perform, but have not produced particularly consistent or interesting results. This may not be a fruitful topic to pursue until there is some understanding of the sources of variability. Furthermore, the implications that serotonin-induced alterations in the recognition of facial expressions have for actual social functioning in everyday life are not clear.

Two recent studies looked at different aspects of social cognition after ATD in healthy participants. In the first, the women rated photographs of happy faces as less attractive, and were less aroused by angry faces, after ATD [76]. In the second study men and women looked at photographs of heterosexual couples with neutral expressions. Half of the
7. Conclusion

Serotonin neurons project from the brainstem, innervating all areas of the brain diffusely. In keeping with what might be expected from the neuroanatomy, serotonin modulates many aspects of brain function. A recent review on the biology of serotonin lists some of those functions, but while aggression is included in the list, regulation of prosocial behaviours is not [78]. The discovery that increasing serotonin can increase prosocial behaviours is relatively recent and so far not much attention has been paid to this topic. This is in spite of the large body of data relating aspects of social behaviour to both physical and mental health, and the fact that most psychiatric disorders are associated in some way with disruptions in the normal patterns of social interactions. Much of the work on social neuroscience related to serotonin has focused more on social cognition and neuroanatomical considerations than actual human social behaviour. When behaviour has been studied it is usually in a laboratory rather than in everyday life [64,79,80]. While research on social cognition and the neuroanatomical basis of social cognition are certainly important, a more balanced approach, with more studies looking at everyday social behaviour, would probably help the field to advance more rapidly.

While the measurement of social behaviour in everyday life using EMA has become as established technique in social psychology its use in more biologically oriented studies is still rare. An important take-home message of this review is that EMA methodology is simple to perform and can produce interesting results when combined with well-established strategies that influence neurotransmitter function.

The studies described in this review suggest that while alterations in serotonin do not always alter mood in humans, effects on social behaviour along the agreeable–quarrelsome axis can occur even in the absence of any change in mood. The effects of serotonin on mood and social behaviour are presumably mediated by different neuroanatomical systems. However, the tone of social interactions can have effects on mood, and mood can have effects on social behaviour. For example, irritability is a common symptom in clinical depression. The two-way interaction between mood and social behaviour could be a fruitful area of research that may reveal more about how both are regulated.

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